Journal of Clinical Immunology (2019) 39:505–511
https://doi.org/10.1007/s10875-019-00648-x

ORIGINAL ARTICLE

Use of TCR $\alpha^+\beta^+$/CD19$^+$–Depleted Haploidentical Hematopoietic Stem Cell Transplant Is a Viable Option in Patients With Primary Immune Deficiency Without Matched Sibling Donor

Tim Brettig[1] · Joanne Smart[1] · Sharon Choo[1] · Francoise Mechinaud[2] · Richard Mitchell[3,4] · Trisha Soosay Raj[2] · Theresa Cole[1]

Received: 24 January 2019 / Accepted: 17 May 2019 / Published online: 6 June 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for many patients with primary immune deficiency (PID). Haploidentical donors have historically been associated with higher rates of graft-versus-host disease (GvHD) and graft failure. Use of T cell receptor (TCR) $\alpha^+\beta^+$/CD19$^+$–depleted grafts has resulted in improved haploidentical HSCT outcomes. We sought to evaluate outcomes of TCR $\alpha^+\beta^+$/CD19$^+$–depleted haploidentical HSCT in pediatric patients with PID at a single center in Australia. Specifically, we evaluated immune reconstitution, looking at time to T cell and B cell reconstitution, and B cell function post-HSCT. Eleven patients with a mean age of 7.92 years (range 0.33–17.17 years) were included. The median time to B cell recovery was 93 days (range 41–205 days), and the median time to cessation of immunoglobulin replacement was 281.5 days (range 41–205 days). All patients who had ceased immunoglobulin replacement had an adequate response to pneumococcal conjugate (Prevenar 13) vaccine. The median time to CD4$^+$ recovery was 132 days (range 30–296 days), and naive T cells were present in all surviving patients by 4 months post-HSCT. Eight of 11 patients are surviving, with six patients having whole blood chimerism greater than 95%, one patient with whole blood chimerism of 82.8%, and another with 76.0%. All of these patients clinically had no evidence of underlying immunodeficiency. Likelihood of overall survival at 2 years post-HSCT was 81.8%. Cumulative incidence of acute GvHD was 27.3%. Cumulative incidence of CMV viremia was 63.6%. All patients previously exposed to CMV had reactivation post-HSCT, but were controlled with pre-emptive CMV treatment. Assuming most children with PID have a haploidentical donor available, use of this technique is likely to result in good outcomes for patients who do not have a suitable matched sibling or matched unrelated donor.

Keywords TCR α+β+/CD19+–depleted haploidentical HSCT · Primary immune deficiency · Immune reconstitution

Introduction

Hematopoietic stem cell transplant (HSCT) is curative for patients with primary immune deficiency (PID) [1]. Although stem cells from a matched related donor are preferred, that option exists for only a minority of patients, leaving alternative donor stem cell sources as the necessity for most [1]. The use of matched unrelated donors (MUD) in HSCT for PID continues to increase, with published survival outcomes approaching those for human leukocyte antigen (HLA)–matched sibling donor HSCT [2]. Use of an HLA-mismatched donor has historically been associated with a lower overall survival rate [3–5] and haploidentical HSCT has historically been limited by high rates of both graft failure and graft-versus-host disease (GvHD) [6].

Selective depletion of $\alpha^+\beta^+$T cells has shown to be effective in a number of small studies for both haploidentical and MUD donors with a high engraftment rate, early immune reconstitution, good immune recovery, and acceptable rates of GvHD [7–10]. Retention of populations of $\gamma^+\delta^+$ T cells may contribute to better engraftment and early immune

✉ Tim Brettig
tim.brettig@rch.org.au

[1] Department of Allergy and Immunology, The Royal Children's Hospital, Melbourne, VIC, Australia

[2] Children's Cancer Centre, The Royal Children's Hospital, Melbourne, VIC, Australia

[3] Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia

[4] School of Women & Children's Health, University of New South Wales, Sydney, NSW, Australia

reconstitution, anti-viral immunity, and anti-tumor effect [10]. This may be particularly advantageous in children with PID coming to transplant with pre-existing infection.

