Recent advances in haploidentical hematopoietic stem cell transplantation using \textit{ex vivo} T cell-depleted graft in children and adolescents

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for children and adolescents with various malignant and non-malignant diseases. While human leukocyte antigen (HLA)-identical sibling donor is the preferred choice, matched unrelated volunteer donor is another realistic option for successful HSCT. Unfortunately, it is not always possible to find a HLA-matched donor for patients requiring HSCT, leading to a considerable number of deaths of patients without undergoing transplantation. Alternatively, allogeneic HSCT from haploidentical family members could provide donors for virtually all patients who need HSCT. Although the early attempts at allogeneic HSCT from haploidentical family donor (HFD) were disappointing, recent advances in the effective \textit{ex vivo} depletion of T cells or unmanipulated \textit{in vivo} regulation of T cells, better supportive care, and optimal conditioning regimens have significantly improved the outcomes of haploidentical HSCT. The \textit{ex vivo} techniques used to remove T cells have evolved from the selection of CD34$^+$ hematopoietic stem cell progenitors to the depletion of CD3$^+$ cells, and more recently to the depletion of $\alpha$$\beta^+$ T cells. The recent emerging evidence for \textit{ex vivo} T cell-depleted haploidentical HSCT has provided additional therapeutic options for pediatric patients with diseases curable by HSCT but has not found a suitable related or unrelated donor. This review discusses recent advances in haploidentical HSCT, focusing on transplant using \textit{ex vivo} T cell-depleted grafts. In addition, our experiences with this novel approach for the treatment of pediatric patients with malignant and non-malignant diseases are described.

Key Words Hematopoietic stem cell transplantation, haploidentical, \textit{ex vivo} T cell depletion, children, adolescents

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for children and adolescents with various malignant and non-malignant diseases. Recent progress in HSCT contributed to the improvement of outcomes for patients with diseases curable by HSCT. While human leukocyte antigen (HLA)-identical sibling donor is the preferred choice, HLA-matched unrelated volunteer donor is also a realistic option for successful HSCT. However, it is not always possible to find a HLA-matched donor for patients requiring HSCT, leading to a considerable number of deaths of patients without undergoing transplantation. The need for alternative donors has driven the development of new transplantation approaches such as transplants from HLA-haploidentical family members or umbilical cord blood.

Recent advances in the effective \textit{ex vivo} depletion of T cells or unmanipulated \textit{in vivo} regulation of T cells, better supportive care, and optimal conditioning regimens have significantly improved the outcomes of haploidentical HSCT [1-7]. The \textit{ex vivo} techniques to remove T cells have evolved from the selection of CD34$^+$ hematopoietic stem cell progenitors to the depletion of CD3$^+$ cells, and more recently, to the depletion of $\alpha$$\beta^+$ T cells [8, 9]. Currently, allogeneic HSCT using an HLA-haploidentical family donor (HFD) is considered an accepted treatment option for patients who cannot find an optimal related or unrelated donor.

Here, we review the major advances in haploidentical HSCT, focusing on the \textit{ex vivo} depletion of T cells. We
will also introduce our experiences with transplantation using this novel approach.

**THE HISTORY OF HSCT FROM A HAPLOIDENTICAL FAMILY DONOR**

HSCT from HFD has several advantages (Table 1): 1) virtually all patients who need HSCT can find a donor; 2) transplantation could be performed without delay, which is critical to patients with high-risk malignant disease or very severe aplastic anemia requiring urgent treatment; 3) further access to the donor for cellular therapy to treat relapse or infection or for additional transplants is easy. In addition, HFD could rescue the patients who experienced early graft failure (GF) which is a life-threatening complication requiring prompt intervention after allogeneic HSCT [10-13].

Even though haploidentical HSCT seemed to be an attractive procedure with the added benefit of readily available donors, the early attempts at haploidentical HSCT from genetically haploidentical family members were disappointing due to the development of refractory graft-versus-host disease (GVHD) and excessively high transplant-related mortality (TRM) [14]. A high rate of graft rejection (GR) and refractory GVHD were major drawbacks to the use of haploidentical HSCT for patients who required transplantation but lacked a suitable donor. In addition, delayed immune recovery and a high prevalence of infections were significant obstacles. Several initial trials revealed that haploidentical HSCTs had a considerably high incidence of GF and GVHD, resulting in high rates of morbidity and mortality [15-18].

