Title

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Journal

Transplantation and Cellular Therapy, 21(10)

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Publication Date

2015-10-01

DOI

10.1016/j.bbmt.2015.07.002

Peer reviewed

Published in final edited form as:

Biol Blood Marrow Transplant. 2015 October ; 21(10): 1714–1720. doi:10.1016/j.bbmt.2015.07.002.

Haploidentical Hematopoietic Stem Cell Transplantation as Platform for Post-transplant Cellular Therapy

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Abstract

Haploidentical transplantation can extend the opportunity for transplantation to almost all patients who lack an HLA-matched donor. Advances in the field of haploidentical transplantation have led to a marked decrease in treatment-related mortality, allowing investigators to focus on developing rationale pre- and peri-remission therapies aimed at preventing disease relapse post-transplant. Due to widespread availability, low treatment-related mortality and cost, haploidentical donors may become the preferred “alternative” donors for allogeneic hematopoietic stem cell transplantation. One of the major advantages of using a related donor is the possibility to collect or generate additional cellular products from the same immediate available donor, which will not be rejected. Infusion of these cells in the peri-transplant period, derived from the same immune system, is opening the possibility to markedly enhance the anti-tumor effects of the graft and hasten immunologic reconstitution post-transplant.

Keywords

Haploidentical transplantation; post-transplantation cyclophosphamide; alpha-beta T-cell depletion; cellular therapy; donor lymphocyte infusion; NK cells; CAR T cells

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Conflict of interest: Some of technology described was advanced through research conducted at the MD Anderson Cancer Center by Laurence J.N. Cooper, M.D., Ph.D. Both MD Anderson Cancer Center and Dr. Cooper have a financial interest in ZIOPHARM Oncology, Inc., and Intrexon Corporation. On May 7, 2015, Dr. Cooper was appointed as the Chief Executive Officer at ZIOPHARM. Dr. Cooper is now a Visiting Scientist at MD Anderson where he will continue to supervise the development of this technology. The rest of authors have no potential conflict of interest to declare.

INTRODUCTION

Allogeneic hematopoietic stem cell transplant (AHSCT) is a potential curative treatment for patients with advanced hematologic malignancies. However, donor availability remains one of the major limitations to extending this treatment modality to all patients in need. Although an HLA-matched sibling is the preferred donor, only a minority of patients will have such donor available.(1) An HLA-matched unrelated donor (MUD) has been considered the next best option; however, identification of a MUD is challenging.(2) Also, the unrelated donor search and procurement of stem cell product takes much longer than the use of a related donor. Many patients urgently need transplantation to prevent disease relapse and a prolonged unrelated donor search is not feasible. Transplantation using stem cells from one HLA haplotype matched first degree relatives, as a related transplant, is the most accessible stem cell source that is also widely available as most patients will have a haplotype matched related donor in the immediate family, typically a parent, child or sibling. In addition, an important advantage that has come recently to the forefront is the immediate availability of the same donor to collect or generate additional cells, such as T cells or T cell subsets, like NK cells, to enhance antitumor effects of the graft.(3) This may provide a significant advantage to haploidentical stem cell transplantation (HaploSCT), which, in addition to low non-relapse mortality (NRM), lower cost compared with unrelated donor transplantation and widespread availability may be an ideal setup for cellular therapy with cells collected from the same donor that may not be rejected as they are part of the same immune system, and, when infused early after transplant, could enhance the anti-tumor effects of the graft and improve immunologic reconstitution. Here we review the use of HaploSCT as a platform to apply post-transplant cellular therapy with cells collected or generated from the same donor to enhance graft-versus-tumor (GVT) effect and discuss current and anticipated developments using cellular therapy in this setting.

