Haploidentical stem cell transplantation is an attractive form of transplantation because of the immediate donor availability, ease of stem cell procurement, and the possibility to further collect donor cells for cellular therapy. Historically, maintaining T cells in the graft has been associated with very high rates of graft-versus-host-disease (GVHD), whereas T cell–depleted haploidentical transplantation has been limited by a higher incidence of graft rejection and nonrelapse mortality related to infectious complications as a result of delayed immune reconstitution posttransplantation. Recent approaches have attempted to eliminate the alloreactive T cells to prevent GVHD posttransplantation. Administration of high-dose cyclophosphamide early posttransplantation in combination with tacrolimus and mycophenolate mofetil has produced engraftment and GVHD rates similar to HLA-matched sibling transplants, suggesting that the most important barriers against successful haploidentical transplantation can be overcome. Future directions should focus on optimizing conditioning regimens for different diseases and prevention of disease relapse posttransplantation.


**KEY WORDS:** Haploidentical stem cell transplantation, T cell depletion, T cell–replete graft, High-dose posttransplantation cyclophosphamide

**INTRODUCTION**

Hematopoietic stem cell transplantation is the treatment of choice for patients with high-risk or advanced hematologic malignancies [1]. Approximately 70% of patients do not have a matched related donor available for transplantation [2]. For these patients, a matched unrelated donor (MUD) transplant produces similar transplant outcomes [3,4]. However, a matched donor can be identified for only 50% to 60% of patients and the donor search and acquisition process requires a median of 4 months. Patients are most likely to have an HLA match among individuals from their own racial and ethnic group. Therefore, the chance of finding such donors varies widely among different major ethnicities [5]. A recent review of all 2117 MUD transplant recipients performed at the University of Texas M.D. Anderson Cancer Center in the past 25 years revealed that 1677 patients (79.2%) were Caucasian, 271 patients (12.8%) were Hispanics, 109 (5%) were African-Americans, and 33 (1.5%) were Asians. A similar racial distribution was noted for patients who received a 9 of 10 MUD at our institution during the same period of time (N = 122) (79.1% Caucasians, 12.2% Hispanics, 6.5% African-Americans, 2.4% Asians). Identification of a MUD is even more challenging for mixed-race individuals. Interracial/interethnic marriages are at an all-time high [6], and recent data from the 2010 U.S. Census Bureau indicates that approximately 3% of the U.S. population identifies itself as mixed race, and the percentage of mixed-race individuals has increased by approximately 50% compared with the year 2000 [7].

Haploidentical stem cell transplantation (HaploSCT) is an alternative treatment usually option for such patients. Parents, children, and half siblings are potential haploidentical donors, so these donors are readily available for most patients. The use of haploidentical-related donors for transplantation has the advantage of almost universal and immediate availability of donor stem cells for transplantation and maintains the possibility to further collect donor cells for cellular therapy, if needed. Here, we review the past experience and future directions in haploidentical transplantation.

Haploidentical transplantations initially performed in the late 1970s were associated with severe graft-versus-host disease (GVHD) and poor outcomes [8,9]. Of 105 patients who underwent HaploSCT without T cell depletion at the Fred Hutchinson Cancer Center, almost 20% had graft failure and 70%
developed GVHD [10]. Powles et al. [11] described a syndrome of multiorgan failure (manifested as seizure, pulmonary edema, intravascular hemolysis, and renal failure) leading to death after infusion of unmanipulated haploidentical stem cells, likely related to alloreactive T cells.

**T CELL–DEPLETED HAPLOIDENTICAL TRANSPLANTATION**

Depletion of T cells effectively prevents GVHD in animal models [12-14]. Human trials using T cell–depleted (TCD) bone marrow transplantation has been extensively evaluated [15-17]. Ex vivo TCD HaploSCT was first performed successfully in an acute leukemic infant [18]. This method proved useful in preventing GVHD and was effectively used in patients with severe combined immune deficiency who could not build a significant host immune response against the transplanted donor cells. Unfortunately, extensive T cell depletion of the bone marrow (BM) graft results in an increased risk of graft rejection, occurring in up to 50% of cases [19]. The risk of graft rejection could be reduced by intensifying the conditioning regimen [20,21], in vivo T cell depletion with antibodies [22], and increasing the BM inoculum (number of CD34+ cells infused) [12].