To date, outcomes of pediatric patients receiving TCR $\alpha^+\beta^+$/CD19$^+$–depleted haploidentical HSCT have been mostly described as a group inclusive of malignant, non-malignant hematological, and PID conditions. Results have been encouraging when compared with historical forms of haploidentical HSCT. Graft failure was reported in a small minority [7–10]. Two-year overall survival was reported between 87 and 96.7%, with the largest non-malignant recipient study describing 68 patients [7–10]. Cumulative rates of acute GvHD were also low, with the majority of studies describing grade I or II acute GvHD [7, 8, 10]. Viral disease is also uncommon, despite frequent viral reactivation. In Laberko et al.'s study, 51% of patients had CMV viremia, with only 6% of those patients having clinical disease [9] and no significant difference in overall survival.

Immune reconstitution is rapid, outlined in Shah et al.'s study describing T cell reconstitution in patients with PID who receive a TCR $\alpha^+\beta^+$/CD19$^+$–depleted graft, with median time to CD4$^+$ recovery (absolute count $> 0.2 \times 10^9$ cells/L on two consecutive tests) of 129 days [10]. Naive T cells appeared at 4 months after transplant in most patients [7, 10]. Memory T cells appeared after 9 months in most patients [7].

Median time to B cell recovery (count $> 0.2 \times 10^9$ cells/L on two consecutive tests) was between 85 days and 12 months [7, 9], with median time to achieve normal IgM (> 0.5 g/L on two separate tests) of 97 days [10]. This was used as a surrogate marker of B cell function for patients on immunoglobulin replacement therapy. There is currently no literature as to the requirement for immunoglobulin replacement post TCR $\alpha^+\beta^+$/CD19$^+$–depleted haploidentical BMT.

With the known benefits of a short time from diagnosis of PID, in particular severe combined immune deficiency (SCID), to HSCT, use of haploidentical TCR $\alpha^+\beta^+$/CD19$^+$–depleted donors is an appealing choice in the absence of a suitable HLA-matched sibling or matched unrelated donor. We sought to evaluate patient outcomes and the time to immune reconstitution and B cell function of children undergoing TCR $\alpha^+\beta^+$/CD19 haploidentical for PID at our center.

Methods

Patients who underwent TCR $\alpha^+\beta^+$/CD19 haploidentical HSCT at The Royal Children's Hospital, Melbourne, between 2014 and 2017 were retrospectively identified from medical record review. Local ethics approval was obtained prior to collection of data. Patients were required to have a diagnosis of PID prior to receiving HSCT through either genetic or clinical phenotype. Information gathered included demographic data, conditioning regime, GvHD prophylaxis, cell dose infused, preceding or active infections at time of HSCT, viral infections and viremia following HSCT, antiviral prophylaxis, immunosuppression, time of neutrophil, platelet, T cell and B cell reconstitution, time until cessation of immunoglobulin replacement, and response to conjugate pneumococcal (Prevenar 13) vaccination.

All grafts were TCR $\alpha^+\beta^+$/CD19$^+$ depleted by using an immunomagnetic method, according to the manufacturer's recommendations (Miltenyi Biotec, Bergisch Gladbach, Germany).

Conditioning therapy choice was made by the clinical team, mostly using treosulfan, fludarabine, and thiotepa. Single agent mycophenolate mofetil (MMF) was used for GvHD prophylaxis, given until day + 42 post-HSCT. One patient (patient 7) received cyclosporin A (CsA) as additional prophylaxis, which was at clinician's discretion.

Neutrophil engraftment was defined as the first of three consecutive days of absolute neutrophil count $\geq 0.5 \times 10^9$/L. Platelet engraftment is defined as a platelet count of $\geq 20 \times 10^9$/L measured a minimum of 7 days after the last platelet transfusion. Acute GvHD was assessed using standard criteria [11]. Chimerism analysis was performed using PCR-based amplification of short tandem repeat sequences. Full donor chimerism is defined as greater than 95% on whole blood analysis. Separated chimerism was performed if whole blood chimerism was less than 90%.