METHODS OF HAPLOIDENTICAL TRANSPLANTATION

HaploSCT was initially performed in late 1970’s using unmanipulated T cell-replete (TCR) stem cell graft and conventional graft-versus-host (GVHD) prophylaxis, led to severe acute GVHD (aGVHD) and graft rejection in most patients.(4, 5) Early evidence suggested that T cells in the graft are responsible for causing aGVHD.(6, 7) In an early attempt to minimize T cell alloreactive reactions across the HLA barrier and decrease the risk of GVHD, complete *ex vivo* T cell depletion (TCD) of the graft was developed. Unfortunately, extensive T cell depletion was associated with an increased risk of graft failure(8–11) and a significant delay in immunologic reconstitution was observed associated with a higher risk of opportunistic infections post-transplant.(12, 13)

Several novel approaches have been subsequently developed to partially deplete T cells from the graft with the goal to preserve immunity and GVT effects and selectively eliminate the cells mostly responsible for GVHD (Table 1). Some if not all of these methods may become a platform for post-transplant cellular therapy.

Co-infusion of regulatory T-cells and conventional T-cells

Regulatory T cells (Tregs) defined by $CD4^+CD25^+$ and the transcription FOXP3 expression, suppress autoreactive lymphocytes and control innate and adaptive immune responses. In preclinical models, Tregs suppressed the early expansion of alloreactive donor T cells and their capacity to induce GVHD without abrogating their GVT effect (14, 15) and when co-infused with $CD4^+CD25^-$ conventional T cells (Tcons), immune recovery was accelerated. (16) Given these observations, immunotherapy with Tregs and Tcons has been explored for clinical applications. The Perugia group treated 28 patients with high-risk hematologic malignancies conditioned with fludarabine, CY, TBI and thiotepa before haploidentical donor derived Tregs infusion followed with TCD stem cell graft combined with Tcons infusion with a ratio of Tcons:Tregs about 1:2. No GVHD prophylaxis was administered. Twenty-six of the 28 patients achieved primary engraftment and only 2 patients developed aGVHD while no patient had chronic GVHD (cGVHD). Even though immune recovery was appeared rapid, NRM occurred in 13 of the 26 evaluable patients including 8 from infection. Long-term results of this study have confirmed a low GVHD and relapse incidence while NRM remains a concern.(17)

Photodepletion of alloreactive T cells

This approach aims to selectively deplete T cells that react against recipient alloantigens to prevent GVHD, yet preserve tumor-specific and pathogen-reactive T cells. It requires the alloactivation of donor T cells by patient-derived antigen-presenting cells. Alloreactive donor T cells then are targeted by their expression of surface activation markers, proliferation in a mixed leukocyte reaction or the preferential retention of photoactive dyes. One of the methods to eliminate these alloreactive donor T cells is using *ex vivo* photodepletion. The principles of this strategy is that alloreactive T cells uptake and accumulate the TH9402 compound then these cells could be lysed after exposure to a specific wavelength of visible light. This approach would spare resting T cells to fight infections. This method also has been found to transform non-Tregs to Treg cells and can help prevent GVHD in HaploSCT patients.(18) This approach is now being studied in a multi-institutional phase II setting.

Depletion of alpha-beta and $CD19^+$ T cells

The αβ T cell receptor (TCR)-positive T cells are a major content of the T cell population and responsible for the occurrence of GVHD.(19) Unlike innate-like γδ T cells, which are capable of directly recognizing their targets in a MHC-independent manner, thereby allowing them to respond to malignancy cells without recognition of alloantigens that could result in GVHD. Several studies have shown that patients who develop increased numbers of donor-derived circulating γδ T cells following HaploSCT or partially mismatched AHSCT experience a prolonged survival.(20, 21) These findings have led to the rationale of selectively elimination of αβ T cells while preserve γδ T cells in the graft approach investigated in HaploSCT with aim to reduce GVHD without abrogating GVT effect. Early results in pediatric population with non-malignant diseases are very encouraging. Twenty-three children received HaploSCT after *ex vivo* elimination of αβ T cells without post-transplant GVHD prophylaxis. Sustained engraftment in the great majority of patients, rapid

immune reconstitution, and low incidence of NRM were observed in this study. With the median follow up duration of 18 months, DFS was 90%. (22) These patients did not receive additional post-transplant immune suppression and had low incidence of aGVHD. Studies evaluating this approach in adult patients are ongoing. The biggest advantage of this approach appears to be the possibility to avoid post-transplant immunosuppression.