Aversa et al. [23] reported on the successful use of “mega-dose” CD34+ cells TCD HaploSCT using granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs) and positive selection of CD34+ cells as a T cell–depletion method, obtaining >10 × 10^6 CD34+ cells/kg in the final product. The number of T cells in the graft was reduced significantly by 3 to 3.5 logs, and the conditioning regimen was intensified with the addition of thiopeta to total body radiation and cyclophosphamide. The Perugia group achieved primary engraftment in 96 of 104 patients with a revised protocol using positively selected CD34+ PBSCs [24]. Although GVHD rates were low and relapse incidence was only 16% among those transplanted in remission, the nonrelapse mortality (NRM) rate approached 40% primarily because of opportunistic infections, likely related to the delayed immunologic reconstitution. Furthermore, a survey by the European Blood and Marrow Transplant Group reported an NRM approaching 50% at 2 years among 266 patients with high-risk acute leukemia who underwent fully HaploSCT with TCD PBSCs [25]. More than one-half of these deaths were because of infections, again highlighting the need for new approaches to decrease treatment-related mortality and improve the immunologic reconstitution after HaploSCT.

Positive selection of CD34+ cells depletes T cells as well as natural killer cells (NK cells), which could be exploited to improve efficacy and safety of HaploSCT. “Alloreactive” NK cells may help eradicate the remaining leukemia cells after the conditioning regimen and clear residual recipient lymphocytes and antigen-presenting cells (APCs), potentially preventing graft rejection and GVHD [26]. Furthermore, NK cells are an important part of the antiviral immunity [27], potentially adding to the fight against viral infections, which are the most common cause of infectious complications post-HaploSCT [28]. Consequently, new regimens involving negative depletion of T cells by immunomagnetic beads were developed [29,30]. Bethge et al. [31] later adapted this approach to adults using negative depletion of CD3- and CD19-positive cells and reduced-intensity conditioning (RIC). Twenty-nine patients with hematologic malignancies underwent HaploSCT with CD3/CD19-depleted peripheral blood grafts after an RIC including fludarabine, melphalan, and thiopeta. Median CD34 cell content of the grafts was considerably less than that given by the Perugia group after CD34-positive selection (7.6 × 10^6/kg versus 13.8 × 10^6/kg). All but 1 patient engrafted with full donor chimerism. Although the regimen was well tolerated, NRM in the first 100 days approached 20%. Incidence of grade II-IV GVHD was 48%. Twenty patients died: 12 because of relapse, 7 because of infections, and 1 because of GVHD. One-year overall survival (OS) remained at 35%. Although this approach demonstrated that megadoses of stem cells higher than 10 × 10^6/kg and full myeloablative conditioning were not required for successful engraftment in HaploSCT, it was complicated with higher relapse rates, possibly because of reduced intensity of the conditioning and persistently delayed immune reconstitution.

