PEDIATRIC TRANSPLANTATION
The Official Journal of the International Pediatric Transplant Association

Repeated CD45RA depleted donor lymphocyte infusion successfully increases donor chimerism in a patient with beta-thalassemia major after haploidentical stem cell transplant

Journal:	*Pediatric Transplantation*
Manuscript ID	PEDTRANS-20-CR-0368.R1
Manuscript Type:	Case Report
Date Submitted by the Author:	n/a
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Keywords:	lymphocyte transfusion, chimerism, beta-thalassemia, bone marrow transplantation, peripheral blood stem cell transplantation, hematopoietic stem cell transplantation
Abstract:	Background Allogeneic hematopoietic stem cell transplantation is curative for transfusion-dependent thalassemia but mixed chimerism (MC) may herald graft rejection. We report a child who failed bone marrow transplant (BMT) from matched unrelated donor (MUD) successfully salvaged with haploidentical peripheral blood stem cell transplant (PBSCT), but had MC in T-lymphocyte compartment despite near-complete donor chimerism in myeloid compartment. MC was successfully improved by repeated CD45RA-depleted donor lymphocyte infusion (DLI). Patient and outcome A 2-year old Chinese girl with beta-thalassemia major underwent 12/12-MUD BMT with HU/AZA/Cy/Flu/Bu/TT conditioning resulted in graft rejection. As donor refused second donation, rescue haploidentical PBSCT was performed with alemtuzumab/fludarabine/treosulphan

	conditioning. Harvest product was CD3/CD45RA depleted with extra products cryopreserved. Split cell chimerism performed 1-month post haplo-transplant showed 97% mother, 3% MUD and 0% host for granulocytes but 38% mother, 62% MUD and 0% host for CD3+ T-cells. In view of low haploidentical donor chimerism in T-lymphocyte compartment, CD45RA-depleted DLI using cryopreserved product was performed on day +38, after thymoglobulin 3 mg/kg given as T-cell depletion 3 days beforehand. T-cell chimerism improved to 51% mother and 49% MUD post-DLI. Second cryopreserved CD45RA-depleted DLI was given 17 days after the first DLI (day +55), and 100% full chimerism of mother's T-cells was gradually established without significant graft-versus-host disease (GVHD) or vial reactivation. Conclusion To conclude, split lineage chimerism determination is beneficial to guide management strategy. For MC in T-cell compartment, CD45RA depleted DLI is a potential alternative to unselected T cells as it carries lower risk of GVHD and infection.

TITLE PAGE

CASE REPORT

Title of the article:

Repeated CD45RA depleted donor lymphocyte infusion successfully increases donor chimerism in a patient with beta-thalassemia major after haploidentical stem cell transplant

Running title: CD45RA depleted DLI improves donor chimerism

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Acknowledgements

We are grateful to Professor Wing Leung for his advice in management of this patient.

Abbreviations

Allo	allogeneic
ATG	antithymocyte thymoglobulin
AZA	azathioprine
Bu	busulphan
CMV	cytomegalovirus
CNS	coagulase-negative Staphylococcus
CSP	cyclosporine
Cy	cyclophosphamide
DLI	donor lymphocyte infusion
DTS	depletion tubing set
Flu	fludarabine
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
MC	mixed chimerism
MMF	mycophenolate mofetil
MSD	matched sibling donor
MTX	methotrexate

MUD	matched unrelated donor
OS	overall survival
PTLD	post-transplant lymphoproliferative disease
RHC	residual host cells
SCID	severe combined immunodeficiency
STR	short tandem repeat
TT	thiotepa
TDT	transfusion-dependent thalassemia

MANUSCRIPT

ABSTRACT

Background

Allogeneic hematopoietic stem cell transplantation is curative for transfusion-dependent thalassemia but mixed chimerism (MC) may herald graft rejection. We report a child who failed bone marrow transplant (BMT) from matched unrelated donor (MUD) successfully salvaged with haploidentical peripheral blood stem cell transplant (PBSCT), but had MC in T-lymphocyte compartment despite near-complete donor chimerism in myeloid compartment. MC was successfully improved by repeated CD45RA-depleted donor lymphocyte infusion (DLI).

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day +38, after thymoglobulin 3 mg/kg given as T-cell depletion 3 days beforehand. T-cell chimerism improved to 51% mother and 49% MUD post-DLI. Second cryopreserved CD45RA-depleted DLI was given 17 days after the first DLI (day +55), and 100% full chimerism of mother's T-cells was gradually established without significant graft-versus-host disease (GVHD) or vial reactivation.