Post-transplant cyclophosphamide for GVHD prevention

Cyclophosphamide (CY) is a highly immunosuppressive alkylating agent, which has been incorporated in various conditioning regimens for AHSCT. High-dose post-transplant cyclophosphamide (PTCY) has been used to selectively deplete alloreactive T cells following TCR HaploSCT. This approach is based on an observation that CY can promote tolerance to allogeneic MHC-mismatched skin grafts in mice.(23) In animal models of AHSCT, CY administered on Day +3 allowed stable engraftment of MCH-incompatible cells and attenuated lethal and non-lethal GVHD.(24) Moreover, Ross, et al. have demonstrated that alloreactive or stimulated T cells, which are responsible for causing graft rejection and GVHD, are more susceptible to the cytotoxic effect of CY than resting or memory T cells.(25) However, concerns about its myelotoxicity have deterred clinical application of high-dose CY in the post-transplantation setting. Kastan and colleagues have shown that human hematopoietic progenitor cells express high levels of cytoplasmic aldehyde dehydrogenase (ALDH) which makes them resistant to the cytotoxic effect of CY. (26) Moreover, both pre-clinical and clinical studies have demonstrated the resistances of regulatory T cells (Tregs) to CY through expression of ALDH, which may contribute to GVHD prevention in this setting.(27, 28) Based on its ability to induce maximal immunosuppression without myeloablation, several clinical trials have been performed at multiple transplant centers to assess the efficacy of PTCY administration to prevent GVHD. An initial phase I clinical trial showed safety and efficacy of PTCY to prevent graft rejection and GVHD after non-myeloablative, TCR bone marrow transplantation from haploidentical donors. This protocol used a conditioning regimen with fludarabine, cyclophosphamide and 2Gy TBI, initially, with only one dose of PTCY of 50 mg/kg on day+3,(29) subsequently modified by adding one more dose on day +4. A remarkably low incidence of aGVHD, cGVHD and NRM were observed in this study. However, more than a half of the patients relapsed after 1 year post-transplant.(30) A recent study by McCurdy and colleagues has shown that disease aggressiveness is the main factor for relapse and survival after non-myeloablative HaploSCT with PTCY.(31) To reduce the risk of relapse especially for patients with high-risk malignancies, a more intense conditioning has been investigated by several groups. In a recent study by Solomon et al., 30 patients with advanced hematologic malignancies were treated with a conditioning regimen using fludarabine and fractionated TBI (total dose 1,200 cGy) and a peripheral blood graft. Donor engraftment occurred in all patients, the cumulative incidence of grade II–IV and III–IV aGVHD was seen in 43% and 23%, respectively, and NRM at 2 years was only 3%. With a median follow-up of 24 months, disease-free survival was 73% at 2 years.(32) Our group recently reported the outcomes of first 100 patients treated at MD Anderson Cancer Center using fludarabine, melphalan, thiotepa conditioning regimen. The 3-year progression free survival for patients with myeloid and lymphoid malignancies were 56% and 62% respectively, with 1-year NRM of 12% and 22% respectively.(33) Other groups reported on alternative conditioning

regimens with similar outcomes.(34) Collectively, these clinical data suggest that the use of PTCY with tacrolimus and mycophenolate mofetil (MMF) is very effective to control GVHD in HaploSCT, can be used with many conditioning regimens, and due to the low NRM, could serve as a platform for cellular therapy after transplant. These improved outcomes were found to be significantly better compare with complete *ex vivo* TCD HaploSCT, due to a more rapid immune reconstitution, lower incidence of severe aGVHD, cGVHD and NRM.(35) Nonetheless, it remains unclear how TCR HaploSCT with PTCY will compare with other *in vivo* and *ex vivo* methods of partial TCD.(36)

A number of other methods to control alloreactivity in haploSCT have been developed by other investigators from different institutions, are not discussed in this review.

