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A REVIEW OF NOVEL CONDITIONING STRATEGIES FOR PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THALASSEMIA MAJOR

Haematology

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ABSTRACT

Hematopoietic stem cell transplantation is a potentially curative treatment modality for children with transfusion dependent thalassemia. In last 30 years since first transplant for thalassemia was done there have been more than 3000 allogeneic transplants performed worldwide. This review provides a brief information of hematopoietic stem cell transplantation in thalassemia with the objective to provide outcome predictions based on modern transplant technologies and some of the known post-transplant complications.

KEYWORDS

Hematopoietic stem cell transplantation, Thalassemia major, Conditioning regimen

BACKGROUND

Allogeneic hematopoietic stem cell transplantation is a curative approach to treat children with transfusion dependent thalassemia.[1] Though hematopoietic stem cell transplant is a curative option however only 25% of the patients will have a fully HLA-matched sibling and finding matched unrelated donors is also challenging therefore HSCT using haploidentical (HLA mis-matched) donor is now being considered a viable therapeutic option with improving outcomes. Haploidentical donor is a widely available option but it carries a high rate of graft rejection and graft-versus-host disease. Most of the published studies related with haplo transplants reported inferior transplant outcomes in children with Thalassemia Lucarelli class III [1,2] due to pre-existing organ dysfunction and alloimmunisation. This necessitated the use of novel pre-transplant immunosuppression and better conditioning regimens for favourable outcomes. All patients with Donor Specific Antibody levels above 1,000 should receive treatment. DSA levels should be repeated after treatment with immunosuppressant, before and after infusion of stem cells to improve outcomes in children with haplo-identical transplants[3,4].

How To Prepare A Child For Transplant (conditioning Regimen)

Preparatory regimens for HSCT of patients must achieve two objectives.

- Elimination of the recipient's marrow and make space for donor's hemopoietic cells.
- Create an environment that will allow the transplanted marrow to survive and thrive.

A prognostic scheme developed by the Pesaro group[5] was based on the following risk factors- Hepatomegaly (liver size of more than 2 cm), Liver fibrosis and Irregular chelation history. Patients were categorized into three risk classes influencing the probability of survival.

- Pesaro Class 1 None of these factors
- Pesaro Class 2 1 or 2 of these factors
- Pesaro Class 3 All of the above factors.

Type Of Donor Transplants And Outcomes Based On Published Literature:

A. Matched sibling donor (MSD) transplant
B. Matched Unrelated donor (MUD) transplant
C. Haplo-identical transplant without graft manipulation and using Posttransplant cyclophosphamide (Haplo PTCy)
D. Haplo-identical transplant with graft manipulation (TCR alpha/Beta depletion with CD45 RO cell preservation)

A. Matched sibling donor transplant (MSD):

When a sibling is 10/10 match with the patient on high resolution HLA testing, this is called as matched sibling and the type of transplant would be called as **Matched sibling donor transplant** (MSD).