**RECENT ADVANCES IN HAPLOIDENTICAL HSCT**

T cell depletion of donor grafts to prevent fatal GVHD is crucial for successful haploidentical HSCT. The methods

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**Table 1. Advantages of haploidentical hematopoietic cell transplantation.**

| Advantage                                      |
|-----------------------------------------------|
| Availability for almost all patients          |
| Immediate donor accessibility                 |
| No racial or ethnic restrictions              |
| Multiple donors                               |
| Continued donor access                        |

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**Table 2. Approaches in T cell depletion for haploidentical hematopoietic cell transplantation.**

| Approach                                      |
|-----------------------------------------------|
| Ex vivo T cell depletion                      |
| Indirect T cell depletion                     |
| Selection of CD34+ cells                      |
| Direct T cell depletion                       |
| Depletion of CD3+ T cells                    |
| Depletion of γδ T cells                      |
| In Vivo T cell depletion                      |
| Anti-lymphocyte antibodies                    |
| Allo-depletion with cyclophosphamide         |

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**Fig. 1. Advances in ex vivo T cell-depleted haploidentical hematopoietic stem cell transplantation.** The ex vivo techniques to remove T cells have evolved from the selection of CD34+ hematopoietic stem cell progenitors to the depletion of CD3+ cells, and more recently, the depletion of γδ T cells. Early attempts with haploidentical HSCT using CD34-selected stem cells, even with a megadose, were complicated by a high rate of infections likely related to delayed immune recovery. To overcome the limitation of CD34+ selection, the concept of direct depletion of T cells using anti-CD3 monoclonal antibody was introduced with the advantage of increasing the number of natural killer (NK) cells, and other immune-modulating cells. Depleting CD3+ cells was superior to selecting CD34+ cells in terms of engraftment speed and immune reconstitution. Although haploidentical HSCT using CD3-depleted grafts successfully reduce lethal infection rates, delayed immune recovery and the high rate of relapse were still problematic. The most recently developed approach using the negative depletion of γδ T cells improved the outcomes of T cell-depleted haploidentical transplant. Although recent advances in haploidentical HSCT, delayed immune reconstitution with subsequent infections and relapse for malignant disease are current major causes of treatment failure. New depletion technique to deplete naïve T cells or adoptive transfer of immune effector cells and cellular therapy based on γδ T cells or other immune cells could further improve the outcomes of haploidentical HSCT.
for T cell depletion (TCD) could be in vivo (T cell-replete transplant) or ex vivo (T cell-depleted transplant). Various approaches have been developed, including the ex vivo selection of CD34+ cells with or without a megadose of purified stem cells, ex vivo depletion of T cells, in vivo T cell depletion using T-cell antibodies such as anti-thymocyte globulin (ATG), or post-transplant cyclophosphamide (Table 2). The ex vivo techniques to remove T cells have evolved from the selection of CD34+ hematopoietic stem cell progenitors to the depletion of CD3+ cells, and more recently, to the depletion of αβ+ T cells (Fig. 1). Compared to the positive selection of CD34+ cells, the direct depletion of CD3+ cells has the advantage of increasing the number of natural killer (NK) cells, monocytes, and other immunomodulating cells [19]. The depletion of CD3+ cells is superior to selecting for CD34+ cells in terms of rapid engraftment and immune reconstitution [20-23]. Moreover, the preliminary report on the new method by the depletion of αβ+ T cells showed further improvements in the outcome of T cell-depleted haploidentical transplants. Depletion of αβ+ T cells produced grafts containing many γδ+ lymphocytes as well as other effector cells. While αβ+ T cells are known to be associated with the initiation of GVHD, γδ+ T cells can enhance immune reconstitution and are not implicated in GVHD [24, 25].

CD3-depleted haploidentical HSCT for pediatric patients

The concept of direct depletion of T cells using an anti-CD3 monoclonal antibody with microbeads was introduced in early 2000 [26, 27]. Previous studies that used megadoses of CD34+ stem cells have found promising results with rapid engraftment as a possible alternative for children lacking suitable matched donors [28-30]. However, haploidentical HSCTs using CD34-selected stem cells were complicated by a high rate of opportunistic infections likely related to delayed immune recovery. To overcome the limitation of CD34+ selection, a method for the negative depletion of T cells was developed. This provided T-cell-depleted grafts containing not only CD34+ stem cells, but also large numbers of NK cells and other effector cells, which were expected to reduce the risk of engraftment failure and facilitate immune reconstitution. There have been several reports on HHCT using CD3-depleted grafts in pediatric patients [31-35].