POST-TRANSPLANT CELLULAR THERAPY

With significant improvement in NRM, disease relapse has become the most important cause of treatment failure in patients undergoing HaploSCT, similar with matched transplantation. Several strategies have been used and novel approaches are being explored to prevent and treat disease relapse post-transplant (Table 2). This may offer a unique opportunity, probably for the first time since the beginning of allogeneic transplantation, to greatly enhance the anti-tumor effects of the graft when administered early post-transplant. Current and foreseeable cell therapy approaches that could be applied after HaploSCT are outlined below.

Unmodified donor lymphocyte infusion (DLI)

Donor lymphocyte infusion (DLI) has been used primarily as a therapeutic option to treat disease relapse after HLA-matched sibling or unrelated donor AHSCT. Considering the readily availability of haploidentical donors, donor lymphocytes can be easily obtained and infused to the recipients to prevent or treat early disease relapse. A higher risk of inducing severe aGVHD using haploidentical DLI (haploDLI) is the most important concern. However, several studies did not show an increase risk of aGVHD after haploDLI compared with DLI from HLA matched donors, probably because the fact that the tolerizing effect to donor cells had already happen. In an early study by Huang et al., this group used G-CSF-primed therapeutic haploDLI in 20 patients with relapse post-transplant, with the median cell dose of 61×10^6 $CD3^+$ T cells/kg. The incidence of grade III–IV aGVHD and cGVHD was 30% and 64%, respectively.(37) A more recent report from the same group, described the experience with haploDLI administered to 124 patients after TCR HaploSCT. The cumulative incidence of aGVHD (53.2% for grade II–IV and 28.4% for grade III–IV) was reduced with post-DLI GVHD prophylaxis.(38) However, with a dose-escalated approach using a lower starting DLI dose, the incidence aGVHD appears to be lower and well tolerated. The Johns Hopkins group administered 52 doses of haploDLI to 40 patients with hematologic malignancies treated with PTCY who relapsed after HaploSCT in a dose-escalation manner, starting with 1×10^5 $CD3^+$ T cells/kg of recipient's ideal body weight. The majority of patients (72.5%) received 1×10^6 $CD3^+$/kg of the DLI dose. Overall, 12 (30%) patients responded to haploDLI, all achieved a complete remission, with a median response duration of 12 months, while aGVHD occurred in only 25% and grade III–IV aGVHD was only 15%.(39) This group recommended 1×10^6 $CD3^+$/kg as starting dose. This

is also a first study confirmed a feasibility of DLI in patients received PTCY as a GVHD prevention. A similar study by Ghiso et al. using DLI from haploidentical sibling donors for treatment of 108 patients who relapsed after HaploSCT, the starting DLI dose was 1×10^4 or 1×10^5 $CD3^+$ T cells/kg. The cumulative incidence of aGVHD grade II–IV was only 14% and none of the patients developed cGVHD. The response rate was 45%, 33% and 70% in patients with molecular relapse, hematologic relapse leukemia and Hodgkin's disease, respectively.(40) Results from these studies suggest that a dose-escalated DLI can be safely administered in patients who relapse after HaploSCT, as no significantly increase GVHD was observed in these patients compared with DLI administered for HLA-matched transplants. The use of unmodified DLI with a "safety switch" as described below is being tested in clinical trials to prevent disease relapse in patients with advanced hematological malignancies.

Unmodified DLI with a "safety switch"