**IMPROVEMENTS IN EX VIVO T CELL–DEPLETED HAPLOIDENTICAL TRANSPLANTATION**

**Infusion of Regulatory T Cells (Tregs)**

Tregs suppress immune reactivity that maintains tolerance to self-antigens, and depletion of Tregs results in a spectrum of autoimmune diseases [32-35]. In murine models of HLA-mismatched transplantation, Tregs suppressed lethal GVHD [36] and favored posttransplantation immune reconstitution when co-infused with conventional T cells [37]. The Perugia group recently reported on a protocol using infusion of donor Tregs following a T cell–depleted haploidential transplant as a means to further reduce the risk of GVHD [38]. Donor Tregs were selected and infused after a myeloablative conditioning regimen followed, 4 days later, by infusion of TCD mega-dose PBSCs and donor conventional T cells. No posttransplantation immunosuppression was administered. Of 28 patients treated, 26 achieved primary sustained
engraftment, whereas 2 patients developed acute GVHD (aGVHD). No patient developed chronic GVHD (cGVHD). A wide T cell repertoire developed rapidly. Thirteen patients died, 8 because of opportunistic infections. At a median follow-up of 12 months, 12 patients were alive and disease-free. This study demonstrated the feasibility of adoptive immunotherapy with Tregs and their potential application to modify GVHD and enhance immune reconstitution after hematopoietic stem cell transplantation. However, the high treatment-related mortality of 50% in this group of patients remains a concern [38].

**Infusion of Selectively Allodepleted T Cells**

Although the use of Tregs with conventional T cells in this TCD transplant model may improve early immune reconstitution, Tregs may also have an inhibitory effect on desirable bystander T cell responses [39,40]. Alternatively, infusion of T cells depleted of cells alloreactive to recipient antigens may improve immune reconstitution while preserving graft-versus-tumor effect, without causing GVHD. Currently available alloreactive T cell depletion methods rely on cocultures with recipients’ cells to activate the alloreactive cells, followed by either targeting the surface activation markers or using photoactive dyes that are preferentially retained in activated T cells [41].

Amrolia et al. [42] investigated the use of an anti-CD25 immunotoxin to deplete alloreactive lymphocytes in TCD HaploSCT patients. This group infused $10^3$-$10^5$ cells/kg allodepleted lymphocytes on 30, 60, and 90 days posttransplantation in 16 patients (median age 9 years) [42]. One patient developed graft failure and subsequently had an autologous reconstitution. Two patients developed grade II and IV aGVHD. Patients who received higher doses of lymphocytes exhibited more rapid recovery of T cells. A higher polyclonal distribution of VÎ³ receptor gene was noted at 4 months after transplantation compared with retrospective controls who did not receive T cell add-back. However, at a median follow-up of 33 months, 9 patients died (56%) because of relapse disease (5), infection (3), and interstitial pneumonitis (1). Despite its small size, this study confirmed the safety of the addition of selectively allodepleted donor T cells after HaploSCT. However, it should be noted that the allodepletion method based on CD25 expression also depletes Tregs. Further studies are needed to assess the efficacy of this approach.

**Anti-HLA Antibodies and Graft Rejection in TCD HaploSCT**

To address the high toxicity of the myeloablative, total body irradiation–based conditioning regimens used in the aforementioned trials, we studied the feasibility of a myeloablative yet RIC regimen consisting of fludarabine, melphalan, and thiotepa for patients with advanced hematologic malignancies undergoing TCD HaploSCT [43]. Of 28 patients enrolled in this phase II trial, 22 (79%) achieved primary engraftment, whereas 5 achieved secondary engraftment either after a second transplant ($n = 4$) or infusion of cryopreserved autologous cells ($n = 1$). None of the patients developed grade III-IV aGVHD, and 4 of 21 patients developed cGVHD as seen in the European trials after TCD HaploSCT. NRM was 40% at 1 year, and most of the deaths were related to infections, which made us change our approach to using a T cell–replete (TCR) allograft to improve immune reconstitution posttransplantation and hopefully decrease the NRM associated with infectious complications [44]. In addition, this study revealed a higher rate of graft failure in the TCD HaploSCT patients, even if megadoses of CD34+ cells were used (median number of CD34+ cells: $10.2 \times 10^6$/kg). This prompted us to look for other causes of graft rejection in these patients and studied the relationship between the donor-specific anti-HLA antibodies (DSA) identified with a solid-phase fluorescent assay and graft failure, based on the association found between anti-HLA antibodies and graft rejection in solid organ transplantation [45,46].