Immune recovery was evaluated using flow cytometry with monoclonal antibodies against lineage-specific surface molecules (T cells, B cells, naive T cells, naive B cells, memory B cells, switched memory B cells).

CD4$^+$ recovery was defined as an absolute count $> 0.2 \times 10^9$ cells/L on two consecutive tests. B cell recovery was defined as an absolute count $> 0.2 \times 10^9$ cells/L on two consecutive tests. Naive CD4 T cell presence was defined as an absolute count equal to or greater than 10×10^6 cells/L. Cessation of immunoglobulin replacement was measured from the day of last immunoglobulin infusion.

Conjugate pneumococcal vaccine (Prevenar 13) was given once immunoglobulin replacement therapy had ceased, with vaccine antibody responses measured 4 weeks following vaccination. An adequate response was defined as conversion of five or more of the seven serotypes tested, with a titer equal to or greater than 0.35 μg/mL antibody [12]. This is the method used in our laboratory and is based on interpretation of children < 2 years of age, given the transplanted immune system is less than this age at time of testing.

Viral surveillance was performed for CMV, EBV, adenovirus, and human herpes virus 6 (HHV-6) at least weekly by quantitative PCR of blood, saliva, nasopharyngeal swab, urine, and stool samples. Viremia was defined as the presence of viral DNA detected in blood PCR in two consecutive samples. Viral reactivation was defined as the presence of viremia in a patient with evidence of previous exposure to the virus.

Viral disease was defined as clinical manifestations of the disease in keeping with infection, or confirmation of infection on histology or tissue PCR.

Data was analyzed using XlStat version 20.4 software. Patients were censored at time of death or last follow-up. The probabilities of overall survival were estimated using the Kaplan-Meier product limit method. The probabilities of acute GvHD were calculated using cumulative incidence with time up to day + 100; chronic GvHD was calculated using cumulative incidence of GvHD greater than day + 100. Probabilities of viremia were calculated using cumulative incidence of viremia up to day + 100. Immune reconstitution was calculated using median and range.

Results

Underlying PID, pre-HSCT clinical state, and HSCT-specific details of the patients included in this study are summarized in Table 1.

Eleven patients underwent HSCT over the study period, with infants (< 1 year old) comprising 27.3% of the cohort. Eight patients (72.7%) did not have significant active disease or infection leading to transplant. One patient (patient 4) with veno-occlusive disease with immunodeficiency (VODI) had persistently high CMV titers prior to transplant, and completed treatment for *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfmethoxazole 13 days prior to transplant. He had a drain in situ for persistent ascites in the context of VODI that was removed 10 days prior to HSCT. Patient 6 had received a previous MUD HSCT in his second year of life but had secondary graft failure approximately 1 year post-HSCT. This patient had known persistent respiratory *Nocardia* infection, not requiring respiratory support prior to HSCT. Patient 10 underwent haploidentical HSCT as a salvage procedure for primary graft failure post MUD HSCT. Immediately prior to HSCT, he was receiving TPN due to persistent vomiting and malabsorption.

Likelihood of overall survival at 2 years post-HSCT was 81.8% (Fig. 1). One patient died of overwhelming CMV infection (on day + 100), having been persistently viremic prior to HSCT. The second patient died of progressive respiratory failure of unclear etiology nearly 2 years post-HSCT. The third patient experienced primary graft failure with haploidentical sibling donor and received a subsequent HSCT using a T cell replete haploidentical paternal donor; however, this patient subsequently passed away from multiple factors including GvHD, thrombotic microangiopathy, and CMV viremia. The median duration of follow-up post-HSCT was 15.7 months (range 3.2–36.8 months).

