

Overview of the progress on haploidentical hematopoietic transplantation

Nosha Farhadfar, William J Hogan

Nosha Farhadfar, William J Hogan, Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN 55905, United States

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Correspondence to: William J Hogan, MBBCh, MRCPI, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. hogan.william@mayo.edu
Telephone: +1-507-2842017
Fax: +1-507-2664972

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Abstract

Allogeneic hematopoietic stem cell transplant (HSCT) remains the only potentially curative option for variety of hematologic disorders. Lack of a suitable fully HLA-matched donor limits this option for many patients. Without a suitable related or unrelated HLA-matched donor,

umbilical cord blood and haploidentical family members provide a potential source of stem cells. Timely donor availability makes haploidentical donors an attractive alternative donor source. Initial attempts at haploidentical HSCT was associated with significantly increased mortality owing to high rates of graft rejection and severe graft-versus-host disease caused by major donor-recipient HLA-disparity. However, over the past decade, outcomes of haploidentical HSCT have improved significantly. Here, we review the advantages and challenges of haploidentical transplantation. We also discuss new developments to attempt to overcome the challenges to a successful haploidentical transplantation.

Key words: Haploidentical donor; Hematopoietic stem cell transplantation; Hematological malignancies; Transplant related mortality

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Core tip: Over the past decade, haploidentical donors have emerged as a viable alternate graft source for patients without a HLA-matched donor. Several strategies including graft manipulation, conditioning regimen optimization and better graft-versus-host disease control have significantly improved the outcomes of haploidentical hematopoietic stem cell transplant (HSCT). Here, we summarize some of the recent advances in the field of haploidentical HSCT in adults.

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INTRODUCTION

Hematopoietic stem-cell transplantation (HSCT) is

considered to be the only potentially curative therapy for several hematologic diseases. Most institutions currently consider a HLA-matched sibling as a preferred donor source, typically followed by either HLA-matched unrelated or an alternative graft source depending on the clinical scenario. The likelihood of having an HLA-matched sibling donor is approximately thirty percent after consideration of factors such as donor consent and health status. The probability of finding a suitable matched unrelated donor is strongly influenced by patient's ethnicity and can range from more than 75% for Caucasians to less than 20% for certain ethnic groups such as African Americans^[1]. In absence of related or unrelated HLA-matched donor, umbilical cord blood and haploidentical family members provide a potential source of graft. The use of haploidentical hematopoietic stem cell transplantation as an alternative graft source has been substantially increasing.

Utility of haploidentical related donors has a number of advantages including immediate donor availability for many patients facilitating a shorter interval to transplant. In addition, having a related donor makes post-transplant donor-derived cellular therapy more easily accessible. Challenges include major donor-recipient HLA-disparity which can cause delayed immune reconstitution, graft failure and severe graft vs host disease (GVHD) due to T-cell alloreactivity^[2,3]. This review highlights the major advances over the past decade to overcome the obstacles to successful haploidentical transplantation.

DONOR SELECTION

In contrast to unrelated donor transplant HSCT where finding the best HLA matched donor is the most important factor in determining transplant outcome, increasing HLA disparity in haploidentical matching does not have the same detrimental impact with dedicated techniques such as modification of post-transplant T cell reconstitution with cyclophosphamide. In 2010, Kasamon *et al*^[4] evaluated the impact of donor and recipient HLA in 185 patients who underwent un-manipulated bone marrow haploidentical transplant. Post-transplant cyclophosphamide was used as GVHD prophylaxis. In this study, the number of HLA-mismatches did not influence the rate of acute GVHD or disease free survival.

Donor characteristics that influence the outcome of haploidentical transplant were also investigated in a large study by Wang *et al*^[5] involving 1210 patients with hematologic diseases. Grafts consisted of G-CSF mobilized T-cell replete bone marrow and peripheral stem cells. Similar to the prior studies, the degree of HLA disparity did not influence the incidence of acute GVHD and treatment related mortality (TRM). Younger donor age (< 30 years) was associated with a lower incidence of acute GVHD compared to older donor age (> 30 years). Younger donor age and male gender were also associated with less TRM and better overall survival (OS). The benefit of male recipient gender was lost when maternal donors were excluded. There was a higher risk of grade II-IV acute

GVHD with maternal donors compared to paternal donors. In a male recipient, a maternal donor also correlated with a higher TRM rate and decreased OS. The impact of non-inherited maternal antigen (NIMA) disparities was evaluated in 264 patients. NIMA mismatched donors conferred a lower incidence of acute GVHD compared to non-inherited paternal antigen (NIPA) mismatched donors. Based on these results, authors concluded younger, male, NIMA-mismatched donor is a preferred donor in setting of T-cell replete haploidentical transplant. This study did not evaluate the influence of natural killer (NK) cell alloreactivity and donor CMV status. In contrast to Wang *et al*^[5], several trials demonstrated decreased risk of relapse and survival advantage with using maternal donors^[6]. A more potent anti-leukemic effect of maternal donor grafts has been attributed to the maternal immune system exposure to fetal antigens during pregnancy^[7].