An early experiment using CD3 antibody conjugated to magnetic microbeads showed that T cells were effectively depleted with a mean log depletion of 3.4 with 82% mean recovery of CD34+ stem cells [26]. This result suggested that a direct negative T-cell depletion method could effectively remove the CD3+ cells responsible for GVHD without negatively affecting the functions of the hematopoietic stem cells. The first published study for the clinical application of CD3-depleted grafts enrolled 22 pediatric patients with refractory hematological malignancies [36]. Reduced-intensity conditioning (RIC) regimen consisting of fludarabine, thiopeta, melphalan and OKT3 without total body irradiation (TBI) was employed to reduce TRM. Since T-cell depletion was one of the well-established risk factors for the development of posttransplant lymphoproliferative disorder (PTLD), in vivo B-cell depletion combined with T-cell depletion was performed using an anti-CD20 antibody. The study showed excellent engraftment (91%) with a low incidence of acute GVHD (9% grade III and no grade IV acute GVHD). The incidence of viremia was low, and no fatal infections were reported. A comparative analysis of the immune recovery profile between reduced-intensity and myeloabative conditioning regimen revealed that the RIC group had a faster recovery of T-cell populations and NK cells, and a much more rapid increase in T-cell receptor excision circles (TRECs). TRECs are small extrachromosomal fragments of DNA produced in T-cells during the rearrangement of T-cell receptor genes in the thymus and indicate the recovery of thymus-dependent T-cell regeneration.

With the introduction of clinically available anti-CD19 antibody, a simultaneous in vitro T- and B-cell depletion method was performed in subsequent studies [27]. An early pilot study showed that CD3/CD19-depleted grafts might have benefits regarding engraftment and immune reconstitution compared with CD34-positive selection [19].

In a study of 46 pediatric patients with acute leukemia and MDS, primary engraftment was achieved in 88% of the patients, and engraftment after salvage transplantation was obtained in 100% of the patients [1]. Grade II acute GVHD and grade III/IV acute GVHD and chronic GVHD developed in 15% and 17%, and 21% of the patients, respectively. TRM was 5% at one year and 20% at 5 years. The 3-year event-free survival (EFS) was favorable (46%) for patients who were in complete remission (CR) when receiving the first haploidentical HSCT, whereas patients with leukemia and were not in CR at the time of transplantation or have received a subsequent HSCT had significantly higher risks of relapse (75% and 88%, respectively). This study showed that haploidentical HSCT using CD3/CD19-depleted allograft is a feasible treatment with low GVHD and low TRM, although the outcomes for patients with active diseases still need to be improved.

Many other studies showed that CD3/CD19 depletion could induce excellent primary engraftment rates, ranging from 83% to 100%, with acceptable GVHD and low TRM, and the survival outcomes were comparable to those of conventional HSCT [21, 31, 32, 34].

Haploidentical HSCT using αβ-depleted grafts in children and adolescents

Although donor T cells have anti-infectious and anti-tumor properties, they are responsible for GVHD in allogeneic HSCT. Gammadelta (γδ) T cells are a subset of T cells that account for 1–10% of the circulating peripheral blood T lymphocytes that express the γδ T cell receptors (TCRs) [37, 38]. The recently introduced method of negative depletion of αβ+ T cell is an effective strategy to dissect graft-versus-tumor effect and anti-infectious activities from GVHD. The γδ+ T cells are a small subset of T cells which can elicit both innate and adaptive immune responses to tumors and infections, while αβ+ T cells, a major subset of T cells, are the main inducers of GVHD [24, 25, 39]. This manipu-
A German group reported promising results of TCRαβ/CD19-depleted haploidentical HSCT [46]. In 41 patients with acute leukemia, MDS, solid tumors and nonmalignant disease, primary engraftment occurred in 88% of the patients. Acute GVHD grade II, III-IV, and extensive chronic GVHD were observed in 10% and 15%, and 9%, respectively. Compared with CD34-selected haploidentical HSCT, recovery of CD3⁺, CD3⁴⁺, and CD56⁺ cells were significantly faster with this method. Patients with leukemia and MDS who received a first haploidentical HSCT in CR1 showed a 1-year EFS of 100%, whereas no patient with active diseases survived. Owing to a short follow-up period, the clinical impact of this accelerated immune recovery remains to be clarified.

