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Unrelated donor stem cell transplantation for transfusion-dependent thalassemia

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Abstract

Thalassemia major is characterized by severe anemia dependent on red cell transfusions from infancy. Conservative management requires a safe source of compatible blood throughout life, strategies to combat iron overload, monitoring and treatment of transfusion-related complications, and management of cardiac and/or hepatic dysfunction from iron accumulation. Complications can result in premature morbidity and mortality. Stem cell transplantation is curative, but outcomes depend on availability of a histocompatible donor, recipient age, and disease related complications. Successful transplantation requires stable donor engraftment and donor-derived erythropoiesis and a low incidence of graft-versus-host disease, organ toxicities, and mortality. This translates to a cure with good quality of life and life span. Since recipients are at a high risk for graft rejection (prior transfusions, immunocompetency), myeloablative transplants have been the norm. Recent modifications to standard preparative regimens have significantly reduced transplant toxicities, resulting in >80% disease-free survival in children. Aiming to further reduce regimen-related toxicities, such as veno-occlusive liver disease and sterility, a recent trial also explored reduced intensity conditioning in unrelated donor transplants utilizing marrow or umbilical cord blood in patients without suitable familial donors. This report summarizes advances in unrelated donor transplantation for thalassemia, focusing on conditioning regimen nuances.

Keywords

stem cell transplantation; unrelated donors; thalassemia; bone marrow; umbilical cord blood

Introduction

Thalassemia major is an autosomal recessive genetic disorder of hemoglobin production characterized by severe chronic microcytic anemia and, consequently, poor growth and development in the homozygous state. It has worldwide prevalence with increased incidence in Southeast Asia, Sub-Saharan Africa, Middle Eastern countries, and Mediterranean regions. About 4.4 of every 10,000 babies born worldwide suffer from thalassemia. The

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global annual incidence of beta thalassemia is estimated at 1 in 100,000. In 2013, 25,000 deaths worldwide were deemed attributable to thalassemia and related complications, an improvement over 36,000 deaths in 1990, perhaps secondary to improved availability of safe and suitable blood products and chelation techniques. Conservative management includes lifelong chronic red cell transfusion therapy. The iron deposition that accompanies this intervention requires aggressive chelation therapy to prevent complications of iron overload and toxicity, especially on the heart and liver. Causes of mortality include inadequate transfusions, transfusion-related complications such as infections, and cardiomyopathy or liver cirrhosis from iron overload due to inadequate or ineffective chelation.[1]

Stem cell transplantation for thalassemia

Successful allogeneic hematopoietic stem cell transplantation (HSCT) renders patients disease free and amounts to a cure. HSCT has better outcomes when performed during childhood (particularly in children <17 years of age) before irreversible disease-related organ damage. Outcomes are also worse with poor chelation pretransplant. The recognition of the close relationship between liver toxicity, iron status, and transplant outcomes led to the development of the Pesaro risk score (risk class 1 to 3) based on adequacy of chelation, presence of clinical hepatomegaly, and portal fibrosis on liver biopsy. Risk class 1 had the best and class 3 had the worst outcomes.[2] The Pesaro group described disease-free survival (DFS) of 87%, 85%, and 80% in children with risk class 1, 2, and 3, respectively, and 65% in adults following HSCT.[3] This was an improvement from 53% DFS reported in the 1990s after conditioning with the standard myeloablative busulfan and cyclophosphamide combination.[4] Better chelation and improved transplant monitoring and supportive care are likely reasons for this improvement. Outcomes vary between countries and may be related to higher risk scores, center experience, and disease status. Registry data in the United States report a DFS of 88% and 62% in children for risk classes 2 and 3, respectively, following matched sibling donor (MSD) marrow transplants.[5] DFS following sibling donor cord transplants from Europe and the United States was 78%.[6] Higher mortality was noted in children over 7 years of age and those with hepatomegaly >5 cm, defining a very-high-risk category of recipients. Causes of death included primarily veno-occlusive disease (VOD), interstitial pneumonitis, and graft rejection (GR).[5]

