Transfusion Outcomes in Patients with Transfusion-Dependent Beta-Thalassemia Following Allogeneic Hematopoietic Stem Cell Transplantation – a Systematic Literature Review

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BACKGROUND

- Beta-thalassemia is a rare hereditary hemoglobinopathy characterized by reduced or absent beta-globin production, leading to ineffective erythropoiesis.[1-4]
- The most severe form of the disease is transfusion-dependent beta-thalassemia (TDT), where patients are dependent on regular red blood cell transfusions (RBCTs) and iron chelation therapies (ICTs) for survival.[1,2]
- Individuals with TDT experience significant clinical complications that impact all organ systems, especially the hepatobiliary, cardiopulmonary, and endocrine systems, which can lead to early mortality in individuals with TDT.[3]
- Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is potentially curative for patients with TDT. There has been limited evaluation of the evidence on transfusion outcomes after allo-HSCT.

OBJECTIVE

- To synthesize evidence from published literature on transfusion outcomes in patients with TDT following allo-HSCT, using a systematic literature review (SLR) approach

METHODS

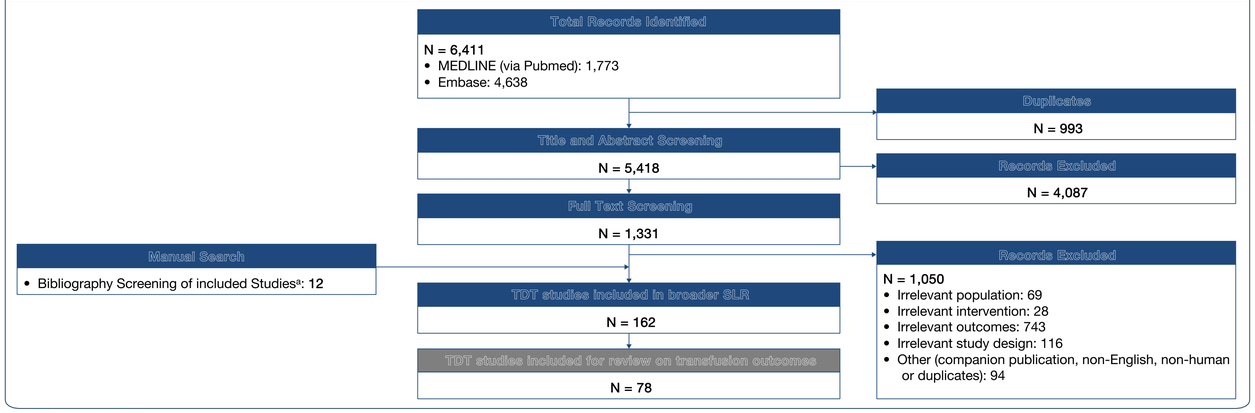
- A comprehensive search was conducted in MEDLINE and Embase to identify English-language publications from interventional and observational studies published from inception of databases up to 12 May 2023, that assessed outcomes in patients with sickle cell disease and TDT after allo-HSCT. Relevant conference proceedings were also searched to identify sources from grey literature. Bibliographies of relevant SLRs and meta-analyses were hand-searched to identify eligible studies that were not identified.
- The results presented here focus on a subset of studies that assessed transfusion outcomes among patients with TDT who underwent allo-HSCT. Specifically, studies that assessed transfusion independence (TI) and/or transfusion dependence (TD) were included. Studies that only reported allo-HSCT-related outcomes were excluded.
  - However, if studies that reported TI and/or TD also provided data on graft failure or graft-versus-host disease (GVHD) then these data were also summarized for the review.
- Study selection and data extraction followed the guidance published by the University of York Centre for Reviews and Dissemination (CRD) and reporting of findings followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023445828).
- Identified articles were screened by title and abstract as well as full-text by two independent reviewers. Data extraction was performed by a single reviewer and all outcomes were independently verified by a second reviewer. Disagreements between reviewers were resolved by a consensus discussion or a third reviewer.
- Proportions of patients experiencing outcomes after allo-HSCT across studies were aggregated and descriptively reported. Data on study-reported TI and TD were harmonized as proportion of patients achieving TI after allo-HSCT.

RESULTS

Study Screening & Characteristics of Included Studies

- The broader SLR identified 6,411 records potentially reporting outcomes in patients with SCD and TDT after allo-HSCT. After title/abstract and full text screening, 162 studies which assessed clinical outcomes after allo-HSCT in patients with TDT were further evaluated. Of these, 78 studies (48.1%) that reported transfusion outcomes on 3,928 patients were included in this review[5-85] (**Figure 1**).
- Most studies included were full-text articles (n = 59 of 78 [75.6%]).
- Most studies included pediatric patients (n = 73 of 75 studies that reported age [97.3%]), employed myeloablative conditioning regimen (n = 60 of 75 studies that reported conditioning regimen [80.0%]), and included patients treated with matched-sibling donor (n = 30 of 76 studies that reported donor type [39.5%]).
- The majority of the included studies were observational by design (n = 73 of 78 [93.6%]) and ex-US studies (top 3 countries of the 78 that reported geography: China, n = 15 [19.2%]; Italy, n = 13 [16.7%]; India, n = 7 [9.0%]). Sample size for included studies varied from 5 to 328 patients.