An Italian research group also reported rapid TCRαβ⁺ T cell reconstitution in 27 children with malignant and nonmalignant diseases after TCRαβ/CD19-depleted haploidentical HSCT [3]. Circulating αβ⁺ T cells are comprised of a major subset expressing the Vδ2 chain and a minor subset expressing the Vδ1 chain. They demonstrated prompt reconstitution of Vδ1 and Vδ2 T cells post-transplantation, and showed expansion of Vδ2 cells in vitro after exposure to zoledronic acid an activating antigen for TCRγδ⁺ T cell. These results suggest that αβ⁺ T-cell depleted haploidentical HSCT can be used as a platform for immunotherapy using zoledronic acid.

In a study of 22 children with nonmalignant disorders such as severe combined immunodeficiency (SCID), severe aplastic anemia (SAA), Fanconi anemia, other bone marrow failure syndrome, and immunodeficiencies, TCRαβ/CD19-depleted haploidentical HSCT showed promising outcome with favorable engraftment rates (80%), low incidence of GVHD (no visceral or chronic GVHD), and low TRM (9.3%) [44]. Recent studies demonstrated that αβ⁺-depleted haploidentical HSCT is an attractive treatment option that can allow stable engraftment and has low toxicity profiles for children who lack suitable donors. Future studies should investigate whether rapid reconstitution of γδ⁺ T cells can translate into improved patient outcome by reducing both TRM and relapse.

## HAPLOIDENTICAL HSCT WITH EX VIVO T CELL-DEPLETED GRANTS AT ASAN MEDICAL CENTER CHILDREN’S HOSPITAL (AMCCH)

Since 2008, haploidentical HSCT using ex vivo depletion of T cells has been practiced at our center. The depletion...
of CD3+ cells was introduced initially, and the depletion of αβ+ T cells was subsequently applied for allogeneic transplantation from HFD with several modifications of the treatment protocol (Fig. 2). The summary of our experience with ex vivo T cell-depleted haploidentical HSCT is provided below.

CD3-depleted haploidentical HSCT

Between July 2008 and January 2013, 28 children underwent haploidentical HSCT using in vitro CD3-depleted peripheral blood stem cells after RIC [2]. Of the 28 patients, 9 had hematologic malignancy (HM) and 18 had non-malignant diseases (NM), including 16 patients with acquired SAA and one with refractory neuroblastoma. Twenty-six patients achieved neutrophil engraftment at a median of 11 days (range, 9–15 d). Two patients failed to achieve primary engraftment and five experienced GR. All seven patients received a second haploidentical HSCT and achieved stable engraftment. The cumulative incidences (CIs) of ≥grade II and ≥grade III acute GVHD were 33.3% and 14.3%, respectively, and the 1-year CI of extensive chronic GVHD was 11.1%. TRMs at 100 days, 1 year, and 2 years were 0.0%, 10.7%, and 14.3%, respectively. At a median follow-up of 32.8 months (range, 17.0–72.5 mo), the 2-year OS was 82.1% (94% for NM and 60% for malignant diseases, P=0.019).

Our trials with CD3-depleted haploidentical HSCT showed a rather higher incidence of GF in the early period of the study; therefore low-dose TBI (LD-TBI) was added to the conditioning regimen in an attempt to decrease GF. In addition, we modified the targeted dose of T cells by add-back of T cells from the negative selection product after a uniform conditioning regimen. We demonstrated that the reduction of target cells is more effective with αβ-depleted T cell-depleted grafts with a target of 1-5×10⁵/kg by add-back of αβ+ T cells with the targeted dose noticeably reduced the incidence of GF and TRM in pediatric patients and could be applied to patients who lack a suitable related or unrelated donor.

