Alternative Allogeneic Donor Sources for Transplantation for Childhood Diseases: Unrelated Cord Blood and Haploidentical Family Donors

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ABSTRACT

Allogeneic stem cell transplantation has been demonstrated to be curative in a wide variety of pediatric malignant and nonmalignant diseases, and can be traced back over 50 years ago to the original report of Thomas et al. HLA matched sibling donors have been the gold standard for pediatric recipients requiring allogeneic donors for both nonmalignant and malignant conditions. However, only 25% of potential pediatric recipients possesses an HLA-matched sibling donor, and the frequency is even less in those with genetic nonmalignant conditions because of genetically affected other siblings within the family. Therefore, 75% to 90% of potential pediatric recipients require alternative allogeneic donor cells for treatment of their underlying conditions. Potential alternative allogeneic donor sources include unrelated cord blood donors, unrelated adult donors, and haploidentical family donors. In this article we review the experience of both unrelated cord blood donor and haploidentical family donor transplants in selected pediatric malignant and nonmalignant conditions.

KEY WORDS

Pediatric • Alternative allogeneic donors • Unrelated donor transplants • Haploidentical transplants

INTRODUCTION

Allogeneic stem cell transplantation has been successful in the treatment of a variety of pediatric malignant and nonmalignant conditions [1]. Unfortunately, only 25% of eligible pediatric recipients will have an HLA-matched sibling donor. Historically, unrelated adult donor HLA-matched allogeneic stem cell transplants have been utilized for pediatric recipients who lack an HLA-matched sibling donor. However, 2 other major allogeneic donor sources are available, including unrelated cord blood donors and haploidentical family matched donors. In this manuscript, we review the recent results of unrelated cord blood transplants for pediatric nonmalignant conditions and haploidentical family donor transplants for specific pediatric malignant disorders.

CORD BLOOD AS AN ALTERNATIVE ALLOGENEIC STEM CELL SOURCE FOR PEDIATRIC RECIPIENTS

It has been over 10 years since we and others demonstrated the successful engraftment of pediatric recipients with both malignant and nonmalignant disease with related [2] and unrelated [3,4] cord blood donor grafts. There are several advantages to utilizing cord blood as a preferred allogeneic donor source including: (1) little or no risk to the donor; (2) rapid availability of processed donor source with prior characterization; (3) extension of the donor pool because of tolerance of 1-2 HLA mismatches of 6; (4) small cryopreserved volume with easy transport capability; (5) low risk of infectious disease transmission of latent viruses such as CMV and EBV; (6) decreased severe acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD); and (7) increased ethnic diversity
in the cord blood bank donor pools [5,6]. However, some major limitations and/or concerns utilizing cord blood donors include: (1) fixed number of cells available with only a median of $1 \times 10^9$ total nucleated cells, which results in increased graft failure; (2) less clinical experience compared to unrelated adult donor transplants; (3) lack of available donor immune cells for post-CBT infusion; (4) few large-size and high-quality units cryopreserved compared to the number of registered unrelated adult donors (400,000 versus 8,000,000); and (5) slower hematopoietic engraftment and immune reconstitution [5-9].

Cell dose, from a single cord blood unit, has been significantly demonstrated to be associated with rapidity of hematopoietic engraftment. In 2 large retrospective analysis, total nucleated cell count/kg of recipient has been significantly associated with both myeloid and platelet engraftment [10,11] (Figure 1A and B). More recently, we have demonstrated that precryopreserved CD34 cell dose/kg of recipient is significantly associated with probability of overall survival (OS) [12,13] (Figure 2A and B).

Although 1 of the unique advantages of utilizing cord blood grafts as an alternative allogeneic stem cell source is the ability to engraft across HLA disparate barriers, it now appears that the degree of HLA disparity significantly influences engraftment and possibly OS. HLA mismatch at 2 or greater antigens compared to <2 antigen mismatch following unrelated cord blood transplantation in children is associated with a significant decrease in survival and a significant increase in treatment-related mortality (TRM) [12,14].