Another factor influencing haploidentical transplant outcome is donor vs recipient NK cell alloreactivity. Tumor cells are able to escape T-cell adoptive immune response by down regulating cell surface MHC class I. NK cells are an important component of innate immunity and have MHC-unrestricted ability to target malignant cells. Cytotoxic activity of NK cells are mainly under the negative feedback control from inhibitory killer immunoglobulin-like receptors (KIRs) through binding to self HLA class I antigen. This phenomenon is known as "missing self"^[8-10]. KIR-KIR ligand mismatched in the donor-recipient direction lead to loss of the inhibitory feedback and activation of donor NK cells targeting recipient hematopoietic cells and leukemic cells. In contrast to allo-reactive T-lymphocytes, NK cells are thought to be capable of inducing graft vs leukemia (GVL) effect without promoting GVHD. In 2002, a study by the Perugia group demonstrated therapeutic efficacy of allo-reactive NK cells in 57 patients with acute myeloid leukemia (AML) following haploidentical transplant^[11]. Twenty out of 57 patients had KIR-ligand incompatibility in the graft vs host direction. The probability of OS at 5 years was markedly improved in patients with AML who had NK allo-reactive donors (60% vs 5%, $P = 0.0005$). Similar results were observed in the updated analysis of 112 patients with high risk AML who received T-cell depleted haploidentical transplants^[12]. Fifty one of 112 patients had NK cell allo-reactive donors. The conditioning regimen included TBI (8 Gy), fludarabine (40 mg/m² per day for 4 d), thiopeta (5 mg/kg per day for 2 d) and rabbit ATG. A significantly lower relapse rate (3% vs 47%, $P < 0.003$) and better EFS (67% vs 18%, $P = 0.02$) was observed in patients transplanted in any CR with NK allo-reactive donors compared to recipients of non-allo-reactive grafts. Although transplantation from NK allo-reactive donors improved survival in the entire cohort, subset analysis suggested that transplantation from NK allo-reactive donors did not decrease the incidence of relapse in patients transplanted at chemo-resistant relapse. There was no significant difference in incidence of acute GVHD between the two cohorts (10% vs 11%). These findings reinforced the theory that GVL activity by allo-reactive NK cells translated into prolonged OS. Subsequently, several

studies revealed a favorable impact of allo-reactive NK cells on transplant outcome in patients undergoing HLA-haploidentical transplant^[11,13-15]. An important role of donor-recipient KIR mismatch was also demonstrated after non-myeloablative T cell-replete haploidentical transplantation using post-transplant cyclophosphamide in a retrospective study involving 86 patients with high risk hematologic malignancies^[16]. On the contrary, a deleterious effect of KIR mismatches was seen in the earlier studies^[17,18]. Due to ongoing controversy, currently the KIR testing is not considered mandatory for donor selection in haploidentical transplant setting.