GR is a major cause of transplant failure in thalassemia and can be fatal without a successful second transplant in the myeloablative setting. GR was encountered in approximately 10% of MSD HSCTs but was higher (at 13%) following unrelated donor (URD) myeloablative transplants.[7] In risk class 3 patients, GR rates escalated to as high as 30%.[2] Similarly, transplant-related mortality (TRM) was also higher (at 20%), resulting in a DFS of 54–80% depending on risk class group. TRM also increased with age and was 30% in adults undergoing URD HSCT for thalassemia.[8] The causes of death in adults were similar to those in children, and included hepatic VOD, hemorrhage, GVHD, and infection, particularly hepatitis C associated with portal fibrosis.[9] Umbilical cord blood is an attractive stem cell source for availability and ability to maintain outcomes with some histocompatible mismatch. Umbilical cord blood transplants (UCBTs) from unrelated donors, however, have fared poorly in thalassemia compared to related UCBTs. As comparison, registry data has revealed a DFS of 78% following MSD UCBT, but a DFS of only 21% after URD UCBT,

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thwarting enthusiasm for the procedure.[6,10] A major reason for this was a high rate of graft rejection (20 of 35 patients), especially when the total nucleated cell dose in the infused product was $<5 \times 10^7$/kg recipient weight. Notably, GR was fatal in five patients following marrow aplasia afforded following myeloablation. Hence, modifications to transplant methods have been sought to decrease toxicity and TRM and promote engraftment of donor cells. Though applicable to all transplants, benefits from such modifications are especially relevant in the URD HSCT setting due to poorer outcomes compared to MSD HSCT.

Improving outcomes with modifications to the HSCT approach

Several transplant groups have worked on improving transplant outcomes in thalassemia by primarily targeting conditioning regimens designed to improve engraftment while simultaneously decreasing toxicity and TRM (Table 1). The addition of hydroxyurea and azathioprine commencing 45 days prior and a course of fludarabine approximately 2 weeks before HSCT was used in MSD HSCT for class 3 patients, all <17 years of age. This strategy was successful in reducing graft rejection, presumably by increased immunosuppression, from 30% to 8% during the early follow-up period, and was a major breakthrough.[11] However, GR rates eventually were noted to be 15% with this strategy.[12] This prompted the addition of thiotepa to the myeloablative regimen consisting of hydroxyurea, azathioprine, fludarabine, busulfan, and cyclophosphamide. In the MSD setting, this intensification was further successful in averting GR and increased DFS from 73% to 92%.[12] The incidence of GVHD was similar with standard regimens of busulfan and cyclophosphamide. Though organ toxicity is a concern and related to the intensity of conditioning, the need to maintain intensity was demonstrated by the 23% GR rate in class 3 patients following MSD HSCT conditioned with lower dose busulfan (50% dose reduction), fludarabine (175 mg/m^2). and total lymphoid radiation (500 cGy).[13]

The availability of MSD is approximately 30% and is a limitation to offering this curative strategy to many thalassemia patients.[5] URD HSCT for thalassemia has been expanding in the recent years. Anurathapan *et al.* described a two-phase pretherapy that was applied to both related and unrelated donor bone marrow HSCT.[14] The pretherapy consisted of fludarabine (40 mg/m^2/day) and dexamethasone (25 mg/m^2/day) for 5 days each on days –56 and –28. This was followed by a standard myeloablative transplant utilizing busulfan, fludarabine, and thymoglobulin. DFS with this strategy was 82% after URD transplants, and the authors noted that there was no increased toxicity from this regimen, although fludarabine was utilized serially. The recent availability of treosulfan, a potentially less toxic alkylating agent with myeloablative properties related to busulfan, has helped achieve successful outcomes following HSCT.[15] A myeloablative preparative regimen consisting of treosulfan, fludarabine, and thiotepa has been studied in several countries for related and unrelated donor HSCT.[16,17] In the unrelated donor setting, a DFS of 84% was reported.[15] The toxicity profile of treosulfan on the liver and other organs may be better, affording the drug an advantage over busulfan. However, it needs coupling with other myelotoxic agents (thiotepa in this case) to allow successful engraftment. Similarly, an intense preparative regimen of a combination of busulfan, cyclophosphamide, fludarabine, and thiotepa coupled with peripheral blood stem cells overcame graft rejection risks with a DFS of 90%.[18]