A higher risk of aGVHD is the main limitation of early administration of an unmodified DLI. To control the development of severe aGVHD if occurs after transplant, infused T cells can be *ex vivo* genetically modified to express a specific suicide gene which may be turned on to induce cell apoptosis, if GVHD occurs. The administration of donor T cells with a "safety switch" can help prevent relapse when administered earlier after transplant, and may accelerate immune reconstitution. The safety and efficacy of this approach have been investigated in several preclinical and early clinical studies.(41–44) In a phase I/II clinical trial by Ciceri et al., donor T lymphocytes engineered to express herpes simplex thymidine-kinase suicide gene (TK cells) were infused to patients with high-risk leukemia who underwent HaploSCT with TCD PB grafts. T cell apoptosis can be triggered by the use of gancyclovir if the patients develop GVHD. No GVHD prophylaxis was used post-transplant. Of 28 patients, 22 successfully engrafted with TK cells. The improvement of immune response against CMV and EBV was seen after TK cell infusions. Ten patients developed aGVHD, which can be abrogated by using gancyclovir. No acute or chronic adverse events were related to the gene-transfer procedure.(45) Correspondingly, a study by Vago et al. has confirmed that TK cell infusion can drive the recovery of thymic activity in adults patients treated with TCD haploSCT, leading to immune reconstitution. In this study, 11 patients developed GVHD after TK cell infusion and all of them achieved complete resolution of all signs and symptoms by the activation of the suicide gene in TK cells through intravenous administration of gancyclovir.(46) However, gancyclovir is a drug commonly used to treat CMV reactivation in AHSCT thus using this drug might not be optimal. Although the expression of the gene encoding herpes simplex virus thymidine kinase has shown promise as a safety switch, but its mechanism of action requires interference with DNA synthesis so the cell killing may take several days and be incomplete, resulting in a delayed in clinical benefit. The Baylor group developed an alternative approach by using T cells engineered to express caspase 9 which can be induced by using a dimerizing agent, AP1903. These inducible caspase 9 T cells provided rapid immune recovery in 10 pediatric patients received AHSCT with TCD. AP1903 administration could rapidly resolved GVHD without a significant effect on anti-viral immune reconstitution.(44, 47) Ongoing and future studies are investigating the efficacy of this approach to prevent disease relapse after HaploSCT.

Gamma-delta donor T cell infusion

The γδ T cells are a subset of T cells, account for 1–10% of circulating human T lymphocytes and are largely outnumbered by T cell receptor αβ $CD4^+$ and $CD8^+$ T cells.(48) Unlike αβ T cells, γδ T cells have directed cytotoxic effect to target cells independent from antigen presentation via HLA molecules, which makes them target and kill tumor cells without causing GVHD. Pre-clinical studies have shown that donor γδ T cells are able to promote alloengraftment and GVT effect yet do not cause lethal GVHD in mice transplanted with MHC-incompatible TCD marrow grafts.(49–51) However, in clinical setting, Immunotherapy with γδ T cells requires their activation and expansion as they comprise only a small percentage of circulating T cells.3 Aminobisphosphonates, e.g., zoledronic acid or synthetic phosphoantigens, e.g., bromohydrin pyrophosphate (BrHPP) and 2-methyl-3-butenyl-1-pyrophosphate (2M3B1PP) have been used with promising results for γδ T cells expansion in clinical setting.(52–54) Also, many clinical studies have demonstrated that γδ T cells immune therapy for hematologic malignancies is a well-tolerated and feasible method with objective tumor responses in patients with various hematologic malignancies.(21, 54–57) In the HaploSCT setting, Airoldi and colleagues assessed functional and phenotypic characteristics of γδ T cells after HaploSCT using αβ T cells and $CD19^+$ B cells depleted graft in 27 children with either malignant or nonmalignant disorders. This group demonstrated that selective depletion of αβ T cells from haploidentical PBSCs enhances the functional and phenotypic reconstitution of γδ T cells and Vδ2 subset of γδ T cells are expanded *in vitro* after exposure to zoledronic acid and efficiently lyse primary lymphoid and myeloid blasts.(58) These new insights may have important implications for the use of γδ T cell infusion post-transplant for prevention or treatment of disease relapse, especially after partially TCD haploidentical grafts where donor γδ T cells can easily be obtained using the same immunomagnetic procedure as the αβ T cell depleted grafts.