Acute GvHD was seen in three of 11 patients, with maximum grade II GvHD. No patient experienced grade III or IV GvHD. Treatment of acute GvHD included corticosteroid (budesonide) and cyclosporin (CsA) in patient 2 with gut GvHD, prednisolone and tacrolimus in patient 9 with grade II skin GvHD, and extra-corporeal photopheresis (ECP) for steroid refractory acute GvHD in patient 11, with grade II liver and gut GvHD. Chronic GvHD was seen in patient 11.

Five of 11 patients previously had exposure to CMV prior to HSCT. One patient had persistently high titers immediately prior to HSCT and was on ganciclovir at time of HSCT infusion. All five patients with previous exposure to CMV had reactivation of CMV. Cumulative incidence of CMV viremia post-HSCT at day + 100 was 63.6% with median time of viremia from HSCT of 18 days (range 0–62 days). Treatment included ganciclovir, followed by valganciclovir. Clinical disease was seen in one patient who subsequently died. This patient had evidence of CMV retinitis on ophthalmologic examination and evidence of central nervous system infection on brain magnetic resonance imaging (MRI). CMV viremia was presumed to contribute to death in another who died as outlined above from aggressive multifactorial disease following a replete haploidentical transplant. The median duration of CMV viremia was 38 days (range 3–208 days), with median duration of treatment for CMV of 81 days (range 14–209). The duration of treatment for CMV is complicated by 2 patients who also received cidofovir and brincidofovir for treatment of adenovirus viremia, which persisted longer than the CMV viremia.

Three patients had adenovirus viremia, with 2 patients receiving pre-emptive treatment (cidofovir, brincidofovir). The median duration of treatment for adenovirus in these two patients was 71 and 92 days (median 81.5 days) respectively. One patient had transient EBV reactivation, which resolved without treatment. Other viremia noted were HHV-6 in one patient and polyoma BK virus in two patients, neither caused disease and no treatment was required.

Immune Reconstitution

The median time to $CD4^+$ recovery (Fig. 2) was 132 days (range 30–296 days) in eight surviving patients. One patient did not achieve a $CD4^+$ count greater than 0.2×10^9/L by day 421 at the last follow-up. This patient had GvHD followed by autoimmune hemolytic anemia and received a prolonged course of corticosteroid. Naive $CD4^+$ cells were present by 4 months in all surviving patients (Fig. 2).

The mean time to B cell recovery was 93 days (range 41–205 days). The median time to immunoglobulin replacement cessation was 281.5 days (range 253–1021 days) in seven patients. Three patients died prior to stopping, and one patient remains on immunoglobulin replacement at day + 421 post-HSCT. This patient received rituximab for autoimmune hemolytic anemia and continued to have an absence of B cells, therefore requiring ongoing immunoglobulin replacement. Of the seven patients who had ceased immunoglobulin