Twenty-four patients were tested for the presence of DSA in pretransplantation serum specimens. Three of 4 patients (75%) with DSA at the time of transplantation developed primary graft failure compared with only 1 of 20 patients (5%) who did not have DSA, suggesting that the presence of DSA is an important cause of graft rejection in patients undergoing TCD HaploSCT [47]. Future studies should attempt to decrease antibody levels before infusion of CD34+ cells to prevent graft failure, if another donor is not available for such patients.

**T CELL REPLETE HAPLOIDENTICAL TRANSPLANTATION**

Because of delayed immunologic reconstitution and higher treatment-related mortality after TCD HaploSCT, alternative transplant options have been sought. Maintaining the T cells in the graft while effectively preventing the development of GVHD posttransplantation could represent a viable alternative to TCD HaploSCT.

**High-Dose Posttransplantation Cyclophosphamide for GVHD Prevention**

Historic experience clearly showed that infusion of a TCR haploidentical graft without effective GVHD prevention was associated with unacceptable toxicity [10]. One of the most promising ways of eliminating alloreactive T cells responsible for both graft rejection and GVHD is the use of cyclophosphamide (Cy) in the
immediate posttransplantation period, when the graft
and host T cells recognize each other as foreign and
generate bidirectional alloreactivity. The use of post-
transplantation Cy was initially used in the 1960s by
Barenbaum and Brown [48], who showed that it can
prevent skin graft rejection when administered 2 to 3
days after allografting in a mouse model. Similarly,
its use in the early posttransplantation period has
been shown to eliminate alloreactive T cells and
facilitate engraftment of donor cells as the hematopoietic stem cells are quiescent cells, which are resis-
tant to cytotoxic chemotherapy because of their high
levels of aldehyde dehydrogenase [49].

Luznik and colleagues [50] subsequently showed
that posttransplantation Cy can attenuate lethal and
nonlethal GVHD in mice and prolong their survival.
O'Donnell et al. [51] demonstrated the feasibility of using
posttransplantation Cy in a small cohort of patients
with high-risk hematologic malignancies treated with
a nonmyeloablative conditioning regimen, TCR haplo-
identical BM stem cells, and posttransplantation Cy of
50 mg/kg on day 3 after transplantation. Relatively low
rates of graft failure and GVHD were noted among 13
patients treated [51]. In a more recent update, Luznik
et al. [52] used Cy on posttransplantation days 3 and 4
and intensified mycophenolate mofetil (MMF) dosing
from twice to three times daily, to further decrease the
graft failure and GVHD rates. Although graft rejection
occurred in 9 of 66 evaluable patients, 8 of those experi-
enced recovery of autologous hematopoiesis. Grade
III-IV aGVHD incidence was 6%. Chronic GVHD in-
cidence was lower among those who received 2 doses of
posttransplantation Cy (5%) compared with those who
received 1 dose (25%). Although NRM rate was rela-
atively low at 15% at 1 year posttransplantation, relapse
incidence at 2 years was 58% [52].

Despite the success of using posttransplantation
Cy in reducing GVHD and graft failure rates without
increased NRM rates, relapses arose as a major treat-
ment failure that could be attributed primarily to the
use of nonmyeloablative conditioning, especially for
patients with myeloid malignancies and acute leukemic.
Recently, the Johns Hopkins group presented
its findings in 17 patients after HaploSCT using mye-
loablative conditioning with busulfan, Cy, and total
body irradiation, and posttransplantation Cy [53].
The cumulative incidence of NRM at 100 days was
higher at 18%, whereas GVHD rates were acceptable
and none of the evaluable patients had graft rejection
[53]. However, the data are not mature, and further
studies are needed to establish the safety and efficacy
of posttransplantation Cy after myeloablative condi-
tioning.

More recently, the Blood and Marrow Transplant
Clinical Trials Network conducted 2 parallel multi-
center phase II trials of double umbilical cord blood
transplantation and TCR HaploSCT for individuals
with lymphoma or leukemia [54]. The conditioning
regimen and GVHD prophylaxis in the HaploSCT
trial were identical to those previously reported by
Luznik et al. [52]. One-year NRM and progression-
free survival were 7% and 48%, reproducing Johns
Hopkins' results in a multicenter trial. Yet again, re-
lapse was the primary cause of death, attributed pri-
marily to the use of nonmyeloablative conditioning
for patients with leukemia, which represented more
than one-half of the patients treated in this trial.