Conclusion

To conclude, split lineage chimerism determination is beneficial to guide management strategy. For MC in T-cell compartment, CD45RA depleted DLI is a potential alternative to unselected T cells as it carries lower risk of GVHD and infection.

Keywords (MeSH terms 2020): lymphocyte transfusion, chimerism, beta-thalassemia, bone marrow transplantation, peripheral blood stem cell transplantation, hematopoietic stem cell transplantation

Abstract word count: 250

Main text word count: 1824

MAIN BODY TEXT

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a well-established curative treatment in transfusion-dependent thalassemia (TDT). Transplants with HLA-matched unrelated donors (MUD) resulted in thalassemia-free survival of 70–90% at 2–3 years in pediatric series (1, 2). Mixed chimerism (MC) may herald graft rejection (3, 4). We report a child who failed MUD bone marrow transplant (BMT) and successfully salvaged with haploidentical peripheral blood stem cell transplant (PBSCT) but had MC of MUD and haploidentical donor in T-lymphocyte compartment despite near-complete donor chimerism (haploidentical) in myeloid compartment. MC was successfully improved by repeated CD45RA depleted donor lymphocyte infusion (DLI).

Case report

A 2-year old Chinese girl first presented to us at 5 months old with haemoglobin level of 5.6 g/dL and hepatosplenomegaly. She was subsequently diagnosed to have beta-thalassemia major (compound heterozygous b0 mutations: codon 41/42 (-TTCT) and codon 17 (A to T)) and was put on regular transfusion since 5 months of age. Serum ferritin level pre-transplant was 1462 ng/ml with T2* magnetic resonance imaging showing mild hepatic and pancreatic iron overloading. Iron chelation had not been initiated prior to transplant. As she had no HLA-matched sibling and a 12/12 MUD of the same ethnicity was identified (24-year old Chinese female with HLA-A/B/C/DRB1/DQB1/DPB1 matched at allelic level, with major blood group mismatch from A+ to B+), bone marrow transplant was performed

at 25 months of age. She was pre-conditioned with hydroxyurea (HU) and azathioprine (AZA), followed by conditioning with cyclophosphamide (Cy)(120mg/kg), fludarabine (Flu)(200mg/m^2), busulphan (Bu) (12mg/kg iv), thiotepa (TT)(10mg/kg), and rabbit antithymocyte thymoglobulin (ATG) 7.5mg/kg (2). Donor's bone marrow was given with nucleated cell dose of 8.23 x 10^8/kg and CFU-GM 7.55 x 10^5/kg. Graft-versus- host disease (GVHD) prophylaxis consisted of short course methotrexate (MTX), mycophenolate mofetil (MMF), and cyclosporine (CSP). Neutrophil engrafted (>0.5 × 10^9/L for 3 consecutive days) on day +17, and platelet engrafted (>20 × 10^9/L) on day +29. Whole blood chimerism by short tandem repeat (STR) on day +30 showed 85% donor and 15% host. There was no acute GVHD. The patient was then transfusion-independent. Post-transplant period was complicated with coagulase-negative Staphylococcal (CNS) and Stenotrophomonas bacteraemia on D+12, and Epstein-Barr virus (EBV) related post-transplant lymphoproliferative disease (PTLD) treated with rituximab at 2 months post-transplant. In view of initial MC in whole blood, split lineage chimerism was performed (negative bead selection for T-cells, density gradient centrifugation for granulocytes). Falling donor chimerism of the myeloid compartment was noted from 81% to nadir of 8% at 5 months post-transplant, with dropping haemoglobin level, despite full donor chimerism in the T-cell compartment (Figure 1). Donor stem cell boost was requested but declined by the donor. Second transplant was performed at 6 months post-transplant with mother as the haploidentical donor of peripheral blood stem cells, conditioned with alemtuzumab (0.6mg/kg), fludarabine (150mg/m^2), and treosulphan (42g/m^2). Cyclosporine was used as GVHD prophylaxis. The initial graft of the rescue transplant consisted of 2 portions processed differently. The first portion was CD3 depleted, containing CD34+