Previous experience of conditioning regimen for matched sibling donor transplant

- **Pesaro Experience:** This study was done between 1985 to 2003, total 498 patients of age less than 17 years of thalassemia class I, II and III were included. All patents underwent Matched sibling donor transplant using a conditioning regimen containing Busulphan 14mg/kg and Cyclophosphamide 200mg/kg. Out of 498 patients, there were 150 ,315 and 33 patients of class 1, Class 2 and Class 3 respectively. The probabilities of overall survival (OS) and thalassemia-free survival (TFS) for class 1 patients were 90% and 87%, for class 2 patients 87% and 85% respectively however for class 3 patients who were treated with the same conditioning regimen thalassemia free survival was very low (53%)[5].
- In order to improve thalassemia free survival in Pesaro class III due to regimen related toxicity the cumulative dose of Cyclophosphamide was reduced from 200mg/kg to 160mg/kg. This was the first approach that has significantly reduced the regimen related toxicity and mortality but it was associated with an increased risk of graft failure from 13 to 35%. The reason for increased graft failure and graft rejection could be because of insufficient immuno-suppression due to highly sensitized lymphoid cells secondary to repeated blood transfusion[6].
- To reduce the risk of graft rejection Sodani et al, modified this regimen and called this protocol 26 which includes a combination of hyper-transfusion, hydroxyurea, and chelation, and by the addition of fludarabine (Flu) and azathioprine to increase the level of immunosuppression (in order to compensate for Cyclophosphamide dose reduction), which resulted in a reduction of the rate of graft rejection from 30% to 8%.In protocol 26, the conditioning regimen was augmented with additional immunosuppression by adding Fludarabine and azathioprine to the pre-transplant preparative regimen[7].
- The overall survival was better in children less than 4 years of Class 1 and class 2 hence they were given Busulphan 14mg/kg, Cyclophosphamide 200mg/kg and thiotepa 10 mg/kg total dose, while patients ≥ 4 years of age received Busulphan 14mg/kg, and Cyclophosphamide 200mg/kg as a preparatory regimen.
- The treatment protocols in use are shown in Table 1.

Table 1. Current treatment protocols[5].

Risk Class	Age	Pre-Conditioning	Conditioning	GVHD Prophylaxis
Class 1 and Class2	>4 years	None	Pc 6 *Bu14 CY200	CSA/MP/MTx
Class 1 and Class2	<4 years	None	Pc 6 *Bu14 CY200	CSA/MP/MTx
Class 3 Before February 2007	<17 years	Day 35 to day 11: AZ, HU Day 16 to day 11: Flu 100 G-CSF, DFO	Pc26 Bu14 CY160	CSA/CY/MP/MTx
Class 3 Since February 2007	<17 years	Day 35 to day 11: AZ, HU Day 16 to day 11: Flu 150 G-CSF, DFO	Pc26 modified i.v. BuTT10 CY160	CSA/CY/MP/MTx

Bu- Busulfan, CY- Cyclophosphamide; MP- methylprednisolone; CSA- Cyclosporine; MTX- methotrexate; TT- thiotepa; Flu-Fludarabine; AZ-Azathioprine; Hu- hydroxyurea; DFO-deferoxamine, G-CSF- granulocyte colony-stimulating factor

Reduced Toxicity Regimen (rtc)

- Li et al, developed NF-08-Thalassemia Major Stem cell transplant protocol based on intravenous Busulphan (Bu), Cyclophosphamide (Cy), Fludarabine (Flu), and thiotepa to treat children with thalassemia. In this protocol, the classic preparative regimen based on BuCy was modified with the addition of thiotepa and Fludarabine, and the dose of Busulphan was reduced by a one-third to decrease lung and liver toxicity. Thiotepa was added for myeloablation and effective immunosuppression, leading to faster engraftment along with reduction in the risk of hepatic veno - occlusive disease[8].
- Chaudhary et al, used Treosulfan/thiotepa/fludarabine (TTF) based conditioning regimens in 28 patients with thalassemia who underwent Matched unrelated transplant between February 2010 to September 2012 and compared the results retrospectively with the patients who underwent Matched sibling donor transplant with Busulfan, cyclophosphamide and anti-thymocyte globulin (Bu/Cy/ATG) based conditioning regimen in 12 patients with median patient age of 9.7 years. They have found no significant differences between the 2 groups (treo/Thio/flu vs Bu/Cy/ATG) in terms of the incidence of acute Graft versus host disease, chronic Graft versus host disease, Transplant related mortality and graft failure[9].

B. Matched Unrelated Donor Transplant

Since every patient has only 25% chance of finding an HLA identical donor in each of his real sibling therefore there is a need to find an Unrelated Blood Stem Cell Donor through various stem cell donor registries. The first successful matched unrelated donor transplant took place in 1973 in a patient with inherited immunodeficiency disorder in Denmark.

As of August 2019, there are more than 35 million donors listed at the World Marrow Donors Association, a network of unrelated donor registries which includes 83 stem cell donor registries and 4 donor centres.