Figure 1. PRISMA Flow Diagram for Selection of TDT Studies

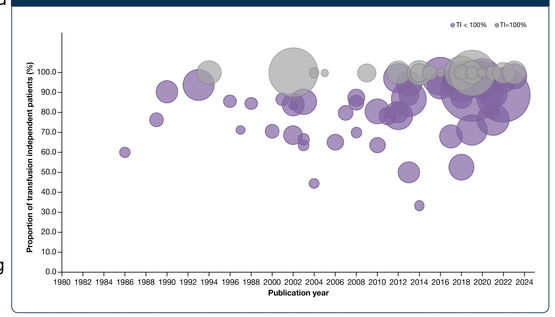


Date of Search: May 12, 2023.
Abbreviation: allo-HSCT, allogeneic hematopoietic stem cell transplantation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCD, sickle cell disease; TDT, transfusion-dependent beta-thalassemia; SLR, systematic literature review.
Note: This SLR focuses on transfusion outcomes in patients with TDT after allo-HSCT and is part of a broader SLR on outcomes in patients with SCD and TDT after allo-HSCT. The SLR protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023445828).
[a]Reviews and systematic reviews including meta-analyses.

Transfusion Outcomes

- Seventy-eight studies assessed transfusion requirements after allo-HSCT. Of these, 55 studies assessed TI[5-10,12-19,21-41,43-47,49-57,59-62,84,86], 20 studies assessed TD[63-82], and 3 studies assessed both.[11,42,58]
- Definition of transfusion outcomes varied considerably between studies; TI was most frequently reported as absence of regular transfusions and TD as dependence on regular transfusions assessed by the end of the study period, after allo-HSCT.
  - There was a lack of reporting on the time duration between completion of allo-HSCT and beginning of assessment of TI, after accounting for planned post-HSCT transfusion support.
  - There is limited reporting on duration of transfusion-free period for TI; 2 studies defined this duration as at least 1 year after allo-HSCT,[14,62] and 2 additional studies defined this as no transfusions starting 2 months after allo-HSCT or no transfusions after engraftment.[21,50]
- A total of 3,715 of 3,928 patients survived until the end of the follow-up period and were assessed for TI. Among them 3,351 (90.2%) patients achieved engraftment and were TI during follow-up after allo-HSCT (range across studies: 33.3%-100.0%; **Figure 2**).
  - Median duration of follow-up varied from 4 months to 288 months after allo-HSCT
- The proportion of patients who achieved TI was similar in a subset of studies with minimum study follow-up duration of 6-months or 12-months to account for planned post-HSCT transfusion support immediately after allo-HSCT.

Figure 2. Proportion of TI Patients at the End of Study Follow-up Among Patients with TDT after Allo-HSCT



Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; TD, transfusion dependence; TDT, transfusion-dependent beta-thalassemia; TI, transfusion independence.
Bubble size reflects sample size across 78 studies that assessed for TD or TI after allo-HSCT. Data on study-reported TI and TD were harmonized and presented in this figure as proportion of patients achieving TI after allo-HSCT.

Transplant-Related Outcomes

- Primary or secondary graft failure was assessed in 56 of 78 studies.[5-8,10,12,14-16,19,23,24,26-36,38,40-43,45,46,,50-52,54-59,65-69,71-75,77-82,86]
- Acute or chronic GVHD was assessed in 59 of 78 studies.[5,8-15,19,21,22,24-33,36-39,41,43,45-47,49-55,57-60,62,65-71,74,75,77-82,86]
- These results are summarized in **Table 1**.

Table 1. Proportion of Patients with TDT Experiencing Graft Failure and GVHD After Allo-HSCT

Outcome	Number of studies that assessed the outcome	Number of studies that reported patients experiencing the outcome after allo-HSCT	Proportion of patients experiencing the outcome after allo-HSCT,[a] median (range across studies)
Primary graft failure	49	34 (69.4%)	10.8% (0.8% - 44.4%)
Secondary graft failure/rejection	27	22 (84.6%)	6.4% (2.7% - 54.5%)
Acute GVHD	54	50 (92.6%)	25.0% (8.3% - 100.0%)
Chronic GVHD	55	46 (83.6%)	16.4% (1.3% - 42.4%)

[a]Among studies reporting patients experiencing the outcome after allo-HSCT.

LIMITATIONS

- The identified evidence reported limited details on transfusion outcomes after allo-HSCT such as time to assessment of TI after accounting for planned transfusion support after allo-HSCT and duration of transfusion-free period to become transfusion independent. There is also a lack of chimerism data in patients who continue to require transfusions which is important to understand disease recurrence.
- Lack of standardized definition for transfusion independence after allo-HSCT potentially results in wide variability in reporting of TI rates.
- Heterogeneity in the definition of TI and TD precludes presenting pooled estimates using a meta-analysis.
- Possibility of publication bias cannot be ruled out given the lack of full-text publications of some conference abstracts.

CONCLUSIONS

- Based on this systematic literature review, a portion of patients with TDT continue to require regular transfusions after allogeneic HSCT.
- These results highlight the limitations of allogeneic HSCT for TDT, particularly those related to inconsistent efficacy profile with TI rates after HSCT and wide variability in safety profile with graft failure, graft rejection, and GVHD.

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DISCLOSURES

- **RN**, **NL**, **SI**, **PK**, and **MDB** are employees of Vertex Pharmaceuticals and may own stock/stock options in the company.
- **KL**, **LZ**, and **MD** are consultants of Maple Health Group, LLC.