There is still significant controversy over whether to choose an unrelated cord blood graft versus an unrelated adult donor allograft [15]. Several retrospective studies have been unable to identify a significant improvement in outcome or survival following unrelated adult donor stem cell transplantation versus unrelated cord blood transplantation. Netcord and European Blood and Marrow Transplantation group (EBMT) compared unrelated cord blood transplantation versus unrelated adult donor allogeneic stem cell transplantation in children with acute leukemia and reported similar 5-year event-free and OS rates [15,16]. More recently, the CIBMTR and NCBP analyzed and compared the results of unrelated donor cord blood allografting with unrelated adult bone marrow transplantation and demonstrated similar leukemia-free survival in children with acute leukemia [14] (Figure 3). Similarly, the risk of developing serious infections was not statistically different in children following unrelated cord blood versus unrelated adult donor allogeneic stem cell transplantation [17].

Future strategies to overcome or circumvent the limitations of cell dose and HLA disparity following unrelated cord blood transplantation in children include the investigation of double cord blood transplantation [18], reduced-intensity conditioning (RIC) [19], ex vivo expansion of cord blood stem cells [20], the use of cord blood T regulatory cells [21], cord blood natural killer (NK) cells [22], and the overall regenerative potential of cord blood stem cells [23]. As more unrelated cord blood units become cryopreserved and available for alternative allogeneic stem cell transplantation, newer investigations will be forthcoming, where future results will assist pediatricians in the decision of which alternative allogeneic stem cell sources to choose from when their pediatric patient...
lacks an HLA matched sibling donor for a medical condition that can be cured by allogeneic stem cell transplant.

**UMBILICAL CORD BLOOD TRANSPLANTATION IN CHILDREN WITH NONHEMATOLOGIC MALIGNANCIES**

Umbilical cord blood transplantation (UCBT) has extended the availability of allogeneic hematopoietic stem cell transplantation (HSCT) to patients who would otherwise not be eligible for this curative approach. Since the first successful UCBT from an HLA-identical sibling in a child with severe Fanconi’s anemia reported by Gluckman et al. in [24] 1989, the number of UCB transplants from related and unrelated donors has increased dramatically, and we estimate that more than 8000 patients have undergone UCBT from unrelated donors to date for a variety of genetic, hematologic, immunologic, metabolic, and oncologic disorders.

The Eurocord registry, on behalf of the EBMT and the Netcord banks, has collected data on 3372 related and unrelated cord blood transplants performed in 373 transplant centers worldwide from 1988 to February 2007. Table 1 lists the patients reported to Eurocord, transplanted with an unrelated cord blood graft, according to age and diagnosis. Most of the UCBT performed in children are for malignant disorders, but 460 transplants (28%) have been already performed in children with nonmalignant disorders. However, very few data analyzing risk factors for outcomes after UCBT for nonmalignancies have been reported.

To know the results and improve the outcomes of UCBT in children with nonmalignant disorders, we have analyzed the interaction of cell dose and HLA in the cohort of children with all nonmalignant disorders and performed specific analyses for more frequent diagnosis.

**Interaction between Cell Dose and HLA in Children with Nonmalignant Disorders**

Multicenter, single-institution, and consortium studies have shown that unrelated donor UCBT in children, most with malignant disorders, have demonstrated the profound impact of cell dose and HLA on engraftment, adverse transplant-related events and survival and relapse [10-13,25,26].

We developed the hypothesis that cell dose and number of HLA disparities will have an impact on the outcomes of UCBT in children with nonmalignant disorders. With this aim, we have studied 268 children with nonmalignant disorders following an unrelated cord blood transplant from 1994 to 2005. The median age of patients at UCBT was 5 years (range 3 months to 10 years), and the median follow-up time was 29 months.Recipient’s CMV serology prior to transplant was positive in 52% of the patients. The diagnosis was bone marrow failure syndrome in 48% (69% Fanconi disease, 18% acquired SAA, 13% congenital BMFS), primary immunodeficiency in 30%, and a hereditary metabolic disorder in 22% of patients.