αβ+ T cell-depleted haploidentical HSCT with post-transplant immunosuppressants

Pharmacologic prevention using immune-suppressive drugs such as calcineurin inhibitors, methotrexate and MMF, commonly in combination, is routine practice after the infusion of stem cells. Although advances in immunosuppressants have effectively prevented the development of acute GVHD, there are many serious toxic side effects and drug interactions requiring serial blood level monitoring [47-50]. Our targeted and ranged T cell dose-strategy improved the outcomes of ex vivo T cell-depleted haploidentical HSCTs. In addition, the depletion efficacy using anti-TCRα monoclonal antibody resulted in an approximately 4-log reduction of αβ+ T cells in most of the depletion procedures. Given that the reduction of target cells is more effective with αβ-depletion methods and considering the adverse effects of post-transplant immunosuppressants, pharmacological prophylaxis to prevent GVHD could be safely eliminated. Recently, seven patients received αβ-depleted haploidentical HSCT without post-transplant immunosuppressants. The median infused doses of CD3+ cells and αβ+ T cells were 6.1×10⁶/kg (range, 3.0–12.8) and 4.9×10⁴/kg (range, 1.0–5.0), respectively. All seven patients achieved a sustained neutrophil engraftment at a median of 10 days (range, 10–12 d). Two patients developed grade II acute GVHD and none developed severe acute GVHD greater than grade III. Early post-transplant outcomes were promising. However, further observations are necessary to assess any negative effects of the lower dose of T cells on immune recovery, relapse rate, and overall survival.

Haploidentical HSCT for hematologic malignancy

Forty-six patients with HM received ex vivo T cell-depleted haploidentical HSCT (9 with CD3-depleted graft and 37 with αβ-depleted graft) between July 2008 and January 2016. Of the 46 patients, 11 had ALL, 21 had AML, 2 had MPAL, 7 had MDS, 2 had JMML, and 3 had NHL. At a median follow-up of 24.6 months (range, 1.5–93 mo), TRM, relapse rate, EFS, and OS at 2 years were 6%, 39%, 55%, and 65%, respectively. The phase of disease was a significant risk factor for EFS [68% for any CR (N=35) vs. 0% for active disease (N=10), P=0.000]. Subsequent transplantations for patients who relapsed after previous allogeneic HSCT showed poorer outcomes compared to the single transplantation [EFS, 31% for subsequent transplants (N=12) vs. 63% for single transplantations (N=34), P=0.008]. Haploidentical HSCT is a feasible treatment option for pediatric patients with HM who have no suitable donors. However, further innovative strategies for the patients with active diseases at the time of transplantation or experience relapse after the initial transplantation should be researches to improve

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Haploidentical HSCT for children

Haploidentical HSCT for acquired severe aplastic anemia

Several notable reports in recent years have supported haploidentical transplant as a viable option for the treatment of acquired SAA [51-58]. In our center, 25 pediatric patients with acquired SAA received haploidentical HSCT (16 with CD3-depleted graft and 9 with αβ-depleted graft) between July 2009 and January 2016. Of the 25 patients, one patient experienced primary GF and four experienced GR. All five of these patients received CD3-depleted graft and achieved sustained engraftment after salvage transplantation. Eight of the 25 patients developed acute GVHD ≥grade II (six grade II and two grade III), leading to a CI of 32%. Twenty-three of the patients survived and were transfusion-independent. At a median follow-up of 40 months (range, 1-80 mo), estimated OS at 3 years was 91%. HSCT from HFD with ex vivo T cell depletion could be offered for children and adolescents with refractory SAA who lack suitable donors.

FUTURE PERSPECTIVES OF HAPLOIDENTICAL HSCT

The recent emerging evidences for haploidentical HSCT has provided additional therapeutic options for pediatric patients with malignant and non-malignant diseases curable with HSCT but do not have a suitable related or unrelated donor. In spite of the promising results for haploidentical HSCT in pediatric patients, there are still several obstacles to overcome. Although our targeted and ranged T cell dose-strategy improved the outcomes of ex vivo T cell-depleted haploidentical HSCTs, our current protocol (Fig. 3) is only a step in the development of a suitable haploidentical transplant protocol for patients who lack a donor. Unresolved issues include optimizing conditioning regimens, donor T cell regulation method, stem cell source, donor selection, management for graft failure, novel strategies to enhance immune recovery, and the prevention of relapse. Delayed immune reconstitution and subsequent infections are not uncommon and are a major cause of death after haploidentical transplantation. New depletion techniques to deplete naïve T cells or the adoptive transfer of immune effector cells such as pathogen-specific T cells could enhance the recovery of immune function after haploidentical HSCT [59-65]. In addition, relapse is another major treatment failure in haploidentical HSCT for malignant diseases. Patients with active diseases or who have relapsed after previous transplantation showed poor outcomes, necessitating further treatment strategies such as cellular therapy based on γδ+ T cells or other immune cells [66-72].