HAPLOIDENTICAL STEM CELL TRANSPLANT STRATEGIES

T-cell depletion

The first successful haploidentical transplants were done in the 1980s in children with severe combined immunodeficiency syndrome (SCIDS) using T-cell depleted bone marrow grafts. T-lymphocyte depletion in this setting mitigated GVHD associated with crossing a major HLA-barrier without compromising engraftment^[19]. Subsequently, this approach was implemented successfully in several studies of patients with SCIDS. In contrast to SCIDS, haploidentical transplantation was less successful in the setting of acute leukemia owing to a high rate of graft failure. Increased risk of graft failure was attributed to host derived T-lymphocytes that survived the conditioning regimen^[20-22]. A decade later, it was shown in preclinical studies (murine models) that infusion of a large number of donor hematopoietic stem cells can overcome the MHC barrier and promote engraftment^[23]. In 1993, cell dose escalation approach was tested in 36 patients with acute leukemia following myeloablative total body irradiation (TBI) based preparative regimen. Mega doses of stem cells (on average $> 10 \times 10^6$ CD34⁺ cells/kg body weight) were obtained by supplementing T cell-depleted bone marrow transplants with granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells. Using this approach, nearly 80% of patients achieved primary engraftment. The sole GVHD prophylaxis consisted of T-cell depletion of the graft. Only 18% of the patients developed grade II-IV acute GVHD^[24,25]. Subsequently, several modifications were introduced to optimize the T-cell depletion of the graft including positive immunoselection of the CD34⁺ cells using the Cephate system in 1995 and Clinimacs device in 1999^[13,26]. In addition, to reduce the toxicity associated with the myeloablative TBI based conditioning regimen, fludarabine was substituted for cyclophosphamide in 1995^[27]. After optimizing the conditioning regimen and graft processing, Aversa *et al.*^[28] investigated haploidentical transplantation in 284 patients with acute leukemia. Ninety five percent of the patients achieved engraftment with minimal GVHD. The relapse rate was 17% in acute myeloid leukemia (AML) and 27% in acute lymphoblastic leukemia (ALL) patients transplanted in any CR. Incidence of TRM was 40% mainly

due to opportunistic infections. Seventeen year DFS was 30% in ALL and 43% in AML patients transplanted in any CR. Among the long term survivors, chronic GVHD was not observed in any patients^[28].

The major disadvantages of using T-cell depleted grafts are the high rate of relapse and life-threatening infections post-transplant^[29]. Due to poor thymic function in adults, post- allogeneic transplant T-cell immune recovery depends on peripheral expansion of donor T-lymphocytes. In a T-cell depleted graft, passive transfer of T-lymphocytes is minimal leading to profound delay in immune recovery. To overcome these obstacles several strategies have evolved over the past decade including selective T-cell depletion, adoptive transfer of donor T-cells post-transplant, and T-regulatory cell (T-reg) add backs.

Selective T cell depletion

The principle behind adoptive T-cell therapy is to eliminate donor allo-reactive T cells responsible for GVHD while sparing other immune cells, which facilitate immune reconstitution. To selectively deplete allo-reactive donor T-cells, *ex vivo* T-cells are activated against host antigen presenting cells. Activated T-cells are removed using several methods including immunotoxin, immune-magnetic selection and photodynamic purging^[30-32].

Another innovative approach is to selectively remove T-cells responsible for GVHD (TCR alpha-beta) while sparing gamma-delta T-cells ($\gamma\delta$ T-cells). Gamma-delta T-cells account for 1% to 10% of peripheral T-cells. Based on *in-vitro* studies, human T lymphocytes which express $\gamma\delta$ T-cells receptor have MHC-unrestricted innate cytotoxic activity against tumor cells^[33,34]. In a recent study, Lang *et al.*^[35] retrospectively evaluated the immune recovery after TCR $\alpha\beta$ /CD19-depleted haploidentical HSCT in 41 pediatric patients with acute leukemia, myelodysplasia and nonmalignant disease. Primary engraftment was seen in 88% of the patients. The incidence of grade II and grade III-IV acute GVHD was 10% and 15% respectively. At one year follow up, the event free survival (EFS) of patients with acute leukemia or myelodysplasia transplanted in CR1-CR3 was 100%. One year EFS of patients with subsequent HSCT (CR2-CR6) or with active disease was 29% and 11%, respectively. The use of TCR $\alpha\beta$ /CD19-depleted stem cells substantially accelerated immune recovery. In comparison to CD34⁺ selected grafts (historic control), patients achieved a higher CD3⁺ at days +30 and +90, CD34⁺ at day +30 and CD56⁺ at day +14. The Italian group also reported similar results in 16 adults with high risk acute leukemia after TCR $\alpha\beta$ /CD19-depleted haploidentical HSCT.

A more recent strategy to separate GVHD and the GVL effect involves selectively depleting naïve T cells identified by CD45RA⁺ expression^[36,37]. Naïve T-cells are shown to be the most allo-reactive amongst the T-cell subsets. *Ex vivo* depletion of CD45RA⁺ T-cells and adoptive transfer of CD45RA-memory T cells hasten the immune reconstitution post-transplant, enhances the GVL effect while abrogating GVHD. This strategy was recently evaluated in a study of