Only 17% were classified as identical for HLA class I antigens and class II allelic typing, whereas 43% had 1 HLA difference, 36% had 2 HLA differences, and the remainder had 3 HLA differences. For patients with 1 HLA mismatch, 72% had a class I difference and 28% a class II difference. For patients with 2 HLA differences, 44% had 2 class I differences, 3% had 2 class II differences, and 53% 1 class I and 1 class II difference.
The median number of nucleated cells (NCs) infused was $7.6 \times 10^7$ NC/kg (range: 0.8-66 $\times 10^7$ NC/kg).

With respect to GVHD prophylaxis, 53% received the combination of cyclosporine (CsA) and steroids. A variety of conditioning regimens were reported according to the disease and transplant center, but many patients received a busulfan based regimen. The utilization of fludarabine was present in 30% of the cases. Anti-T immunotherapy was given before day 0 to 84% of the recipients.

At day 100, the cumulative incidence (CI) of neutrophil recovery was 69.3% and CI of platelet recovery was 50%. Both outcomes were significantly correlated with the median number of cells infused ($P < .0001$). HLA was also an important factor associated with neutrophil recovery, with a statistical difference between 0 and 1 and ≥2 HLA mismatches ($P = .046$). The role of HLA mismatching was abrogated by increasing cell dose because patients given a higher cell dose ($>3.5 \times 10^7$/kg) even with 0, 1, 2, and 3 HLA disparities had a higher probability of recovery compared to those given lower cell dose with the same disparities. There was no correlation between neutrophil recovery and class of HLA mismatching (class I or class II, or HLA-A, -B, or -DRB1).

The CI of aGVHD grade II-IV was 32% and grade III-IV 18%, and was only associated with the number of HLA incompatibilities ($P = .0029$). The CI of cGVHD was 24% and was also associated with the number of HLA incompatibilities ($P = .01$). The probability of OS at 100 months was 49%. OS was influenced by cell dose and by the number of HLA


| Table 1. Number of Unrelated CBT Reported to Eurocord Registry According to Diagnosis and Recipient Age |
|---------------------------------------------------------------|---------------------------------|---------------------------------|
| Diagnosis                                                      | Children ($\leq 16$ Years, n = 1609) | Adults ($>16$ Years, n = 1136) |
| Acute lymphoblastic leukemia                                   | 579 (36%)                         | 269 (23.7%)                     |
| Acute myelogenous leukemia                                     | 257 (16%)                         | 356 (31.3%)                     |
| Secondary acute leukemia                                       | 58 (2%)                           | 63 (5.5%)                       |
| Myelodysplastic syndrome                                       | 120 (7.5%)                        | 97 (8.5%)                       |
| Chronic myelogenous leukemia                                   | 40 (2.5%)                         | 119 (10.5%)                     |
| Chronic lymphocytic leukemia                                    | —                                | 16 (1.4%)                       |
| Hodgkin/non-Hodgkin lymphomas                                  | 31 / – (2%)                       | 97 / 32 (11.4%)                 |
| Myeloma                                                        | —                                | 20 (1.8%)                       |
| Solid tumors                                                    | 9 (0.7%)                          | 5 (0.4%)                        |
| Histiocytosis                                                   | 60 (3.5 %)                        | 1 (0.1%)                        |
| Congenital and acquired bone marrow failure syndromes          | 157 (9.5%)                        | 50 (4.4%)                       |
| Hemoglobinopathies                                              | 7 (0.5%)                          | —                               |
| Primary immunodeficiencies                                     | 170 (10%)                         | 1 (0.1%)                        |
| Metabolic diseases                                              | 126 (8%)                          | 5 (0.4%)                        |
| Other disease                                                   | 11 (0.8%)                         | 5 (0.4%)                        |
mismatches. The group who received an UCBT with $<3.5 \times 10^7$ NC/kg at infusion and a 2-3 HLA-mismatched transplant had $<10\%$ survival. Increasing cell dose partially abrogated the effect of HLA mismatches. There was no statistical difference between the groups who received a cell dose of $>3.5 \times 10^7$ NC/kg with a 0, 1, 2, or 3 HLA-mismatched UCBT (Figure 4) (unpublished Eurocord data).