Table 1 Patient summary table

No.	Sex	Age	Diagnosis	Pre-HSCT clinical condition	Donor	Conditioning	CD34 cells $\times 10^6$/kg	TCR $\alpha^+\beta^+$ cells $\times 10^4$/kg	B cells $\times 10^5$/kg	Time to neutrophil engraftment	aGvHD	Viremia	WB chimerism	Separated chimerism	Follow-up (days)	Survival
1	M	16.4 years	XIAP	No active infection or viremia, clinically stable	Father	Flu/Mel/TT	5.90	1.40	0.57	10 days	No	No	97%	–	1119	Yes
2	M	7.8 years	WAS	No active infection or viremia, clinically stable	Father	Treo/Flu/TT	15.03	1.00	25.40	10 days	Grade II	CMV	99.9%	–	1451	Yes
3	M	14.3 years	WAS	No active infection or viremia, clinically stable	Father	Treo/Flu/TT	3.70	0.90	307.84	11 days	No	CMV	99.9%	–	912	Yes
4	M	5 months	VODI	CMV infection with high titers prior to HSCT, PJP requiring intubation and ventilation. Active veno-occlusive disease.	Father	Treo/Flu/TT	19.90	0.90	80.70	8 days	No	CMV	100%	–	100	No
5	F	6 months	SCID (RA-G1)	No active infection or viremia, clinically stable	Mother	Treo/Flu/TT	19.88	2.50	54.99	12 days	No	No	99.9%	–	729	Yes
6	M	17.2 y	CGD	Active *Nocardia* infection (lung). Previous early graft rejection (MUD)	Sister	Treo/Flu/TT	7.20	0.30	62.22	10 days	No	CMV	99.9%	–	132	No
7	M	3.9 years	CGD	No active infection or viremia, clinically stable	Father	Treo/Flu/TT	15.58	2.61	0.90	13 days	No	No	76.0%	T, 51.9% B, 95.1% T-B, 90.6%	589	Yes
8	M	16.4 years	DOCK8	No active infection or viremia, clinically stable	Mother	Treo/Flu/TT	7.40	1.10	102.19	11 days	No	CMV, adenovirus	82.8%	T, 99.6% B, 88.3% T-B, 76.9%	757	Yes
9	F	4 months	STAT1 LOF	No active infection or viremia, clinically stable	Father	Bu/Flu/TT	19.94	2.00	9.00	12 days	Grade II	No	99.9%	–	608	Yes
10	M	6.1 years	STAT3 GOF	Failed previous HSCT—early graft rejection (MUD). Gut failure requiring TPN in addition to PEG feeds.	Father	Bu/Flu/TT	19.94	2.00	9.00	12 days	No	CMV, adenovirus	99.5%	–	722	No
11	M	3.7 years	CD40L	No active infection or viremia, clinically stable	Father	Treo/Flu/TT	20.81	2.00	0.14	12 days	Grade	Adenovirus	97.9%	–	421	Yes

Pre-transplant condition, evidence of active infection clinical condition in the immediately prior to HSCT history; *inactive*, no active infection and clinically stable immediately prior to HSCT; *XIAP*, X-linked Inhibitor of apoptosis protein deficiency; *WAS*, Wiskott-Aldrich syndrome; *VODI*, hepatic veno-occlusive disease with immunodeficiency; *CGD*, chronic granulomatous disease; *STAT3 GOF*, STAT3 gain of function; *DOCK8*, DOCK8 deficiency; *SCID*, severe combined unrelated donor. *TPN*, total parental nutrition; *PEG*, percutaneous endoscopic gastronomy; *Flu*, fludarabine; *Mel*, melphalan; *TT*, thiotepa; *Treo*, treosulfan; *BU*, budesonide; *MMF*, mycophenolate mofetil; *CsA*, cyclosporin; *WB chimerism*, whole blood chimerism; *Separated Chimerism*, *T*, *B*, *and T-B-*, refers to T cell ($CD3^+$), B cell ($CD19^+$), and T-B- (CD3-/CD19-) cell chimerism respectively