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However, the benefits of such intense preparative regimens need to be balanced with early and late toxicities, especially in patients with high-risk disease.

Unrelated UCBT efforts for thalassemia have been thwarted by increased GR and thus low DFS, as previously mentioned. The best outcomes following unrelated UCBT were described by Jaing *et al.* who used up to two antigen-mismatched cords with suitable cell doses (>2.8 × 10^7/kg nucleated cells) and a standard preparative regimen of busulfan, cyclophosphamide, and anti-lymphocyte/thymocyte immunoglobulin.[19]. With a median follow-up of 36 months, this group described GR rates of 11% and a DFS of 73% with this strategy.

Reduced intensity unrelated donor transplantation for thalassemia

Myeloablation is associated with short- and long-term risks, such as hepatic and pulmonary toxicity, growth impairment, and sterility.[20] This makes a case for attempting reduced intensity conditioning directed at averting such toxicities that are particularly relevant to the pediatric age group who deal with these effects throughout life. It is also an advantage in those at risk for TRM due to organ toxicity from iron overload (older patients, class 3 risk group). The concern in this circumstance, however, is GR. In an URD transplant trial called the URTH trial for thalassemia that was supported by the Thalassemia Clinical Research Network (TCRN) and the Pediatric Blood and Marrow Transplant Consortium (PBMTC), we explored a reduced intensity conditioning approach for HSCT utilizing either matched (at eight major histocompatibility loci) unrelated marrow or matched/mismatched (at a single antigen locus mapped at regions A, B, and DRB1) UCB. Immunoablation was utilized to facilitate engraftment. The regimen comprised hydroxyurea, alemtuzumab, fludarabine, melphalan, and thiotepa. With 31 patients enrolled to date, the 2-year DFS is 82% and 79% for marrow and cord, respectively, with a single instance of GR, and comparable rates of GVHD (manuscript in preparation). This demonstrates that reduced-intensity conditioning can be considered for this disorder, provided adequate immunoablation is provided. Precautions with this strategy include surveillance and prompt treatment of infections until adequate immune reconstitution, which can take up to 1 year.[21]

Summary

HSCT and gene therapy are the only two curative options for transfusion-dependent thalassemia. While HSCT efforts have been underway for several years, gene therapy–related investigation is still early and not yet widely available. Matched sibling donor transplantation performed in the young before iron accumulation–related organ damage has the best outcomes. Current efforts are directed at achieving better outcomes in higher-risk settings: patients with advanced age or disease or extension of HSCT to unrelated donor stem cell options such as marrow, peripheral blood, and umbilical cord blood. Transplant-related complications that effect outcomes and need to be overcome include graft rejection, graft-versus-host disease, organ toxicity such as VOD, late effects, and TRM. Modern methods of transplant continue to overcome these obstacles with greater success. As described in this report, the field has moved toward transplants utilizing less toxic myeloablative conditioning. More recently, substituting myeloablation with reduced-

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intensity conditioning was able to support donor cell engraftment from bone marrow or cord blood cells, thus increasing transplant options further for patients with thalassemia.