We are investigating the use of posttransplantation
Cy in a phase II clinical trial ongoing at the M.D.
Anderson Cancer Center. To date, more than 40 pa-
tients were treated, and outcomes for the first 24 con-
secutive patients were recently reported in abstract
format [44]. Patients received the same conditioning
regimen (fludarabine, melphalan, thiotepa) previously
reported by us in TCD HaploSCT, followed by post-
transplantation Cy on days +3 and +4, tacrolimus,
and MMF. Median age was 47 years (range: 24-65 years)
and 66% were ethnic minorities. All 23 evalu-
ables patients engrafted with 100% donor cells after a
median of 19 days. Day 100 NRM was 14% for first
transplants, and no patient <50 years of age died
because of treatment–related mortality. Grade II-IV
aGVHD occurred in only 4 patients, all immediately
after the MMF was abruptly discontinued on day 35
posttransplantation. We are now continuing MMF
until day 100 posttransplantation and tapering weekly
thereafter. After a median follow-up of 6 months for
these patients (range: 3-22 months), OS was 71% for
first transplants and progression-free survival was 80%
for patients in remission at the time of transplantation.
No patient died of NRM after 6 months in this group.
These early results suggest that outcomes with TCR
HaploSCT are better compared with our previous ex-
perience with TCD HaploSCT primarily because of im-
proved immune recovery posttransplantation. Longer
follow-up is necessary to confirm these findings [44].

**Alloanergized HaploSCT after Ex Vivo Costimulatory Blockade**

T cell activation requires 2 signals from antigen
presenting cells (APCs): displayment of an immuno-
genic peptide on major histocompatibility complex
to T cell receptor and a costimulatory signal, most
commonly through CD80/86 on APCs to CD28
receptor on T cells. Blockade of the latter may result
in induction of anergy [55] and could allow successful
transplantation of histoincompatible allografts [56].
Guinan et al. [57] demonstrated the feasibility of Hap-
loSCT using a BM graft of which donor T cells were
anergized through incubation with the recipient's
mononuclear cells and CTLA-4-Ig. CTLA-4 is a
counterreceptor for CD80/86 and has a much higher
affinity for it than CD28. Of 12 patients transplanted,
1 died early posttransplantation, 11 patients achieved sustained engraftment, and 3 had aGVHD. No deaths because of GVHD occurred in this group. In a recent update, Davies et al. [58] reported their experience in 24 patients with high-risk hematologic malignancies or BM failure. Five patients developed severe aGVHD, and 12 patients died within 200 days of transplantation (5 because of infection). Eight patients were alive and free of disease with a median follow-up of 7 years. Of concern, none of the patients older than 18 years survived the first 200 days. A similar protocol revised to minimize the early transplant-related mortality using RIC and mega-doses CD34+ hematopoietic stem cell transplantation is currently in trials.

The Combination of G-CSF Primed Bone Marrow and Mobilized PBSCs

G-CSF can induce T cell hyporesponsiveness and a skewing toward a T_{H2} phenotype through an increase in plasmacytoid dendritic cells and down-regulation of CD28-CD80/86 signaling [59,60]. Based on these findings, Chinese researchers developed a HaploSCT protocol using myeloablative conditioning, intensified immunologic suppression with antithymocyte globulin, and a donor graft composed of G-CSF primed bone marrow and PBSCs [61]. In their most recent update including 250 acute leukemic patients [62], of whom 149 (60%) were transplanted while in first complete remission with standard-risk genetics, donors were treated with G-CSF 5 mg/kg/day subcutaneously and BM cells were harvested on fourth day of G-CSF followed by collection of PBSCs on fifth day. GVHD prophylaxis included cyclosporine, MMF (both initiated on transplantation day −9), antithymocyte globulin 2.5 mg/kg from days −5 to −2, and methotrexate on days +3, +6, and +11. The early posttransplantation mortality rate approached 13%, and the cumulative incidence of grade 2 to 4 aGVHD was relatively high at 45.8%. The cumulative incidence of cGVHD was 53.9% at 3 years, which comes in sharp contrast with cGVHD rates obtained with posttransplantation Cy. Overall, the 3-year cumulative incidence of relapse was less than 20%, and leukemia-free survival approached 70% among acute myelogenous leukemia patients with standard risk disease (first or second complete remission without Philadelphia chromosome) [62]. Even though a higher disease-free survival was achieved—partly because of inclusion of standard- and good-risk patients—the concern remains that a higher incidence of GVHD is usually associated with a higher treatment-related mortality and higher cost of care for these patients.