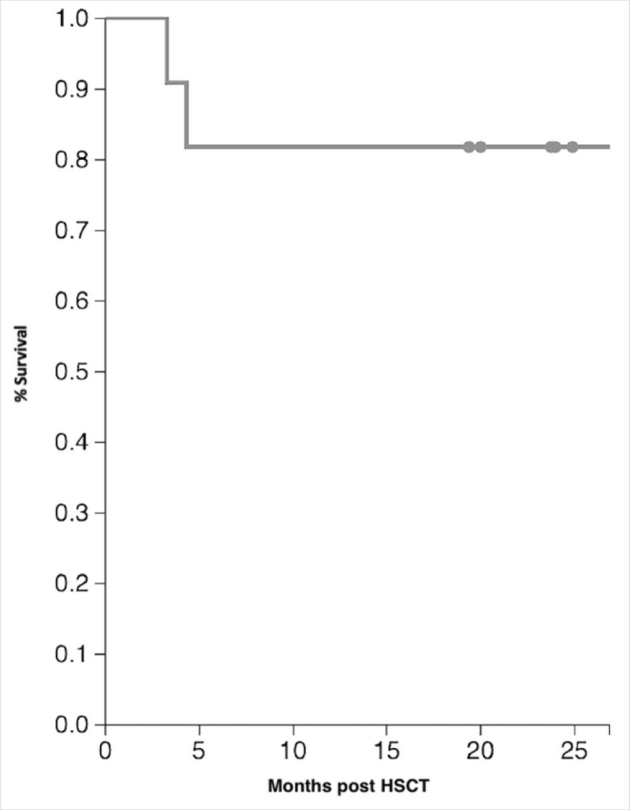

Fig. 1 Likelihood of overall survival distribution. Dots are surviving patients at time of the last follow-up. Solid line is overall survival

replacement therapy, four were eligible for assessment of antibody response to conjugate pneumococcal vaccine (Prevenar 13), and all four had an adequate response [12]. Memory B cells ($CD19^+/CD27^+$) were present ($> 0.01 \times 10^9$/L) at a mean of 428.62 days (range 78–1091 days) in 8 patients. The mean time to detectable levels ($> 0.01 \times 10^9$/L) of switched memory B cells ($CD19^+/CD27^+$/IgM-/IgD-) was 528 days (range 230–1091 days).

Discussion

This report describes a single-center experience with TCR $\alpha^+\beta^+/CD19^+$–depleted haploidentical HSCT in children with PID. Use of this donor source with ex vivo depletion methods provides access to HSCT in patients who would otherwise have no donor. Improved donor access has a significant impact on mortality and morbidity of these patients. Likelihood of overall survival at 2 years in our study was similar to that described in other studies [7, 8, 10].

Immune reconstitution of other cell lines in this study was similar to that of other studies [10], with median time to $CD4^+$ recovery being 132 days, compared with 128 days [10]. Naive T cells were present by 4 months in all patients, again in keeping with other studies. This suggests that the immune reconstitution process in this study is typical and reproducible. In Fig. 2, patient 5 had a high $CD4^+$ and naive $CD4^+$ count compared with the group, which did not have a clear cause such as concurrent infection.

The mean time to B cell reconstitution was 93 days, similar to that shown in Shah et al.'s study [13]. We measured time to immunoglobulin cessation as a clinical measure of B cell function. The median time to cessation of immunoglobulin replacement was 281.5 days. Cessation of immunoglobulin replacement has been associated with a normal quality of life post-HSCT [14], and as such should be recorded as an important marker post-HSCT. Of the patients who were eligible (four of seven patients), antibody responses to conjugate pneumococcal vaccine were all adequate, demonstrating good function of the donor B cells. This is the first study that measures this and is an important clinical marker given that other interventions, such as vaccination, will rely on this. Clinical decision-making for cessation of immunoglobulin is multifactorial and includes overall clinical health of the patients, infection, and timing of year, as immunoglobulin would typically not be stopped in the winter months.