Thus, patients with a nonmalignant disease must receive a higher cell dose to obtain engraftment compared to patients with a malignant disease. The minimum UCB cell dose should not be below $4.9 \times 10^7$ NC/kg at collection and $3.5 \times 10^7$ NC/kg at infusion. In nonmalignant disorders, HLA mismatching played a major role in engraftment, GVHD, TRM, and survival, which was abrogated by increasing cell dose. A CB graft containing 2 or more HLA disparities with a cell dose inferior to $3.5 \times 10^7$ NC/kg should be avoided. Experience of double cord blood transplantation in nonmalignant disorders is still too limited to allow routine recommendation of this type of transplant, and is currently under investigation.

Fanconi Anemia Disease

In the group of children with bone marrow failure syndromes the majority of UCBT recipients have a Fanconi anemia (FA) phenotype. We have analyzed risk factors associated with outcome after unrelated UCBT in 93 FA patients. Median age at transplantation was 8.6 years (1-45). The units transplanted were HLA-A, -B, and -DRB1 identical in 12 cases, 1 HLA difference in 35 cases, and 2 or 3 HLA differences in 45 cases. The median number of NC and CD34+ cells infused of recipient weight was $4.9 \times 10^7$/kg and $1.9 \times 10^5$/kg, respectively. Participating centers selected the conditioning regimen of their choice; in 57 patients (61%), the majority of the conditioning regimens included fludarabine. CI of neutrophil recovery was $90\% \pm 5\%$ at day +60. In a multivariate analysis, a fludarabine-containing preparative regimen and NC number infused $\geq 4.9 \times 10^7$/kg were associated with a higher probability of neutrophil recovery. CI of grade II-IV aGVHD and of cGVHD were $32\% \pm 5\%$ and $16\% \pm 4\%$, respectively. The 3-year probability of survival was $40\% \pm 5\%$. In univariate analysis, favorable factors associated with survival were: age younger than 16 years at transplant ($P = .05$), HLA compatibility ($P = .009$), <20 RBC transfusions before transplantation ($P = .008$), recipient’s negative CMV serology ($P = .0003$), use of Fludarabine in the conditioning regimen ($P = .01$) $>4.9 \times 10^7$ nucleated cells/kg infused ($P = .04$). In multivariate analysis, these latter 3 factors remained statistically significant [27]. In conclusion, factors easily modifiable such as donor selection and a Fludarabine containing regimen can considerably improve survival in FA patients given an UCBT. These data are the basis for designing prospective protocols.

Severe Primary Immunodeficiencies

Outcomes of 93 unrelated UCBT in children with severe primary immunodeficiencies (SPID) reported to Eurocord by 40 centers were analyzed (J. Ortega on behalf of Eurocord; unpublished data). Median age was 0.9 years (range: 0-26), and median weight 8 kg (3-39). Diagnosis included severe combined immunodeficiency (n = 61), Wiskott-Aldrich syndrome (n = 20), and other (n = 12). Fifty-six patients were matched or had 1-HLA difference with the CB unit. The median number of NC infused was $8.3 \times 10^7$/kg (0.1-94), and the median CD34+ cell number $3.4 \times 10^5$/kg (0.4-33). Conditioning regimens varied according to disease and transplant centers protocol. In fact, 11 patients (12%) did not receive any conditioning, 44 (46%) Bu/Cy, 24 (26%) a Fludarabine containing regimen, 7 (8%) irradiation-based regimen, and 7 (8%) other regimens. Seventy-four patients received cyclosporine/steroids as GVHD prophylaxis. CIs for neutrophil and platelet recoveries were 85% and 77%, respectively. CIs for acute grades II-IV and cGVHD were 41% and 23%, respectively. TRM at 2 years was 31%. Survival at 2 years was 68% overall; 78% if patient/CB unit were matched or had 1 HLA-disparity, and 58% with 2 to 3 HLA differences (multivariate analysis, $P = .04$).