17 adults with high risk hematologic malignancies (16 AML and 1 myelodysplasia) with KIR receptor-ligand mismatched haploidentical donor^[38]. The conditioning regimen included total lymphoid irradiation (8 Gy), fludarabine (150 mg/m²), cyclophosphamide (60 mg/kg), thiotepa (10 mg/kg) and melphalan (140 mg/m²). Patients received a CD34⁺ selected stem cell graft on day 0 followed by an infusion of CD45RA-depleted stem cells on day +1. NK cell infusion was given on day +6. Post-transplant GVHD prophylaxis included sirolimus and mycophenolate mofetil (MMF). All patients achieved primary engraftment. Neutrophil and platelet engraftment was rapidly achieved at median day +11 and +17 respectively. Acute GVHD was not seen in any of the patients. There was no infection related mortality. A phase II study of selective depletion of CD45RA⁺ T Cells from allogeneic peripheral blood stem cell grafts from HLA-matched related and unrelated donors for prevention of GVHD is currently under investigation^[39].

SELECTIVE T-CELL ADD BACK

Con-infusion of donor-derived regulatory T-cells (Tregs) with conventional T-cells (Tcons) is another method to manipulate the T-cell depleted graft to improve haploidentical transplant outcome. In pre-clinical studies of bone marrow transplantation, infusion of donor-type CD4⁺CD25⁺Tregs abrogated GVHD without compromising the cytotoxic ability of T-cons against tumor cells^[40,41]. A first in human study by Di Ianni *et al.*^[42] investigated infusion of Tregs, followed by Tcons in 28 patients with high risk hematologic malignancies who underwent haploidentical transplantation. After TBI containing conditioning regimens, patients received infusion of donor derived Tregs (2 × 10⁶ Tregs) on day-4. CD34⁺ stem cells were infused on day 0 followed by Tcons. Two out of five patients who received 2 × 10⁶ Tcons/kg developed acute GVHD which led to decreasing the cell dose of Tcons to 1 × 10⁶ cells/kg. Chronic GVHD was not observed in any patients. All patients achieved primary engraftment. Compared to conventional mismatched HSCT, pathogen specific CD4⁺ and CD8⁺ were detected earlier in the study cohort (as early as 2 mo vs 9-12 mo). CMV-related death, a major cause of mortality in original T-cell depleted HSCT, was not observed. At median 1 year follow up, 46% of the patients were disease free. Subsequently, Martelli *et al.*^[43] evaluated the impact of Tregs - Tcons infusion in reducing post-transplant relapse risk in 43 adults with acute leukemia. This method significantly reduced the risk of relapse and ameliorated GVHD. Grade 2 or more acute GVHD was seen in 15% of patients. At median follow up of 46 mo, only two patients relapsed resulting in an incidence of relapse that was significantly lower than historical controls. Despite promising results of T-cell depleted haploidentical transplant, this approach is costly, technically demanding and labor intensive which limits its application to highly experienced centers.

T CELL REPLETE GRAFT

Earlier attempts at using un-manipulated haploidentical

transplant were associated with an unacceptably high rate of GVHD related mortality due to donor T-cell alloreactivity. To overcome this obstacle, several strategies have evolved over the past decade including G-CSF primed graft^[44,45] and more recently post-transplant high dose cyclophosphamide.

HIGH-DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating chemotherapeutic agent which has been used for many years as a component of conditioning regimens. Preclinical trials in the early 1970s revealed short course of cyclophosphamide after bone marrow transplantation can target allo-reactive T-cells and reduce the risk of GVHD^[46-48]. In contrast to calcineurin inhibitors, cyclophosphamide is capable of inducing T-lymphocyte apoptosis^[49]. Hematopoietic stem cells are resistant to high dose cyclophosphamide due to expression of high levels of aldehyde dehydrogenase^[50]. Original clinical trials exploring cyclophosphamide efficacy as the post-transplant GVHD prophylactic agent were performed in the haploidentical transplant setting. In 2002, O'Donnell *et al.*^[51] evaluated the transplant outcome of 13 patients with high risk hematologic malignancies who received T-cell replete haploidentical transplant after a non-myeloablative conditioning regimen with TBI and fludarabine. GVHD prophylaxis included post-transplant cyclophosphamide 50 mg/kg on day +3 in combination with MMF and tacrolimus. Due to high rate of graft failure (2 out of 3 patients) the protocol was amended to add cyclophosphamide 14.5 mg/kg to the conditioning regimen. Subsequently, 8 of 10 patients obtained primary donor cell engraftment. After 99 d follow up, 6 patients (46%) developed acute GVHD. Six months incidence of DFS was 50%. This study demonstrated the feasibility and possibility of rapid engraftment in a non-myeloablative haploidentical transplant setting using post-transplant cyclophosphamide.