Infusion of T cells with chimeric antigen receptors (CARs)

This approach offers a targeted anti-tumor effect without added risk for the development of GVHD by using T cells engineered to express a chimeric receptor with an extracellular domain that can recognize a specific antigen on the tumor cells and an intracellular domain that can activate the cytotoxic T cells.(59) CARs have been used successfully in tumors that express the CD19 antigen such as B-cell ALL or B-cell non-Hodgkin's lymphomas. Kochenderfer et al. reported outcomes of 10 patients who received anti-CD19 CARs for post-transplant relapse B-cell malignancies. Three patients had regression of their malignancies and none of the patients developed GVHD after CARs infusion.(60). Maude et al. conducted a pilot clinical trial using autologous T cells transduced with a CD19-directed chimeric antigen receptor (CTL019) lentiviral vector in 30 patients with relapsed or refractory ALL. Twenty-seven of 30 patients (90%) were in a morphologic remission at 1 month after the infusion of CTL019. Of those who had a morphologic remission, 22 patients had negative minimal residual disease. These investigators also demonstrated that CTL019 cells proliferated *in vivo* and were detectable in the blood, bone marrow, and cerebrospinal fluid of patients who responded.(61) We are exploring the use of Haplo-donor-derived CAR T cells generated using the *Sleeping Beauty* system and administered early after HaploSCT to prevent disease relapse, as a part of a multi-arm clinical trial.(62) Four HaploSCT recipients received CAR T cells in escalating doses up to $1\times10^7/m^2$ so far, 3 with ALL and 1

with primary induction failure large B cell lymphoma who never achieved remission after multiple different courses of chemotherapy. CAR T cells are administered 6–12 weeks following stem cell infusion. CAR T cells were detected in all patients 2–4 weeks after the infusion. All patients received MMF until day+90 and tacrolimus until 6 months post-transplant. Overall 3 of 4 patients remain in remission at last follow-up. These results are very promising and show that allogeneic CAR T cell therapy can be safely administered early post-HaploSCT without significant GVHD in the presence of non-steroid based immunosuppression.

Infusion of ex vivo expanded NK cells

Natural Killer (NK) cells are part of the innate immune system involved in identifying and killing tumor cells or virally infected cells. NK receptors specific for HLA class I molecules called killer immunoglobulin-like receptors (KIRs), play a major role in the anti-tumor effect in AHSCT. NK cells express KIRs which mediate inhibition by recognizing specific HLA class I alleles. Missing expression of the KIR ligand on mismatched allogeneic cells can therefore enhance NK cell alloreactivity.(63–66) In HaploSCT, HLA mismatches can trigger donor versus recipient NK-cell alloreactivity without causing GVHD as they target hematopoietic cells sparing other body organs making them ideal in the HaploSCT setting.(67) This concept was first observed in the TCD HaploSCT setting, where patients with a KIR-mismatch had a lower incidence of relapse.(65) It also has been demonstrated in both animal and clinical studies that donor NK cells inhibit donor T cell proliferation and increase apoptosis, resulting in reduced severity and delayed progression of GVHD.(68–70) Besides mismatch of KIR ligand, several studies suggested a lower risk of relapse with donors who possess specific activating KIR genes such as KIR2DS1, KIR2DS2 or the KIR “B” haplotype.(69, 71–73) There is currently great interest in this evolving field to identify HaploSCT donors with a KIR-mismatch to possibly maximize the GVT effects also the potential benefit of using NK cells for adoptive cellular immunotherapy to prevent disease relapse, which has been used successfully in children with AML.(74) However, the major obstacle for NK cell therapy, especially in adult patients, is the relatively low number of NK cells that can be obtained from the donor, and much like with T cell therapy, in which a higher cell number proportional to the estimated number of tumor cells is needed, it is likely that the higher numbers of NK cells are needed for effective NK cell therapy.(75) In addition, multiple studies have shown that NK cells generated early post-transplant have an immature phenotype and a relative lack of function.(76–79) To address these problems and increase cytotoxic effect of NK cells, various *ex vivo* expansion methods have been developed and tested in pre-clinical and early clinical studies.(80–84) Choi et al. generated donor NK cells from the $CD3^+$ cell–depleted portion of the mobilized leukapheresis product and expanded using human IL-15 and -21. Expanded doses of NK cells up to 2×10^8/kg were then infused into 41 patients with hematologic malignancies underwent HaploSCT after reduced-intensity conditioning containing busulfan, fludarabine, and antithymocyte globulin. When compared to 31 historical control patients who had undergone HaploSCT using the same conditioning regimen without high-dose NK cell infusion, no significant difference in the cumulative incidences of major transplant outcomes. However, a reduction in leukemia progression was seen in patients who received a high NK cell dose and they found that post-transplantation NK cell infusion was an independent predictor for less leukemia progression.