In Vivo Depletion of T Cells

The anti-CD52 antibody, alemtuzumab (Campath®), has been used for in vivo depletion of host and donor T cells to increase engraftment and decrease GVHD rates in transplants from matched sibling or unrelated donors [63-65]. Rizzieri et al. [66] treated 49 patients with hematologic malignancies using non-myeloablative conditioning and alemtuzumab. The preparative regimen included fludarabine and Cy on days −5 to −2, and alemtuzumab 20 mg/day on days −4 to 0. Further GVHD prophylaxis included MMF 2 g/day for 45 days, with or without cyclosporine. Three and 4 patients experienced primary and secondary graft failure, respectively. Twenty-four (49%) and 11 (22%) patients died of progressive disease and infections, respectively, whereas 2 (4%) patients died of posttransplantation lymphoproliferative disease. One-year OS was 31%. The relatively high relapse rate observed was attributed partly because of the reduced intensity of the conditioning. However, the disease relapse rate may be further increased by the use of alemtuzumab, as recently reported in a Center for International Blood and Marrow Transplant Research registry analysis [67].

NK Cells in HaploSCT

As previously detailed, NK cell alloreactivity may be exploited to improve the efficacy and safety of HaploSCT. It is thought that NK cells recognize their targets through both inhibitory and activating receptors. Various algorithms explaining NK cell alloreactivity have been proposed [26,68-70]. According to the widely used "missing self" model, an NK cell recognizes a cell as foreign when the particular cell lacks 1 or more HLA class I alleles specific to the inhibitory receptors (killer immunoglobulin-like receptors, KIRs) on the NK cell [26,71]. NK cells attack primarily hematopoietic cells sparing the solid organs, rendering them almost incapable of causing GVHD [72]. Therefore, if the recipient cells lack the HLA class I alleles specific to the donor KIRs, donor NK cells may decrease the risk of GVHD and disease relapse by killing the residual recipient APCs and leukemia cells. Furthermore, following stem cell transplantation, including TCD HaploSCT, NK cells are the first lymphoid cells to recover by rapid differentiation from engrafted stem cells [73].

Several studies evaluated the feasibility of NK cell infusions after HaploSCT to utilize innate immunity against different tumors [74-76]. Recently, Yoon et al. [77] reported on a series of 14 patients with acute leukemia or myelodysplastic syndromes in which patients were infused with donor NK cells derived from CD34+ hematopoietic cells 6 to 7 weeks after TCR HaploSCT. There were no acute side effects, and 4 patients developed cGVHD. Four patients were alive and disease-free 18 to 21 months posttransplantation. Two patients who received NK cell infusion during active leukemia did not have a response
DONOR SELECTION

Most patients have more than 1 potential haploidentical donor, and various factors have been implicated in selection of the most suitable donor for HaploSCT. We provide a summary of the most relevant studies, which outlines the various factors considered in the decision to use 1 haploidentical donor versus another.