Metabolic Diseases: Hurler Syndrome

Small series of patients with very encouraging results have been reported in children with Krabbe’s and Hurler’s disease [28,29]. Hurler’s syndrome (HS), the most severe form of mucopolysaccharidosis type-I, causes progressive deterioration of the central nervous system and death in childhood. Hematopoietic allogeneic-stem cell transplantation before the age of 2 years halts disease progression and prolongs life. Graft failure and mixed chimerism (40%-50%)
limits the success of HSCT for HS. Unrelated-cord blood transplants are suggested to be a good alternative option for bone marrow; however, little is known about risk factors for outcomes after UCBT for this disease. We have analyzed 93 children with HS given an UCBT from 1995 and 2007 reported to Eurocord or transplanted at Duke University. Median age at UCBT was 1.3 (0.2-4) years, and median follow up was 24 (3-140) months. The donors were HLA-identical (HLA-A and -B by low resolution and HLA-DRB1 by high resolution) in 13 cases (16%) and incompatible in 67 cases (84%: most with 1 [54%] and 2 HLA disparities [26%]). The median NC dose/kg and CD34+7/kg at infusion were, respectively, 7.2 (2-22) x 10^7 and 2.3 (0.5-17) x 10^5. With the exception of 5 patients, all received a busulfan/cyclophosphamide (+ fludarabine: n = 6) regimen. All patients received ATG or Campath (n = 4). Median days to neutrophil and platelet recovery were 22 (10-46) and 35 (13-82) days, respectively. Mixed chimerism was found in only 6%. All patients had normal enzyme levels after engraftment. In multivariate analyses for neutrophil recovery, a CD34+ dose of >2.3 x 10^7/kg (hazard ratio [HR] = 2.0; P = 0.015) was associated with increased probability of recovery. aGVHD (grade II-IV) was observed in 27%, whereas cGVHD was seen in 10% at 2 year. Two years OS and disease-free survival (DFS) were 78% and 70%, respectively. For 2 year OS, time from diagnosis to UCBT lower than 6 months was associated with better OS (94%) for those children transplanted earlier and 70% for those transplanted later (P = .04). Transplantation improved somatic features of HS. More detailed long-term follow up is currently ongoing. In conclusion, outcomes following UCBT for Hurler’s syndrome are encouraging. UCB is a good alternative allogeneic stem cell source to transplant children with HS, and is associated with low frequencies of mixed chimerism. Earlier transplantation and higher cell dose are associated with better outcomes after UCBT for HS patients [30].

Cord Blood Transplantation for Patients with Hemoglobinopathies

Very few patients with Thalassemia (thal) or sickle cell disease (SCD) have been transplanted with an unrelated cord blood transplantation. Seven children with hemoglobinopathies have been reported to Eurocord. Clinical data is available in 4 children, 2 with thal and 2 with SCD. All 4 patients are alive and well without transfusion dependency.

A specific analysis has been performed and published for 44 children with thal and SCD following a related UCBT [31]. We have updated this analysis and confirmed that all 63 patients are alive, and the 5-year DFS is 78% in the 44 thal patients, and 94% for the 19 SCD patients. The absence of methotrexate (MTX) in the GVHD prophylaxis and the use of fludarabine in the conditioning regimen were the most important factors associated with increased DFS. The Eurocord group is currently performing a comparative study between bone marrow and cord blood in HLA identical sibling transplants for children with thal or SCD.

In summary, these results demonstrated that unrelated UCBT can be considered as a source of allogeneic stem cells for transplantation for those children with genetic and metabolic diseases, who need an HSCT and who lack an HLA identical sibling donor. Outcomes are associated with patient, disease, and transplant characteristics. Therefore, better patient selection and factors easily modifiable such as cord blood unit selection and changes in conditioning regimens or GVHD prophylaxis can improve outcome. Currently, there is no study comparing results of UCBT and other HSCT in children with nonmalignant disorders, but based on the studies comparing unrelated cord blood with bone marrow in children with malignant disorders [32] we can strongly suggest that the search for an UCB unit should be started simultaneously as for BM unrelated donors also, in children with nonmalignant disorders. Because HLA and cell dose are also very important in this setting, cord blood banks should increase their inventories, with the aim of finding more closely matched CB grafts.