Subsequently, Luznik *et al.*^[52] compared safety and efficacy of administration of cyclophosphamide on day +3 and +4 rather than only on day +3 among 68 patients with hematologic malignancies after non-myeloablative haploidentical bone marrow transplant. Primary engraftment was achieved in 87% of the patients. Notably, a very low incidence of grade III acute GVHD (6%) with no grade IV acute GVHD was observed at one year follow up. The only difference between the two cohorts was a trend toward a lower incidence of chronic GVHD after two doses of post-transplant cyclophosphamide (5% vs 25%, *P* = 0.05). The 2-year OS and EFS rates were 36% and 26%, respectively. A major contributor to the low OS rate was a high incidence of relapse (58% at 2 years).

A similar outcome was observed in a large phase II study of high dose post-transplantation cyclophosphamide as GVHD prophylaxis after non-myeloablative HLA-haploidentical bone marrow transplantation in 210 patients with hematologic malignancies^[53]. Sustained donor cell

engraftment was obtained in 87% of the patients. The cumulative incidences of grades II-IV acute GVHD was 27%. At 5 year follow up, OS and EFS were 35% and 27%, respectively. As seen in the prior studies, relapse was a major cause of mortality. Five year cumulative incidence of relapse was 55%.

In parallel multicenter phase 2 trials, BMT CTN 0603 and BMT CTN 0604, patients with acute leukemia or lymphoma underwent reduced intensity bone marrow haploidentical transplantation (0603) or double cord blood transplant (0604)^[54]. The conditioning regimens contained 200 Gy TBI in addition to fludarabine and cyclophosphamide. In CTN 0603, the GVHD prophylaxis consisted of post-haploidentical transplant cyclophosphamide 50 mg/kg on day +3 and +4 followed by tacrolimus and MMF. In CTN 0604, GVHD prophylaxis included MMF and cyclosporine after double umbilical cord transplant. Among haploidentical transplant recipients, 100-d incidence of grade II-IV acute GVHD and 1-year incidence of chronic GVHD were 32% and 13%, respectively. After double cord transplant 100-d incidence of grade II-IV acute GVHD and 1-year incidence of chronic GVHD were 40% and 24%, respectively. One year cumulative incidence of relapse after haploidentical and double umbilical cord transplant were 45% and 31%, respectively. The OS and EFS rates were 62% and 48% respectively after the haploidentical transplants. Similar OS (54%) and EFS (46%) were seen after double cord transplant. The authors concluded that both RIC haploidentical and double umbilical cord HSCT are valid options in patients with hematologic malignancy. Currently a multicenter randomized phase III trial (BMT CTN 1101) is investigating the effectiveness of haploidentical and double umbilical transplant in patients with leukemia or lymphoma^[55].

Despite relatively low rates of GVHD with non-myeloablative haploidentical transplant, a high incidence of relapse has remained the main challenge in high risk hematologic malignancies. To address this obstacle, use of more intense (myeloablative) preparative regimens and peripheral blood stem cell graft was explored. In a prospective study by Solomon *et al*^[56], 20 adults with high risk (relapsed/refractory) hematologic malignancies were treated with myeloablative conditioning followed by peripheral blood derived haploidentical transplant. The conditioning regimen consisted of fludarabine 30 mg/m² for 4 d, intravenous busulfan 130 mg/m² per day for 4 d, and Cy 14.5 mg/kg per day for 2 d. GVHD prophylaxis included high dose cyclophosphamide on day +3 and +4 followed by tacrolimus and MMF. All patients achieved primary engraftment. One year cumulative incidence of grade II-IV acute GVHD and chronic GVHD were 10% and 5%, respectively. At median follow up of 20 mo, DFS and OS were 69% and 50%, respectively. The cumulative incidence of relapse was approximately 40%. The major drawback of this trial was high incidence of hemorrhagic cystitis due to BK virus infection. This adverse event was observed in two third of the patients. This was attributed to the combination of high dose busulfan and cyclophosphamide. Association