![Fig. 3. Current haploidentical HSCT strategy for pediatric patients at AMCCH. The donor will receive G-CSF for a minimum of four consecutive days and peripheral blood mononuclear cells (PBMCs) will be collected on days -1 and 0. The αβ+ T cells will be depleted by negative depletion using the CliniMACS system (Miltenyi-Biotec, Bergisch-Gladbach, Germany). The final dose of αβ+ T cells is targeted ≤5×10^4/kg by adding back αβ+ T cells from the negative selection product. The patient will receive conditioning regimen consisting of fludarabine (FLU), cyclophosphamide (CY), rabbit ATG (r-ATG), and low-dose total body irradiation (LD-TBI). After that, stem cells will be infused on day 0 without any post-transplant immunosuppressants. The patient will also receive rituximab post-transplant to deplete B cells at approximately day +28 or earlier if EBV was detected with PCR. For cytomegalovirus (CMV) prophylaxis, the CMV-seropositive patient will receive ganciclovir prior to transplant and foscarnet after transplantation up until engraftment. After engraftment, ganciclovir or valganciclovir will be administered until 100 days post-transplantation with CD4+ cells at >100/μL.

Abbreviations: HSC, hematopoietic stem cells; αβ, αβ+ T cells; γδ, γδ+ T cells; DC, dendritic cells; B, B cells; HR, high-risk.](image-url)
CONCLUSIONS

Haploidentical HSCT using ex vivo T cell depleted grafts is a promising therapeutic approach for the treatment of patients without an optimal related or unrelated donor. Currently, substantial progress in haploidentical HSCT has been achieved in pediatric patients, providing a chance to cure the patients in need of HSCT. Further improvements to decrease the rates of GF and GVHD, to enhance immune recovery to reduce serious infections and to develop effective prevention and management strategies of relapse will enable haploidentical HSCT to become an established therapy for pediatric patients lacking a suitable donor. In addition, future clinical trials with larger number of patients will help to establish the most effective conditioning regimen, the best donor source, and the optimal regulation of donor T cells, thus maximizing the outcome of this novel approach.