HAPLOIDENTICAL TRANSPLANTS FOR CHILDHOOD HEMATOLOGIC MALIGNANCIES

Haploidentical HSCT has been limited by obstacles intrinsic to alloreactivity between unmatched donor-recipient pairs: graft failure, GVHD, postransplant lymphoproliferative disease (PTL PD), and prolonged immunodeficiency [33-35]. Advances in graft engineering, supportive care, increased usage of peripheral blood stem cell (PBSC) grafts with high stem cell content, and observations that a graft-versus-leukemia (GVL) effect may exist in killer immunoglobulin-like receptor (KIR) mismatched donor-recipient pairs have resulted in improved outcomes, making it an attractive, potentially curative option for those patients who either lack a matched related donor or who do not have time to wait for an unrelated donor to become available. Mismatched family member (MMFM) donors are highly motivated and readily available throughout the transplant process for initial and subsequent product donation, can be rapidly evaluated for product donation, and may provide an immunologic GVL effect if the donor-recipient pair are mismatched for KIRs [36]. Donor evaluation, performed at the recipient’s transplant center, avoids conflicts with another donor center and the time for an unrelated donor search.

T-lymphocyte depletion of grafts is typically necessary to reduce the risk of severe GVHD.
Historically, methods of T cell depletion (TCD) were inadequate, resulting in GVHD, or excessive, resulting in graft failure and prolonged immunosuppression. Newer, more precise graft engineering strategies allow more rigorous control of graft content of hematopoietic progenitor or immunologic cell populations. Typically, CD34+ selection using immunomagnetic columns, resulting in a 5-log CD3 depletion of the graft, eliminates posttransplant GVHD prophylaxis requirements [37]. These highly purified grafts, containing megadoses of CD34+ hematopoietic stem cells (>10^10 CD34+/kg) and essentially no B cells, overcome engraftment barriers and make PTLPD rare [38]. One study using megadoses of highly purified CD34+ hematopoietic cells demonstrated full donor engraftment in all 43 patients treated [39]. No patient developed GVHD. With a median follow-up of 18 months, 12 of the 43 patients were alive in remission. A subsequent trial of haploidentical HSCT in 104 patients received CD34+-positive selected grafts with no pharmacologic GVHD prophylaxis [40]. aGVHD occurred in 8 of 100 evaluable patients; cGVHD occurred in 5 of 70 assessable patients. At a median of 22 months, event-free survival was 48% for AML and 46% for ALL patients transplanted in remission. A recent trial of 34 children with leukemia who received an ablative regimen reported an actuarial 1-year survival rate of 48% and 40% for standard-risk and high-risk patients, respectively. A subsequent report of 239 patients described comparable rates of cGVHD, TRM, relapse, and survival in non-TCD MMFM graft recipients (n = 135) compared to matched sibling recipients (n = 158). All engrafted with 40% of MMFM recipients developing grade III-IV aGVHD. These trials, in a relatively well-defined, homogenous population suggest that in vivo T cell depletion may be sufficient in some circumstances.

Alternate strategies to reducing GVHD risk after MMFM HSCT include the induction of tolerance. One strategy cocultured recipient antigen-presenting cells and T-replete donor marrow in the presence of agents to selectively inactivate host-reactive T cells [47]. All 12 received a TBI-based regimen and a bone marrow graft treated as described above. Only 3 patients developed GVHD despite posttransplant immunosuppression, and 5 remain alive in remission at 4.5 to 29 months after transplantation.

Recently, clinicians have employed reduced-intensity or nonmyeloablative conditioning regimens in an attempt to reduce toxicity, especially in older patients and those with comorbidities. Haploidentical HSCT has been successfully performed with graft engineering and long-term disease responses in patients with hematologic malignancies, including those with refractory disease [43,44]. Of 49 patients receiving ablative regimens with cyclophosphorine, 94% were engrafted [48]. Treatment-related mortality was 10% and 8% had severe GVHD. The 1-year survival rate was 31%; the 19 standard-risk patients had a 63% 1-year survival rate, demonstrating that nonablative regimens result in favorable outcomes, particularly for patients transplanted in remission.