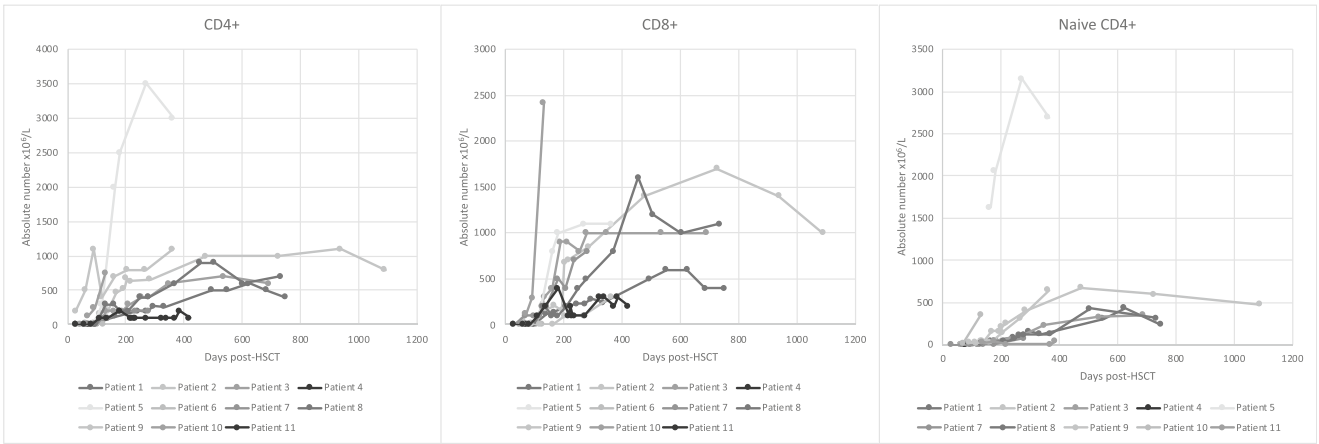

Fig. 2 $CD4^+$, $CD8^+$, and naive $CD4^+$ recovery post-HSCT

Cumulative incidence of CMV viremia at 1 year was also similar to that of Balashov et al.'s study [8]. This study had a higher rate of previous CMV exposure prior to HSCT (45.5% compared with 35.1%), which was likely to have occurred due to the higher mean age seen in this study, therefore more time to come into contact with the virus. All five patients in this study who had previous CMV exposure had reactivation post-HSCT and were treated pre-emptively, as is consistent with other studies [7, 8, 10]. Patient 4 carried active CMV viremia into HSCT in our study, and he did not survive, with evidence of CMV disease post-HSCT. Our finding reinforces other studies in that CMV reactivation is seen commonly with the HSCT type, but this does not affect overall survival [7, 8]. Carrying active CMV disease into transplant is associated with poorer outcomes [10]. CMV viremia still ideally needs to be controlled prior to HSCT, which is true for all types of HSCT.

Chimerism for all patients who survived remained high up to 24 months post-HSCT, with no clinical evidence of PID recurrence in any patient. Patients with many forms of PID do not require 100% donor chimerism for cure [15], and noting the mean follow-up, the results from this study suggest adequate chimerism to consider this a reasonable treatment option in PID.

Other clinical outcomes in this study were comparable with other similar studies. GvHD was comparable with other studies using other donor options such as matched sibling or matched unrelated donors [7, 8, 10]. This gives further evidence that TCR alpha/beta deplete HSCT is associated with a low rate of acute GvHD.

This study is a retrospective descriptive study of a small population, and as such is difficult to draw statistically significant conclusions from. In future, a larger prospective study would be beneficial to identify clinical significance when looking at outcomes for this patient group. Evaluating viral specific outcomes, including the impact on T cell and B cell reconstitution, and the impact of this on duration of IVIg replacement therapy, rates of infections and quality of life and long-term survival would be useful outcomes to measure.

Conclusion

This study adds further evidence to the existing literature that use of TCR $\alpha^+\beta^+$/CD19$^+$–depleted haploidentical HSCT is a good option in patients who do not have a matched sibling or matched unrelated donor available. Immune reconstitution in surviving patients is very good, for both T and B cell lineages. The majority of patients are able to cease immunoglobulin replacement therapy, which is associated with normal quality of life post-HSCT [14]. B cell function has been described using both time to cessation of immunoglobulin replacement and an adequate antibody response to conjugate pneumococcal vaccine.

Use of this donor option results in a high engraftment rate and chimerism, low incidence of significant GvHD, and a similar likelihood of overall survival at 2 years post-HSCT to other donor options. This form of HSCT is a viable option for children with PID who do not have an HLA-matched sibling or matched unrelated donor option, or in patients where rapid neutrophil engraftment is particularly beneficial. Assuming most children have a haploidentical donor available, use of this technique is likely to result in a shorter interval between diagnosis and HSCT, due to availability and accessibility of a family donor. This is likely to result in better outcomes in both morbidity and mortality for this vulnerable patient population.