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References

1. Ceci A, Baiardi P, Catapano M, et al. Risk factors for death in patients with beta-thalassemia major: results of a case-control study. Haematologica. 2006; 91:1420–21. [PubMed: 16963395]
2. Lucarelli G, Clift L, Galimberti M, et al. Marrow transplantation for patients with thalassemia: results in class 3 patients. Blood. 1996; 87:2082–8. [PubMed: 8634461]
3. Gaziev J, Sodani P, Polchi P, Andreani M, Lucarelli G. Bone marrow transplantation in adults with thalassemia: treatment and long-term follow up. Ann N Y Acad Sci. 2005; 1054:196–205. [PubMed: 16339666]
4. Gaziev D, Polchi P, Galimberti M, Angelucci E, Giardini C, Baronciani D, et al. GVHD after BMT for thalassemia: an analysis of incidence and risk factors. Transplantation. 1997; 63(6):854–60. [PubMed: 9089226]
5. Sabloff M, Chandy M, Wang Z, Logan B, Ghavamzadeh A, Li C, et al. HLA-matched sibling bone marrow transplantation for β-thalassemia major. Blood. 2011; 117(5):1745–50. [PubMed: 21119108]
6. Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li C, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood. 2013; 122(6):1072–8. [PubMed: 23692854]
7. La Nasa G, Argiolu F, Giardini C, Pession A, Fagioli F, Caocci G, et al. Unrelated bone marrow transplantation for {beta}-thalassemia patients: the experience of the Italian Bone Marrow Transplant Group. Ann N Y Acad Sci. 2005; 1054:186–95. [PubMed: 16339665]
8. La Nasa G, Caocci G, Argiolu F, Giardini C, Locatelli F, Vacca A, et al. Unrelated donor stem cell transplantation in adult patients with thalassemia. Bone Marrow Transplant. 2005; 36(11):971–5. [PubMed: 16205730]
9. Angelucci E, Muretto P, Nicolucci A, Baronciani D, Erer B, Gaziev J, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood. 2002; 100(1):17–21. [PubMed: 12070002]
10. Ruggeri A, Eapen M, Scaravadou A, Cairo M, Bhatia M, Kurtzberg J, et al. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant. 2011; 17(9):1375–82. [PubMed: 21277376]
11. Sodani P, Gaziev D, Polchi P, Erer B, Giardini C, Angelucci E, et al. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. Blood. 2004; 104(4):1201–3. [PubMed: 15039283]
12. Gaziev J, Isgrò A, Sodani P, Marziali M, Paciaroni K, Gallucci C, et al. Optimal Outcomes in Young Class 3 Patients With Thalassemia Undergoing HLA-Identical Sibling Bone Marrow Transplantation. Transplantation. 2015
13. Hussein A, Al-Zaben A, Ghatasheh L, Natsheh A, Hammada T, Abdel-Rahman F, et al. Risk Adopted Allogeneic Hematopoietic Stem Cell Transplantation Using a Reduced Intensity Regimen for Children with Thalassemia Major. Pediatr Blood Cancer. 2013; 60(8):1345–9. [PubMed: 23424175]
14. Anurathapan U, Pakakasama S, Rujkijyanont P, Sirachainan N, Songdej D, Chuansumrit A, et al. Pharmacologic Immunoablation Followed by Reduced-Toxicity Conditioning and Stem Cell Transplantation in High-Risk Thalassemia: A Safe Approach to Disease Control. Biol Blood Marrow Transplant. 2013; 19(8):1259–62. [PubMed: 23648235]
15. Bernardo M, Zecca M, Piras E, Vacca A, Giorgiani G, Cugno C, et al. Treosulfan-based conditioning regimen for allogeneic hematopoietic stem cell transplantation in patients with thalassemia major. Br J Haematol. 2008; 143(4):548–51. [PubMed: 18986389]