of BK induced hemorrhagic cystitis and high dose busulfan in setting of mismatched HSCT was reported previously in several studies^[57]. To alleviate this problem, the conditioning regimen was changed to TBI-based myeloablative regimen in the subsequent study^[58]. In this phase II prospective trial, 30 patients underwent peripheral stem cell haploidentical transplant using fludarabine 25 mg/m² per day for three days and 1200 cGy TBI as the preparative regimen. All patients achieved primary engraftment. Median time to neutrophil and platelet engraftment was 16 d and 25 d, respectively. Incidence of grade II-IV acute GVHD was 23%, whereas moderate to severe chronic GVHD occurred in 22% of patients. In the entire cohort, 2-year NRM and OS were 3% and 78%, respectively. Among patients with low or intermediate risk disease NRM and OS were 0% and 100%, respectively. Relapse rate was significantly reduced in comparison to patients treated at the same center with matched related transplant. Incidence of post-transplant BK virus associated hemorrhagic cystitis was significantly reduced after TBI-based regimen compared to the busulfan-based conditioning regimen (30% vs 75%, $P = 0.005$).

Similar results were observed in several other trials of myeloablative haploidentical transplant^[59,60]. Raiola *et al*^[59] confirmed the low rate of GVHD and encouraging rate of DFS and OS in 50 patients with high risk hematologic disease (23 patients in CR and 27 patients with active disease) after un-manipulated myeloablative haploidentical transplant^[59]. GVHD prophylaxis contained post-transplant cyclophosphamide on day +3 and +5 followed by cyclosporine and MMF. In the entire cohort, 12% of the patients developed grade II-III acute GVHD. Moderate chronic GVHD was seen in 10% of patients. The actuarial 22-mo DFS for patients transplanted in CR and patients with active disease was 68% and 37%, respectively^[61]. The overall risk of relapse after myeloablative haploidentical HSCT was approximately 40% which compares favorably with that reported for non-myeloablative haploidentical HSCT. Therefore, despite the lack of randomized trials, myeloablative haploidentical transplant may be a reasonable option in younger patients with high risk hematologic malignancy in absence of timely access to a conventional donor.

Haploidentical related donor vs matched related sibling or matched unrelated donor (Table 1)

Encouraging results of haploidentical transplant compared to matched related or matched unrelated transplant has been suggested by several non-randomized studies. In 2015, a large retrospective study compared the transplant outcome of 868 patients with acute leukemia after haploidentical transplant and 9815 patients with HLA-matched sibling donor (MRD)^[62]. However, leukemia free survival was significantly longer after matched sibling donor transplant compared to haploidentical transplant (T-cell depleted or T-cell replete grafts). Haploidentical transplant was associated with higher TRM. The probability of relapse was not significantly different between the two

Table 1 Unmanipulated haploidentical hematopoietic stem cell transplant *vs* matched related and matched unrelated hematopoietic stem cell transplant