KIR Mismatch

KIR mismatch between recipient and donor has been associated with improved outcomes after HaploSCT in several studies [78,79]. Ruggeri et al. [78] reported improved graft rejection, GVHD, and disease relapse rates among patients with acute myelogenous leukemia who received stem cells from donors with KIR mismatches in the graft-versus-host direction compared with those without. More recently, Symons et al. [79] reported similar results in a cohort of 86 patients with various hematologic malignancies who underwent TCR HaploSCT with nonmyeloablative conditioning and posttransplantation Cy with improved NRM, OS, and event-free survival among those transplanted with KIR mismatch donors compared with those without [79]. Conversely, Huang et al. [80] found KIR mismatch to be an independent risk factor for aGVHD, relapse, and decreased OS in a cohort of 116 patients after TCR HaploSCT using myeloablative conditioning. The conflicting results may be partly because of differences in stem cell sources, treated diseases, type of conditioning, and variations in the definition of KIR mismatch. Although NK cell alloreactivity is likely to play a role in the success of HaploSCT, further studies are needed to better define the role of KIR mismatch in donor selection and exploit the NK alloreactivity to improve outcomes post transplantation.

Mismatched Maternal HLA antigens

Several clinical observations suggested that the development of immunologic tolerance between mother and fetus during pregnancy [81,82] could impact the transplantation outcomes because of a lifelong down-regulation of immune responses, if the mismatched haplotype is of maternal origin, as happens in transplants from a mother to her child, or between siblings mismatched for noninherited maternal HLA antigens (NIMA) compared with noninherited paternal antigens (NIPA). Accordingly, patients with maternal donors were found to have longer OS after HaploSCT compared with those with paternal donors in a Japanese registry study [83]. Subsequently, van Rood et al. [84] demonstrated lower aGVHD and cGVHD rates and lower treatment-related mortality in T cell–replete haploidentical transplant recipients NIMA compared with NIPA mismatched. Separate studies later confirmed these findings in patients transplanted from NIMA compared with NIPA mismatch donors after both myeloablative and nonmyeloablative regimens [85,86].

Number of HLA Mismatches between the Donor and Recipient

Historically, increasing degrees of HLA mismatch have been associated with shorter survival and higher GVHD rates after Haplo SCT [10,87,88]. Recently, the Johns Hopkins group reported that greater HLA disparity was not associated with worse outcomes after TCR HaploSCT with posttransplantation Cy [89]. In this retrospective analysis of 185 patients with various hematologic malignancies, having 3 or 4 total antigen or allele mismatches was not associated with increased risk of grade II-IV aGVHD compared with fewer mismatches. Moreover, in multivariate analysis, the event–free survival of patients having 3 or 4 total antigen or allele mismatches appeared to be better compared with those with fewer mismatches because of a lower relapse rate [89]. Although limited by its retrospective nature, this study suggested that, by using posttransplantation Cy, the higher treatment-related mortality rates usually associated with more mismatches can be eliminated, and improved outcomes could be potentially achieved compared with matched transplantation, as recently reported by the Chinese group [90].

A multivariate analysis in a large cohort of patients is needed to further elucidate the role of these factors in donor selection for HaploSCT.

FUTURE DIRECTIONS

Because of the universal and immediate availability of haploidentical related donors for almost all patients, including those from minority groups or with mixed race, and the lower cost of HaploSCT compared with unrelated donor transplantation, improvement in this form of transplantation is warranted. Although various methods have been used to overcome the significant HLA barriers in HaploSCT, so far none has excelled over another. However, we are encouraged by the use of posttransplantation Cy because it provides a straightforward, effective way to control GVHD posttransplantation without affecting engraftment. This approach limits treatment-related mortality because of GVHD and possible infectious complications, which, in our experience, occur more frequently in TCD HaploSCT. However, relapse after HaploSCT remains an issue because depletion of
alloreactive T cells eliminates graft-versus-leukemia effect, regardless of the method used. Future directions will likely include improvement in conditioning regimens tailored to myeloid and lymphoid diseases, the use of cellular therapy posttransplantation in an attempt to decrease disease relapse, and possible replacement of cyclophosphamide with other drugs to selectively deplete alloreactive T cells posttransplantation in the future.

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