In India, there are five common organizations listing donors for unrelated donor recipients:

- DKMS Registry in which approx. 21,695 donors are listed in its database www.dkms-bmst.org
- Be The Cure Registry-Jeevan Foundation with appox 6449 donors www.**jeevan**.org
- Datri Blood Stem Cells Registry with more than 450000 donors www.datri.org
- GeneBandhu with 7,991 donors *www.genebandhu.org*
- The Marrow Donor Registry India with 35,768 donors www.mdrindia.org

Preparatory regimen for MUD transplant

- Bernard et al used thiotepa, treosulfan, and fludarabine(TTF) based reduced toxicity conditioning regimen in 60 thalassemia patients in which 27 were children and 12 patients were adults with a median age of 7 years. Out of 60 patients 20 were matched sibling and 40 were unrelated donor transplants. The overall incidence of graft failure and transplantation-related mortality was 9% and 7%, respectively. The 5-year probability of survival and thalassemia-free survival were 93% and 84%, respectively with a median follow-up of 36 months (range, 4-72). In this study the treosulfan-based conditioning found to be safe and effective for thalassemia patients underwent allogeneic hematopoietic stem cell transplant[10].
- Kharya et al used their own APOLLO protocol for Haplo family donor-Stem cell transplant to matched unrelated donor setting with increased dose of TBI to 4Gy, in a small subset of patients and documented 100% myeloid engraftment with no risk of acute or chronic Graft versus host disease.[11]
- Bernard et al used Treosulfan/thiotepa/fludarabine (TTF) based conditioning regimen along with anti-thymocyte globulin in 20 thalassaemia patients and found very safe as only 2 patients experienced graft failure and one died of acute graft-versus-host disease. The transplant-related mortality and graft failure was only 5% and 11%, respectively. This regimen was also very effective in high risk thal patients as the probability of survival at 2 years and thalassaemia-free survival were 95% and 85%, respectively[12].

Comparison Of Matched Unrelated Donor Vs Matched Sibiling /matched Related Donor Transplant In Thalassemia Major

- Mathew et al reviewed outcome of Hematopoietic stem cell transplant in 56 children with Thalassemia who underwent Matched Related donor (n=43) and Unrelated donor (n=14) transplants with Thiotepa treosulfan and fludarabine (TTF) based conditioning regimen. The overall survival in Matched related and unrelated donor groups was 87.6±5.2% and 85.7±9.4% at a median follow-up of 25 months and 22.5 months, respectively (P=0.75). The thalassemia-free survival was 87.6±5.2% and 77.1±11.7% with a median follow-up of 24 and 16.5 months, respectively (P=0.48). This study showed comparable overall and thalassemia free survival among Matched related and unrelated donor groups with treosulfan-based regimen.[13.]
- Swaminathan and R. Raj et al have done a retrospective study between July 2007 to December 2018 in 264 children using myeloablative conditioning regimen (treosulfan/thiotepa/fludarabine in 93% and busulfan/cyclophosphamide in 7%.) with a median age of 6 years and the graft source was matched related donor in 76% and unrelated donor in 22%. A statistically significant difference was found in the incidence of graft versus host disease, both acute and chronic between the MUD versus MRD groups, 60% versus 20% and 41% versus 17%, respectively. Thalassemia-free survival in our cohort was 96% and 84% with a median follow-up of 65 months in the matched sibling donor, and matched unrelated donor groups, respectively.[14].

C. Haplo-transplants With A Novel Approach Of Pretransplant Immuno-suppression (ptis)

Hematopoietic stem cell transplant with matched sibling donor or unrelated donor transplant is well known strategy to cure thalassemia however it's still hard to find matched related or unrelated donor hence there was a need to explore haplo transplant in hemoglobinopathies as well however the graft failure was the major obstacle in haplo transplants hence various strategies have been tried and still evolving to decrease the risk of GVHD and graft failure in cases of haplo transplants.