cells $7.7x10^6$/kg with $1.7x10^5$/kg residual CD3+ T cells, given on Day 0. The second portion was CD45RA depleted, containing CD34+ cells $4.3x10^5$/kg, CD45RO+ cells $5x10^6$/kg and undetectable CD45RA+ cells given on Day 1. Data on number of NK cells or gamma-delta T cells in the products was not available (5). The remaining CD45RA depleted product was cryopreserved in 2 bags, each containing $1x10^7$/kg CD45RO+ cells (The subsequent two DLIs each contained double amount of cells than those given on day 1, i.e., CD34+ cells $8.6x10^5$/kg, CD45RO+ cells $1x10^7$/kg and undetectable CD45RA+ cells). Split cell chimerism at 1 month post-second transplant showed 97% mother, 3% MUD donor and 0% host for granulocytes but 38% mother, 62% MUD donor and 0% host for CD3+ T-cells. In view of low haploidentical donor chimerism in T-lymphocyte compartment, CD45RA-depleted DLI using the cryopreserved product was performed on day +38, after thymoglobulin 3 mg/kg given as T-cell depletion 3 days beforehand. T-cell chimerism improved to 51% mother and 49% donor post-DLI. Second cryopreserved CD45RA-depleted DLI was given 17 days after the first DLI (day +55), and 100% full chimerism of mother's T-cells was gradually established **(Figure 1)**. Full haploidentical donor chimerism was also maintained in the myeloid compartment and the patient remained transfusion-independent. On both DLIs to rescue falling donor chimerism, the cell dose was 1 x 10^7/kg CD45RO+ve T-cells without any CD45RA+ cells. There were no significant adverse effects from the 2 DLIs apart from mild grade 1 skin GVHD which resolved with topical steroid. Transient low-grade viral reactivation of EBV and cytomegalovirus (both serum DNA PCR less than 10^3 copies/ml) was encountered at 2 months post-DLI, which resolved spontaneously on serial monitoring with RT-PCR. Patient had been followed up for more than 33 months since DLI in at the time of publication and had sustained full donor

chimerism and transfusion-independency. No features of chronic GVHD were encountered. Immunoreconstitution was satisfactory with normal immunoglobulin level and lymphocyte subset counts at 4 months post DLI (6 months post-transplant) with total CD3 2119/μL, CD4 833/μL, CD8 1134/μL, CD56 584/μL and CD19 769/μL. There was no clinically significant infection.

Discussion

1. Unavailability of MSD in China with one-child policy and selection of MUD

Traditional treatment of TDT with lifelong regular transfusion and chelation is cumbersome, difficult to adhere, costly and not without adverse effects. (6-8). Allo-HSCT is currently the only well-established curative treatment. Allo-HSCT using bone marrow or cord blood from human leukocyte antigen (HLA) matched sibling donor (MSD) can achieve overall survival (OS) of about 85-98% (9) and is now routinely offered to TDT patients as soon as possible before development of iron overload and iron-related tissue damage, as recommended by the European Blood and Marrow Transplantation (EBMT) Inborn Error Working Party and the Paediatric Diseases Working Party (10). However, only about one-quarter of patients with siblings were able to identify MSD. (11) This approach is also not applicable to China with one-child policy as well as certain proportion of TDT patients in Hong Kong who were immigrants from China, thus alternative donor sources have to be sought, using high resolution molecular typing for both HLA class I and class II loci (HLA-A, B, C, DRB1, DQB1, DPB1) and following stringent criteria of compatibility with recipient (12, 13).

2. Rationale of CD3/CD45RA depleted haploPBSCT as rescue HSCT

Allo-HSCT from an HLA-matched unrelated donor (MUD) was increasingly employed to treat TDT patients with similar survival and reasonably low rate of severe complications such as graft-versus-host disease (GVHD)(2, 14, 15). Li from China reported 3-year OS and transfusion-free survival of 92.3% and 90.4% respectively for MUD HSCT in 84 TDT patients (2). Our child with no HLA-matched sibling reported here thus underwent first 12/12 MUD BMT after meticulous counselling employing NF-08 TM HSCT protocol (2) in view of the excellent outcome reported. Despite good initial engraftment and donor chimerism of 97% at post-transplant 2 months, secondary graft failure occurs. As donor declined further stem cell donation, second haploidentical HSCT had to be performed to salvage the patient from marrow aplasia. PBSC was chosen as stem cell source (16) with CD3 and CD45RA depletion (5) and treosulphan-based conditioning (17) to lower rejection risk.

3. Employment of split chimerism to guide clinical management decision

Andreani et al. described the outcome of thalassemia patients with mixed chimerism post-HSCT (18). Residual host cells (RHC) of more than 25%, especially detected within 2 months post-transplantation, were predictive of graft rejection. In patients with mixed chimerism in whole blood as in our patient, split lineage chimerism determination is beneficial to guide management strategy (19, 20). For very low chimerism in myeloid compartment, donor stem cells or second transplant may be needed, as experienced by our patient in the first graft rejection. On the other hand, for mixed chimerism in T-cell compartment, manipulation of dosages of immunosuppressants or infusion of donor T-cells (DLI) with

or without ATG might improve donor chimerism.