Ref.	Disease	Conditioning regimen (n)	Graft type (n)	GVHD prophylaxis	Neutrophil engraftment	Grade II-IV acute GVHD	Chronic GVHD	Relapse rate	DFS	OS
Bashey <i>et al</i> ^[69] 2013 n = 271	Acute leukemia/ CML/ myeloma/ lymphoma/ MDS	RIC (102) MA (169)	MRD (117) MUD (101) Haplo (53)	CNI based CNI based CNI + MMF + PT-Cy	NR	6 mo 27% 39% 30% (P = NS)	2 yr 54% 54% 38% (P < 0.05)	2 yr 34% 34% 33% (P = NS)	2 yr 53% 52% 60% (P = NS)	2 yr 76% 67% 64% (P = NS)
Di Stasi <i>et al</i> ^[70] 2014 n = 227	AML/MDS	RIC (227)	MRD (81) MUD (108) Haplo (32)	CNI + MTX CNI + MTX + ATG CNI + MMF + PT-Cy	30 d 99% 96% 97% (P = 0.44)	100 d 24% 19% 26% (P = 0.68)	3 yr 46% 42% 24% (P = 0.52)	1 yr 28% 23% 33% (P = 0.75)	3 yr 36% 27% 30% (P = 0.12)	NR
Luo <i>et al</i> ^[71] 2014 n = 305	Acute leukemia/ lymphoma/ MDS	MA + ATG (305)	MRD (90) MUD (116) Haplo (99)	CNI + MMF + MTX CNI + MMF + MTX CNI + MMF + MTX	15 d 97% 97% 78% (P < 0.001)	3 mo 15.60% 39% 42% (P < 0.0001)	2 yr 24% 41% 41% (P = NS)	5 yr 34% 21% 14% Haplo <i>vs</i> MRD P = 0.008 Haplo <i>vs</i> MUD P = 0.17	5 yr 63% 58% 58% (P = 0.57)	5 yr 77% 63% 60.80% Haplo <i>vs</i> MRD P = 0.026 Haplo <i>vs</i> MUD P = 0.38
Ciurea <i>et al</i> ^[63] 2015 n = 2174	AML	RIC (825) MA (1349)	MUD (737) Haplo (88) MUD (1245) Haplo (104)	CNI + MMF or MTX CNI + MMF + PT-Cy CNI + MMF or MTX CNI + MMF + PT-Cy	30 d 93% 96% (P = 0.25) 90% 96% (P = 0.02)	3 mo 19% 28% (P = 0.05) 16% 33% (P = 0.001)	3 yr 34% 52% (P = 0.002) 30% 53% (P < 0.0001)	3 yr 58% 42% (P = 0.006) 44% 39% (P = 0.37) (P = 0.14)	3 yr 9% 23% (P = 0.0001) 14% 20% (P = 0.14)	3 yr 46% 44% (P = 0.71) 45% 50% (P = 0.38)
Wang <i>et al</i> ^[64] 2015 n = 450	AML in CR1	MA (ATG in haplo cohort)	MRD (219) Haplo (231)	CNI + MMF + MTX CNI + MMF + MTX	NE engraftment 2 d longer after MRD P = 0.004	100 d 36% 13% (P < 0.001)	1 yr 42% 15% (P < 0.001)	3 yr 15% 15% (P = 0.98)	3 yr 74% 78% (P = 0.34)	3 yr 79% 82% (P = 0.36)
Ghosh <i>et al</i> ^[67] 2016 n = 987	Lymphoma	RIC (987)	MRD (807) Haplo (180)	CNI based PT-Cy ± CNI	28 d 95% 97% (P = 0.31)	100 d 25% 27% -0.84 (P < 0.001)	1 yr 45% 12% (P < 0.001)	3 yr 37% 40% (P = 0.51)	3 yr 48% 48% (P = 0.98)	3 yr 62% 61% (P = 0.82)
Kanate <i>et al</i> ^[72] 2016 n = 917	Lymphoma	RIC (917)	MUD + ATG (241) MUD (491) Haplo (185)	CNI based CNI based PT-Cy based	28 d 97% 97% 94% (P = 0.32)	100 d 17% 12% 8% (P = 0.44)	1 yr 33% 51% 13% (P < 0.001)	3 yr 36% 28% 36% (P = 0.07)	3 yr 38% 49% 47% (P = 0.02)	3 yr 50% 62% 60% (P = 0.2)

AML: Acute myeloid leukemia; ATG: Anti-thymocyte globulin; CR: Complete remission; CNI: Calcineurin inhibitor; DFS: Disease free survival; GVHD: Graft *vs* host disease; Haplo: Haploidentical; MMF: Mycophenolate mofetil; MTX: Methotrexate; RIC: Reduced intensity conditioning; MA: Myeloablative; MDS: Myelodysplasia; MUD: Matched unrelated donor; MRD: Matched related donor; NE: Neutrophil; NR: Not reported; NS: Not significant; OS: Overall survival.

cohorts. Therefore, the authors concluded haploidentical GVL effect is similar to MRD.

Ciurea *et al*^[63] also retrospectively compared the transplant outcome of patients with AML after haploidentical transplant ($n = 192$) using post-transplant cyclophosphamide and MUD ($n = 1982$). In the haploidentical cohort, 104 patients received MA and 88 had reduced intensity conditioning. In MUD cohort, 1245 patients (63%) received MA and 737 (37%) received RIC regimens. Compared to MUD, thirty day neutrophil engraftment was lower after haploidentical transplant in

MA setting (97% *vs* 90%, $P = 0.02$). In RIC setting, day 30 neutrophil engraftment rate was similar between the two cohorts (96% and 93%, $P = 0.25$). Acute and chronic GVHD was notably lower after haploidentical transplant. In the MA setting, three month incidence of acute GVHD (16% *vs* 33%, $P < 0.0001$) and 3-year incidence of chronic GVHD (30% *vs* 53%, $P < 0.0001$) were significantly lower with haploidentical in comparison to MUD transplant. Similar results were obtained in RIC setting. A lower rate of GVHD with haploidentical transplant was attributed to the use of bone marrow as a graft source and the use

of post-transplant cyclophosphamide. Among patients receiving myeloablative and RIC regimens, three-year DFS and OS were comparable in haploidentical and MUD transplant.