Authorship Contributions Tim Brettig 50%, Theresa Cole 20%, Trisha Soosay Raj 15%, Richard Mitchell 10%, Joanne Smart, Sharon Choo, Francoise Mechinaud (5% combined).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Abbreviations HSCT, Hematopoietic stem cell transplant; PID, Primary immune deficiency; GvHD, Graft-versus-host disease; TCR, T cell receptor; CMV, Cytomegalovirus; MUD, Matched unrelated donor; HLA, Human leukocyte antigen; SCID, Severe combined immune deficiency; MMF, Mycophenolate mofetil; CsA, Cyclosporin A; HHV-6, Human herpes virus-6; VODI, Veno-occlusive disease with immunodeficiency; ECP, Extra-corporeal photopheresis; MRI, Magnetic resonance imaging

References

1. Smith AR, Gross TG, Baker KS. Transplant outcomes for primary immunodeficiency disease. Semin Hematol. 2010;47(1):79–85.
2. Szabolcs P, Cavazzana-Calvo M, Fischer A, Veys P. Bone marrow transplantation for primary immunodeficiency diseases. Pediatr Clin N Am. 2010;57:207–37.
3. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol. 2010;126(3):602–10.
4. Fernandes JF, Rocha V, Labopin M, Neven B, Moshous D, Gennery AR, et al. Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood? Blood. 2012;119:2949–55.
5. Rousso SZ, Shamriz O, Zilkha A, Braun J, Averbuch D, Or R, et al. Hematopoietic stem cell transplantations for primary immune deficiencies: 3 decades of experience from a tertiary medical center. J Pediatr Hematol Oncol. 2015;37:295–300.
6. Kongtim P, Cao K, Ciurea SO. Donor specific anti-HLA antibody and risk of graft failure in Haploidentical stem cell transplantation. Adv Hematol. 2016;2016:1–10.

7. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-haploidentical stem cell transplantation after removal of alpha beta+ T and B cells in children with nonmalignant disorders. Blood. 2014;124(5):822–6.
8. Balashov D, Shcherbina A, Maschan M, Trakhtman P, Skvortsova Y, Shelikhova L, et al. Single-center experience of unrelated and haploidentical stem cell transplantation with TCRab and CD19 depletion in children with primary immunodeficiency syndromes. Biol Blood Marrow Transplant. 2015;21:1955–62.
9. Laberko A, Bogoyavlenskaya A, Shelikhova L, Shekhovtsova Z, Balashov D, Voronin K, et al. Risk factors for and the clinical impact of cytomegalovirus and Epstein-Barr virus infections in pediatric recipients of TCR alpha/beta- and CD19-depleted grafts. Biol Blood Bone Marrow Transplant. 2017;23:483–90.
10. Shah RM, Elfeky R, Nademi Z, Qasim W, Amrolia P, Chiesa R. T-cell receptor alpha-beta+ and CD19+ cell-depleted haploidentical and mismatched hematopoietic stem cell transplantation in primary immune deficiency. J Allergy Clin Immunol. 2018;141(4):1417–26.
11. Przepiorka. Consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15:825–8.
12. Bryant KA, Block SL, Baker SA, Gruber WC, Scott DA, PCV13 Infant Study Group. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. Pediatrics. 2010;125(5):866–75.
13. Brodsky RA, Luznik L, Bolaños-Meade J, Leffell MS, Jones RJ, Fuchs EJ. Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases. Bone Marrow Transplant. 2008;42:523–7.
14. Abd Hamid IJ, Slatter MA, McKendrick F, Pearce MS, Gennery AR. Long-term health outcome and quality of life post-HSCT for IL7Ra-, Artemis-, RAG1- and RAG2-deficient severe combined immunodeficiency: a single center report. J Clin Immunol. 2018;38:727–32.
15. Hartz B, Marsh R, Rao K, Henter JI, Jordan M, Filipovich L. The minimum required level of donor chimerism in hereditary hemophagocytic lymphohistiocytosis. Blood. 2016;127(25):3281–90.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.