4. Usage of CD45RA-depleted DLI

DLI has been used to salvage a dropping donor chimerism by enhancement of graft-versus-host alloreactivity, but data are scarce (21, 22). However, the risk of GvHD after infusion of unselected donor T-cells is high. CD45 is a receptor-like protein tyrosine phosphatase which is expressed on all nucleated hematopoietic cells while CD45RA as one of the six isoforms of CD45 is expressed on naïve T cells and effector memory T (TERMA) cells (23). Selective CD45RA+ T-cell depletion removes all naïve T cells while preserving memory T cell. By depleting CD45RA+ naïve T-cells, the risk of GvHD is substantially reduced, and the remaining memory T-cells might augment donor T-cell recovery and protect against infections (24). There had been case reports suggesting the use of CD45RA-depleted DLI in treating severe combined immunodeficiency (SCID) (25) and refractory colitis caused by cytomegalovirus (CMV) (26), while its usage for salvage of mixed chimerism in TDT patients post-HSCT had never been reported to the best of our knowledge.

5. Controversy on cell dose and dosing interval of CD45RA-depleted DLI and use of ATG prior to DLI

The dose of CD45RA depleted DLI from haploidentical donor has not been well defined. A lower starting dose may be considered, especially if there are residual CD45RA+ cells in the product. In our case, the depletion was very efficient and CD45RA was undetectable. Recently, there had been published phase 1 dose escalation study result on CD45RA depleted DLI, with maximum cell dose set at $1x10^7$/kg (27),

which was the cell dose administered to our patient in the 2 DLIs.

The use of ATG upfront to DLI is not conventional. It is hypothesized that ATG given prior to DLI might delete residual recipient T cells, hence suppressing the T-cell mediated rejection, giving the donor T cells some advantage to revert to better donor chimerism. As the effect of ATG might still persist at the time DLI was given, the risk of GVHD is lowered but at the cost of possibly reducing the efficacy of DLI at the same time. Those are the rationale behind using a high dose of CD45RA negative DLI. Such hypotheses need to be tested in future studies.

As for the dosing interval, according to a study conducted by Rujkijyanont et al (28), DLI can be given every 2 to 4 weeks. Since the patient did not develop GVHD after the first DLI, the second DLI was given 17 days after the first DLI in our patient. Further studies are suggested to elucidate the optimal dosing interval for CD45RA-depleted DLI.

With safety profile demonstrated, it is proposed that CD45RA depleted DLI is a potential alternative to unselected T-cells for management of MC in TDT patients post-HSCT. It is useful to cryopreserve some of the initial CD45RA depletion product for later use in patients at high risk of mixed chimerism or graft rejection.

Conclusion

To conclude, split lineage chimerism determination is beneficial to guide management strategy. For mixed chimerism in T-cell compartment, CD45RA depleted DLI is a potential alternative to unselected T cells as it carries lower risk of GVHD and infection.

Disclosure

All authors have disclosed no conflicts of interest.

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Figure legends

Figure 1 Trend of split cells chimerism in relation to donor lymphocyte infusion


MUD CD3+ T cells


MUD granulocyte

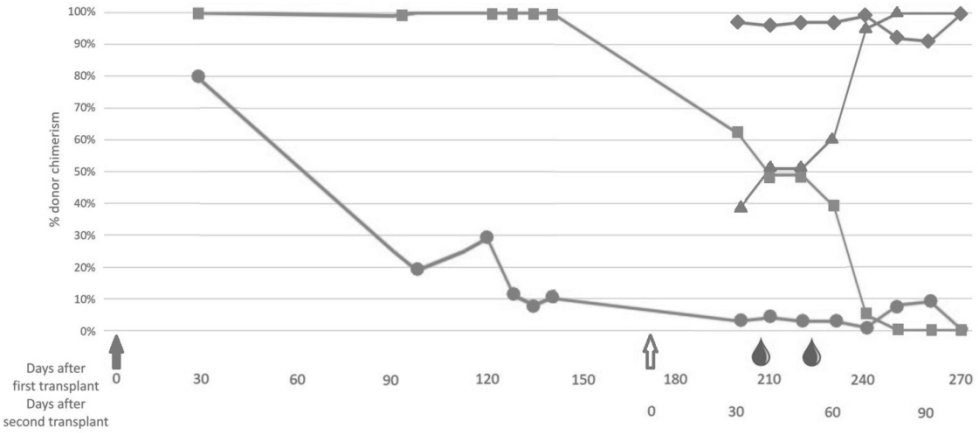

Mother's granulocyte


Mother's CD3+ T cells


MUD BMT


HaploPBSCT


Donor lymphocyte infusion



Trend of split cells chimerism in relation to donor lymphocyte infusion

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