Transplant results of matched sibling donor (MSD) transplant and T-cell replete haploidentical transplant was also evaluated by Wang *et al.*^[64]. In this prospective, multicenter, nonrandomized trial, 450 patients with acute leukemia in CR1 underwent MSD ($n = 219$) or haploidentical ($n = 231$) transplant. Cyclosporine, MMF, and low dose methotrexate was used as GVHD prophylaxis regimen in both groups. All individuals in both cohorts achieved donor-cell engraftment. The median time to achieve neutrophil engraftment was 2 d longer after MSD transplant. The 100-d cumulative incidence of grade II-IV acute GVHD after haploidentical and MSD transplant was 36% and 13% ($P = 0.001$), respectively. The incidence of chronic GVHD was significantly higher after haploidentical transplant compared to MSD (42% vs 15%, $P < 0.001$). However, the rate of GVHD related death was similar in both groups. Among haploidentical and MSD recipients, the 3 year probability of DFS (74% vs 78%, $P = 0.34$) and OS (79% vs 82%, $P = 0.36$) were comparable. There was no difference in 3-year cumulative incidence of relapse between the two cohorts (15% vs 15%, $P = 0.98$). Lower incidence of GVHD after MSD was attributed to combination of cyclosporine, methotrexate and MMF for GVHD prophylaxis. Prior studies also reported significantly lower rate of GVHD using this combination in recipients of MSD transplant^[65,66].

More recently Ghosh *et al.*^[67] performed a registry analysis comparing outcomes of 987 patients with lymphoma following reduced intensity haploidentical HSCT ($n = 180$) with MSD HSCT ($n = 807$). GVHD prophylaxis for the haploidentical group consisted of post-transplant cyclophosphamide with or without calcineurin inhibitor and MMF. GVHD prophylaxis for the MSD group contained calcineurin inhibitor based approaches. The cumulative incidence of grade II-IV acute GVHD was similar between the two cohorts (27% in haploidentical cohort vs 25% in MSD cohort, $P = 0.84$). Cumulative incidence of chronic GVHD was significantly lower with haploidentical HSCT (12% vs 45%, $P < 0.001$). Chronic GVHD was the main cause of death in 5 patients in MSD cohort. There was no significant difference in the three-year cumulative incidence of relapse (37% in haploidentical vs 40% in MSD, $P = 0.51$), DFS (48% vs 48%, $P = 0.96$) and OS (61% vs 62%, $P = 0.82$). Therefore, based on this retrospective registry study in patients with lymphoma, RIC haploidentical HSCT using post-transplant cyclophosphamide provides comparable survival outcome to MSD HSCT with significantly lower risk of chronic GVHD.

CONCLUSION

HSCT is the only curative option for a large number of hematologic diseases. A minority of patients (30%) have a suitable HLA-identical sibling donor. For patients who lack MSD, MUD HSCT is frequently the preferred graft source.

However, the presence of a suitably matched unrelated donor depends on factors such as the ethnicity of the patient, with a likelihood of finding an acceptably matched unrelated donor less than 20% in certain minorities compared to approximately 80% in Caucasians. A major disadvantage of MUD transplant is the prolonged time from patient referral to donor identification and collection of stem cells. Delay in the process of unrelated donor search due to logistical issues may increase the risk of disease progression or relapse^[68]. Immediate availability of a haploidentical donor makes this approach an attractive treatment option for patients who lack an HLA-identical MSD or those for whom a MUD cannot be found in a timely manner. The field of haploidentical HSCT has matured significantly over the past two decades. In earlier studies of haploidentical HSCT, HLA-incompatibility barrier resulted in unacceptably high rate of GVHD and graft rejection leading to inferior OS. While effective T-cell depletion followed by infusion of mega doses of highly purified stem cells permitted high engraftment rates and reduced incidence of GVHD, higher risk of relapse and delay in immune reconstitution remained a significant obstacle. Newer methods of graft manipulation including adoptive T-cell immunotherapy and selective T-cell depletion have been shown to hasten immune recovery and reduce the risk of relapse. Despite the promising results, these approaches are costly and labor intensive, hence may not be globally available. In recent years, use of post-transplantation cyclophosphamide for GVHD prophylaxis after T-cell replete haploidentical HSCT has yielded encouraging results in adults. In several non-randomized studies, survival outcomes following haploidentical HSCT with post-transplant cyclophosphamide have been comparable to MSD or MUD transplant. Ultimately, a prospective randomized controlled trial such as BMT CTN 1101 is needed to determine the optimal approach to haploidentical transplant.

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