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16. Mathews V, George B, Viswabandya A, Abraham A, Ahmed R, Ganapule A, et al. Improved Clinical Outcomes of High Risk β Thalassemia Major Patients Undergoing a HLA Matched Related Allogeneic Stem Cell Transplant with a Treosulfan Based Conditioning Regimen and Peripheral Blood Stem Cell Grafts. PLoS One. 2013; 8(4):e61637. [PubMed: 23637873]
17. Choudhary D, Sharma S, Gupta N, Kharya G, Pavecha P, Handoo A, et al. Treosulfan-Thiotepa-Fludarabine-Based Conditioning Regimen for Allogeneic Transplantation in Patients with Thalassemia Major: A Single-Center Experience from North India. Biol Blood Marrow Transplant. 2013; 19(3):492–5. [PubMed: 23160007]
18. Li C, Wu X, Feng X, He Y, Liu H, Pei F, et al. A novel conditioning regimen improves outcomes in β-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. Blood. 2012; 120:3875–81. [PubMed: 22968457]
19. Jaing T, Hung I, Yang C, Chen S, Chung H, Tsay P, et al. Unrelated cord blood transplantation for thalassaemia: a single-institution experience of 35 patients. Bone Marrow Transplant. 2012; 47(1): 33–9. [PubMed: 21383683]
20. De Simone M, Olioso P, DiBartolomeo P, DiGiralmo G, Farello G, Palumbo M, et al. Growth and endocrine function following bone marrow transplantation for thalassemia. Bone Marrow Transplant. 1995; 15(2):227–33. [PubMed: 7773211]
21. Shenoy S, Murray L, Walters M, Chaudhury S, Soni S, Pulsipher M, et al. Multicenter Investigation Of Unrelated Donor Hematopoietic Cell Transplantation (HCT) For Thalassemia Major After a Reduced Intensity Conditioning Regimen (URTH Trial). Blood. 2013; 122:543.

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Table 1

Modifications made to transplant regimens to improve outcomes

Ref	Median follow-up	Recipient / transplant characteristics	Modification in preparative regimen	OS (%)	DFS (%)	Graft rejection (%)
22	36 months	HLA-matched related donors Risk class 3 Age < 17 years	Transfusions chelation (desferroxamine) hydroxyurea azathioprine + busulfan / cyclophosphamide	93	85	8 (Eventual risk 15%)
7	39 months	Unrelated donors Recipient risk class 1-3	Busulfan + fludarabine / cyclophosphamide Thiotepa added for GR	79 96 (C 1–2) 65 (C 3)	65 80 (C 1–2) 55 (C 3)	20 (C 1–2) 11 (C 3)
13	64 months	Related donors Class 3	Low dose busulfan, fludarabine, TLI, and ATG	100	77	23
12	41 months	HLA-matched related donors Risk class 3 Age < 17 years	Transfusions, chelation (desferoxamine) hydroxyurea azathioprine + busulfan / fludarabine/ cyclophosphamide/thiotepa	92	92	0
14	39 months	High risk ≫10 years Hepatomegaly Unrelated donors	A subset received RIC: fludarabine / dex × 2; then busulfan/fludarabine/ATG	94	82	0
23	36 months	Related and unrelated donors	Treosulfan, thiotepa and fludarabine	93	82	9
18	24 months	Unrelated donor group PBSC transplants	Busulfan, cyclophosphamide, fludarabine	92	90	1.9
19	36 months	Unrelated donor cord	Busulfan, cyclophosphamide, antilymphocyte globulin	88	73	17
21	41 months	Unrelated donor cord or marrow	HU, alemtuzumab, fludarabine, melphalan, thiotepa	87	83	1.9

Risk factors: Inadequate iron chelation, hepatomegaly > 2cm, portal fibrosis on liver biopsy.

Risk class 1: No risk factors; risk class 2: one or two factors; risk class 3: all 3 risk factors present.

GR, graft rejection; C, risk class; HU, hydroxyurea; RIC, reduced-intensity conditioning; Dex, dexamethasone; Bu, busulfan; Flu, fludarabine; TLI, total lymphoid irradiation; ATG, antithymocyte globulin; Dex, dexamethasone; PBSC, peripheral blood stem cell; OS, overall survival; DFS, disease-free survival; FU, follow-up

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