(84) While these results are encouraging, they are not conclusive of a beneficial effect in reducing relapse or improving survival and further studies are needed. We are currently exploring infusion of *ex vivo* expanded NK cells using the mb-IL21 method developed at MD Anderson Cancer Center in patients treated with a HaploSCT in a phase I/II clinical trial evaluating the safety and efficacy of these NK cells to prevent disease relapse in patients with advanced myeloid malignancies when administered early post-transplant. Six patients were treated on study with escalating doses between 1×10^5 to 1×10^7/kg. All engrafted and no adverse effects of aGVHD was observed as compared with a recent published report in which aGVHD was a major complication after NK cell infusion especially in unrelated donors.(85)

CONCLUSIONS

The field of HaploSCT has significantly grown over the past several years. A significant advantage to use haploidentical donors is in the possibility to use cells obtained from the same donor and immune system, and represents a major opportunity to greatly enhance the anti-tumor effects of the graft and potentially improve immunologic reconstitution, key components for the success of allogeneic hematopoietic stem cell transplantation.

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Highlights

- Haploidentical transplantation can serve as platform for cellular therapy using additional donor cells.
- A number of cellular therapy products (NK cells, CAR T cells, etc.) are being investigated to enhance GVT effect and immunologic reconstitution.

Table 1

Current selective approaches to haploidentical transplantation

Approach	Rationale and advantages
Tregs and Tcons co-infusion(14–17)	• Prevent GVHD by Tregs while promoting immune reconstitution by addition of Tcons
Photodepletion of alloreactive T cells(18)	• *ex vivo* depletion of alloreactive T cells with TH9402 that accumulates in activated T cells
Selective αβ T cell depletion(19–21)	• Removing αβ T cells that are most responsive for aGVHD • Remaining γδ T cells are thought to have an innate immune like response capability without inducing GVHD.
High-dose post-transplantation cyclophosphamide(28–35)	• Eliminates early alloreactive T cells. • Rapid immune recovery with low rate of infectious complications • Acceptable rates of GVHD • Lower cost

Tregs – T regulatory cells, Tcons – conventional T cells, GVHD – graft-versus-host disease; aGVHD – acute graft-versus-host disease

Table 2

Post-transplant cellular therapy approaches aimed at decreasing disease relapse after haploidentical transplantation

Approach	Advantages and limitations
Unmodified DLI(37–40)	• Increase graft-versus-malignancy effect • Non-selective
Unmodified DLI with a “safety switch”(41–46)	• Increase graft-versus-malignancy effect • Control of GVHD, if develops • Non-selective
γδ donor T cell infusion(49–54, 57, 58, 86)	• Infusion of selected gamma-delta T cells • No GVHD potential • Unclear efficacy
T cells with chimeric antigen receptors (CARs)(60–62)	• T cells engineered to recognize specific antigens (e.g. CD19) provides graft-versus-malignancy effect for B-cell lymphoid malignancies (ALL, NHL) • Efficacy demonstrated in small series • No GVHD potential
Infusion of *ex vivo* expanded NK cells(80–85)	• Potential graft-versus-malignancy for myeloid malignancies • No GVHD • Efficacy unclear

DLI - donor lymphocyte infusion; GVHD – graft-versus-host disease; ALL – acute lymphoblastic leukemia; NHL – non-Hodgkin’s lymphoma; NK – natural killer cells; CAR – chimeric antigen receptor