REFERENCES

1. Lang P, Teltschik HM, Feuchtinger T, et al. Transplantation of CD3/CD19 depleted allografts from haploidentical family donors in paediatric leukaemia. Br J Haematol 2014;165:688-98.
2. Im HJ, Koh KN, Suh JK, et al. Refinement of treatment strategies in ex vivo T-cell-depleted haploidentical SCT for pediatric patients. Bone Marrow Transplant 2015;50:225-31.
3. Airoldi I, Bertainia A, Prigione I, et al. γδ T-cell reconstitution after HLA-haploidentical hematopoietic transplantation depleted of TCR-αβ+/CD19+ lymphocytes. Blood 2015;125:2349-58.
4. Chang YJ, Huang XJ. Improving the clinical outcome of unmanipulated haploidentical blood and marrow transplantation. Bone Marrow Transplant 2015;50(Suppl 2):S21-3.
5. Fuchs EJ. HLA-haploidentical blood or marrow transplantation with high-dose, post-transplantation cyclophosphamide. Bone Marrow Transplant 2015;50(Suppl 2):S31-6.
6. Apperley J, Niederwieser D, Huang XJ, et al. Reprint of: haploidentical hematopoietic stem cell transplantation: A global overview comparing Asia, the European Union, and the United States. Biol Blood Marrow Transplant 2016;22(Suppl 3):S15-8.
7. Ciurea SO, Bayraktar UD. "No donor"? Consider a haploidentical transplant. Blood Rev 2015;29:63-70.
8. Or-Geva N, Reisner Y. The evolution of T-cell depletion in haploidentical stem-cell transplantation. Br J Haematol 2016;172:667-84.
9. Booth C, Lawson S, Veyes P. The current role of T cell depletion in paediatric stem cell transplantation. Br J Haematol 2013;162:177-90.
10. Lang P, Mueller I, Greil J, et al. Retransplantation with stem cells from mismatched related donors after graft rejection in pediatric patients. Blood Cells Mol Dis 2008;40:33-9.
11. Yoshiihara S, Isegame K, Taniguchi K, et al. Salvage haploidentical transplantation for graft failure using reduced-intensity conditioning. Bone Marrow Transplant 2012;47:369-73.
12. Park JA, Koh KN, Choi ES, et al. Successful rescue of early graft failure in pediatric patients using T-cell-depleted haploidentical hematopoietic SCT. Bone Marrow Transplant 2014;49:270-5.
13. Rådestad E, Wikell H, Engström M, et al. Alpha/beta T-cell depleted grafts as an immunological booster to treat graft failure after hematopoietic stem cell transplantation with HLA-matched related and unrelated donors. J Immunol Res 2014;2014:578741.
14. Powles RL, Morgenstern GR, Kay HE, et al. Mismatched family donors for bone-marrow transplantation as treatment for acute leukaemia. Lancet 1983;1:612-5.
15. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med 1985;313:765-71.
16. Anaeseti C, Amos D, Beatty PG, et al. Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. N Engl J Med 1989;320:197-204.
17. Anaeseti C, Beatty PG, Storb R, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol 1990;29:79-91.
18. Ash RC, Horowitz MM, Gale RP, et al. Bone marrow transplantation from related donors other than HLA-identical siblings: effect of T cell depletion. Bone Marrow Transplant 1991;7:443-52.
19. Lang P, Schumm M, Greil J, et al. A comparison between three graft manipulation methods for haploidentical stem cell transplantation in pediatric patients: preliminary results of a pilot study. Klin Padiatr 2005;217:334-8.
20. Bethge WA, Faul C, Bornhäuser M, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: an update. Blood Cells Mol Dis 2008;40:13-9.
21. Handgretinger R, Chen X, Pfeiffer M, et al. Feasibility and outcome of reduced-intensity conditioning in haploidentical transplantation. Ann N Y Acad Sci 2007;1106:279-89.
22. Lang P, Handgretinger R. Haploidentical SCT in children: an update and future perspectives. Bone Marrow Transplant 2008;42(Suppl 2):S54-9.
23. Handgretinger R, Lang P. The history and future prospective of haplo-identical stem cell transplantation. Cytotherapy 2008;10:43-51.
24. Daniele N, Scarpa MC, Caniglia M, et al. Transplantation in the onco-hematology field: focus on the manipulation of αβ and γδ T cells. Pathol Res Pract 2012;208:67-73.
25. Miculescu L, Sengelov H. The role of gamma delta T cells in haematopoietic stem cell transplantation. Scand J Immunol 2015;81:459-68.
26. Gordon PR, Leimig T, Mueller I, et al. A large-scale method for T cell depletion: towards graft engineering of mobilized peripheral blood stem cells. Bone Marrow Transplant 2002;30:69-74.
27. Barfield RC, Otto M, Houston J, et al. A one-step large-scale method for T- and B-cell depletion of mobilized PBSC for allogeneic transplantation. Cytotechnology 2004;6:1-6.
28. Handgretinger R, Klingebiel T, Lang P, et al. Megadose transplantation of purified peripheral blood CD34(+) progenitor cells from HLA-mismatched parental donors in children. Bone Marrow Transplant 2001;27:77-83.
29. Lang P, Greil J, Bader P, et al. Long-term outcome after haploidentical stem cell transplantation in children. Blood Cells Mol Dis 2004;33:281-7.
30. Locatelli F, Pende D, Maccario R, Mingari MC, Moretta A, Moretta L. Haploidentical hematopoietic stem cell transplantation for the treatment of high-risk leukemias: how NK cells make the difference. Clin Immunol 2009;133:171-8.

31. Bader P, Soerensen J, Jarisch A, et al. Rapid immune recovery and low TRM in haploidentical stem cell transplantation in children and adolescence using CD3/CD19-depleted stem cells. Best Pract Res Clin Haematol 2012;24:331-7.

32. Palma J, Salas L, Carrión F, et al. Haploidentical stem cell transplantation for children with high-risk leukemia. Pediatr Blood Cancer 2012;59:895-901.

33. González-Vicent M, Molina B, Andión M, et al. Allogeneic hematopoietic transplantation using haploidentical donor vs. unrelated cord blood donor in pediatric patients: a single-center retrospective study. Eur J Haematol 2011;87:46-53.

34. Pérez-Martínez A, González-Vicent M, Valentín J, et al. Early evaluation of immune reconstitution following allogeneic CD3/CD19-depleted grafts from alternative donors in childhood acute leukemia. Bone Marrow Transplant 2012;47:1419-27.

35. Dufort G, Pisano S, Incoronna A, et al. Feasibility and outcome of haploidentical SCT in pediatric high-risk hematologic malignancies and Fanconi anemia in Uruguay. Bone Marrow Transplant 2012;47:663-8.

36. Chen X, Hale GA, Barfield R, et al. Rapid immune reconstitution after a reduced-intensity conditioning regimen and a CD3-depleted haploidentical stem cell graft for paediatric refractory haematological malignancies. Br J Haematol 2006;135:524-32.