- The Johns Hopkins protocol consisting of ATG, FluCyTBI and GVHD prophylaxis with Post transplant cyclophosphamide, mycophenolate mofetil, and calcineurin inhibitors like tacrolimus and sirolimus were used for haploidentical SCT to overcome the risk of graft failure.
- A novel pre transplant immunosuppression preparative regimen which included cyclophosphamide 1000 mg/m2 on day 1, Fludarabine 30 mg/m2 for 3 days and dexamethasone 20 mg/m2 for 5 days preceding myeloablative conditioning in patients with hemoglobinopathies was used in 15 children with the median age of 5 years. The overall survival and disease-free survival were 92.3% in a median follow up of 12 months[15].
- In a study by Anurathapan et al, explored the use of Pre transplant immunosuppression (PTIS) in 31 patients underwent haplo transplants with a median age of 10 years. All patients received two courses of PTIS with fludarabine and dexamethasone, followed by a conditioning regimen consisting of Rabbit anti-thymocyte globulin, Fludarabine and IV busulfan. Graft versus Host disease (GVHD) prophylaxis consisted of cyclophosphamide (Cy) on days +3 and +4, and on day+5 tacrolimus or sirolimus was started together with a short course of mycophenolate mofetil. Out of all patients only two patients suffered primary graft failure. The overall and event-free survival rates at 2 years were 95% and 94%, respectively in a median follow up of 12 months.[16]
- Suradej Hongeng et al, conducted a study between Jan 2013 and August 2014 on 12 thalassemia patients underwent haplo-transplant received 2 courses of PTIS consisting of fludarabine (Flu) 40 mg/m2 /d for 4 days together with dexamethasone (dexa) 25 mg/m2 /d for 5 days followed by a reduced-toxicity conditioning regimen consisting of thymoglobulin, Fludarabine and busulfan. GVHD prophylaxis consisted of cyclophosphamide 50 mg/kg/d on day +3 and day+4. Thalassemia free survival and overall survival rates were 100% in a median follows up of 12 months[17].

D. Haplo-transplant With Graft Manipulation (tcr Alpha/beta Depleted Graft)

- Javid Gaviev et al, analyzed the outcomes of haplo-transplant using T-cell receptor $\alpha\beta^+$ ($TCR\alpha\beta^+$)/$CD19^+$-depleted grafts in 14 children with hemoglobinopathies with a preparative regimen consisting of busulfan, thiotepa, cyclophosphamide, and anti-thymocyte globulin preceded by fludarabine, hydroxyurea, azathioprine and demonstrated a reduced incidence of graft failure[18].
- Pietro sodaniet al, have performed hematopoietic stem cell transplantation in 22 patients using Flu/Cy and ATG conditioning preceded by hydroxyurea and azathioprine. All patients received haplo identical graft from a mismatched mother and out of 20 patients only 2 patients died due to infections, 6 patients reject their grafts, and 14 showed full chimerism with a median follow-up of 40 months.[19]
- Hundsdörfer P and Hakimeh D et al, reviewed current approaches in haplo-transplant by using (TCRα/β+/CD19+)depleted grafts in patients with transfusion dependent thalassemia or sickle cell disease in two European transplant units. Eleven Thalassemia and three sickle cell Disease patients received a preparative regimen consisting of Busulphan/Thiotepa/Cyclophosphamide and Anti thymocyte globulin preceded by fludarabine/hydroxyurea/azathioprine. The overall survival and disease-free survival in thalassemia patients were 84 and 69%, respectively, while OS and DFS were 100% in Sickle cell Patients. These data confirm that TCR-α/β+/CD19+ depletion is a well-adopted strategy bone marrow transplant for children with hemoglobinopathies[20]

CONCLUSION

Hematopoietic stem cell transplant is one of the curative treatments for thalassemia which has evolved significantly in terms of the conditioning regimen used before transplant, improved supportive care and risk of complication have significantly reduced and hence the number of transplants being done across the globe including haplo transplants in children have also increased significantly. Therefore, we need modify our institutional conditioning strategies based on the results published in the literature in an attempt to reduce transplant-associated morbidity and mortality.

Conflict Of Interest: None

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