37. Vantourout P, Hayday A. Six-of-the-best: unique contributions of γδ T cells to immunology. Nat Rev Immunol 2013;13:88-100.

38. Norell H, Moretta A, Silva-Santos B, Moretta L. At the Bench: Preclinical rationale for exploiting NK cells and γδ T lymphocytes for the treatment of high-risk leukemias. J Leukoc Biol 2013;94:1123-39.

39. Hu Y, Cui Q, Luo C, Luo Y, Shi J, Huang H. A promising sword of tomorrow: Human γδ T cell strategies reconcile allo-HCT complications. Blood Rev 2015. [Epub ahead of print]

40. Lamb LS Jr, Lopez RD. gammelta T cells: a new frontier for immunotherapy? Biol Blood Marrow Transplant 2005;11:664-73.

41. Vandermeeren R. New approaches to graft engineering for thymic microangiopathy in blood and marrow transplant patients receiving tacrolimus or cyclosporine A. Transfusion 2003;43:78-84.

42. Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thymic microangiopathy after hematopoietic stem cell transplantation. Biol Blood MarrowTransplant 2005;11:571-5.

43. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.

44. Koh KN, Park M, Kim BE, Im HJ, Seo JJ. Early central nervous system complications after allogeneic hematopoietic stem cell transplantation in children. Korean J Hematol 2010;45:164-70.

45. Ciceri F, Lupo-Stanghellini MT, Korthof ET. Haploidentical transplantation in patients with acquired aplastic anemia. Bone Marrow Transplant 2013;48:183-5.

46. Lang P, Feuchtinger T, Tetzschek HM, et al. Improved immune recovery after transplantation of TCRβ/CD19-depleted allografts from haploidentical donors in pediatric patients. Bone Marrow Transplant 2015;50(Suppl 2):S6-10.

47. Sarkodie-Aduo C, Sorisescu D, Sensenbrenner L, et al. Thrombotic microangiopathy in blood and marrow transplant patients receiving tacrolimus or cyclosporine A. Transfusion 2003;43:78-84.
62. Feuchtinger T, Opherk K, Bethge WA, et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. Blood 2010;116:4360-7.

63. Feucht J, Joachim L, Lang P, Feuchtinger T. Adoptive T-cell transfer for refractory viral infections with cytomegalovirus, Epstein-Barr virus or adenovirus after allogeneic stem cell transplantation. Klin Padiatr 2013;225:164-9.

64. Gerdemann U, Katari UL, Papadopoulou A, et al. Safety and clinical efficacy of rapidly-generated trivirus-directed T cells as treatment for adenovirus, EBV, and CMV infections after allogeneic hematopoietic stem cell transplant. Mol Ther 2013;21:2113-21.

65. Icheva V, Kayser S, Wolff D, et al. Adoptive transfer of Epstein-Barr virus (EBV) nuclear antigen 1-specific t cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. J Clin Oncol 2013;31:39-48.

66. Wilhelm M, Kunzmann V, Eckstein S, et al. Gammadelta T cells for immune therapy of patients with lymphoid malignancies. Blood 2003;102:200-6.

67. Gomes AQ, Martins DS, Silva-Santos B. Targeting γδ T lymphocytes for cancer immunotherapy: from novel mechanistic insight to clinical application. Cancer Res 2010;70:10024-7.

68. Fisher JP, Hesijerans J, Yan M, Gustafsson K, Anderson J. γδ T cells for cancer immunotherapy: A systematic review of clinical trials. Oncoimmunology 2014;3:e27572.

69. Wilhelm M, Smetak M, Schaefer-Eckart K, et al. Successful adoptive transfer and in vivo expansion of haploidentical γδ T cells. J Transl Med 2014;12:45.

70. Rubnitz JE, Inaba H, Ribeiro RC, et al. NKAML: a pilot study to determine the safety and feasibility of haploidentical natural killer cell transplantation in childhood acute myeloid leukemia. J Clin Oncol 2010;28:955-9.

71. Choi I, Yoon SR, Park SY, et al. Donor-derived natural killer cells infused after human leukocyte antigen-haploidentical hematopoietic cell transplantation: a dose-escalation study. Biol Blood Marrow Transplant 2014;20:696-704.

72. Shah NN, Baird K, Delbrook CP, et al. Acute GVHD in patients receiving IL-15/4-1BBL activated NK cells following T-cell-depleted stem cell transplantation. Blood 2015;125:784-92.