Delayed engraftment and graft failure are concerns after transplantation of TCD grafts. TCD shifts the immunologic balance in favor of the host, augmenting the risk of graft rejection. Time to neutrophil engraftment has been abbreviated with reduced intensity conditioning regimens, less intensive TCD, growth factor administration, and PBSC grafts containing megadoses of hematopoietic precursors. Recent reports confirm rapid neutrophil engraftment in recipients of MMFM grafts, in contrast to the delayed recovery after cord blood HSCT [43,44,49]. Rapid engraftment shortens the neutropenic period, reduces blood product transfusions, and curtails hospitalizations. Weekly peripheral blood chimerism monitoring can identify early disease recurrence or graft rejection [47,50,51].

Improved TCD methodologies have dramatically reduced the incidence of severe GVHD. In fact, calcineurin inhibitors, which are associated with significant study describing 171 patients, all were engrafted with 23% developing grade III-IV aGVHD and 47% developing cGVHD, leading to a 2-year DFS of 68% and 42% in standard-risk and high-risk patients, respectively. A subsequent report of 239 patients described comparable rates of cGVHD, TRM, relapse, and survival in non-TCD MMFM graft recipients (n = 135) compared to matched sibling recipients (n = 158). All engrafted with 40% of MMFM recipients developing grade III-IV aGVHD. These trials, in a relatively well-defined, homogenous population suggest that in vivo T cell depletion may be sufficient in some circumstances.

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Improved TCD methodologies have dramatically reduced the incidence of severe GVHD. In fact, calcineurin inhibitors, which are associated with significant
toxicities, can be omitted [49,51]. For grafts partially depleted of CD3+ cells, single agents that have fewer side effects such as mycophenolate mofetil (MMF) can be used [43,44]. Immune reconstitution is more rapid, reducing the risks of infectious complications in patients receiving less intense pharmacologic immunosuppression. In fact, with low incidences of severe GVHD, permissible GVHD may be allowed in an effort to reduce relapse rates in high-risk patients.

Delayed immune reconstitution remains a significant challenge. One recent study demonstrated that immune reconstitution may be hastened in recipients of conditioning regimens omitting TBI or ATG [52]. In this group of heavily pretreated patients with refractory malignancies, CD3+ lymphocytes recovered more rapidly than was observed in patients with standard-risk hematologic malignancies receiving an ablative conditioning regimen containing TBI and ATG. This observation may be because of the preservation of T-lymphocyte reconstitution in the absence of ATG and the thymic protection afforded by omitting TBI. Finally, infusion of nonalloreactive CD3+ cells after haploidentical transplantation has resulted in acceptable GVHD rates with improved immune reconstitution [53]. Serial monitoring of immunologic recovery is important to ascertain infection risk; rapid high-throughput methodologies have been developed to expedite this testing [54]. Patients should be serially monitored for EBV, CMV, and adenovirus DNA reactivation so that preemptive therapy can be initiated early [55-57].

Additional donor cellular product infusions may be required after transplantation; haploidentical donors are continuously available for timely donation. Stem cell boosts have restored hematopoietic graft function without conditioning in cytopenic patients with donor cell engraftment after transplantation [58]. Donor lymphocyte infusions (DLIs) can treat early disease recurrence, restore donor hematopoiesis, and treat infections. The risk of GVHD can be reduced by administering DLIs with low CD3+ content [59].

Donor-recipient NK cell alloreactivity in KIR mismatched donor-recipient pairs may result in lower relapse rates, particularly in patients with myeloid malignancies, or may hasten engraftment and immune reconstitution [60,61]. Unpurified NK cell infusions from haploidentical donors for patients with cancer receiving an intense immunoblative chemotherapy regimen have been performed safely with in vivo expansion of donor NK cells with administration of interleukin-2 [62]. Other investigators have been able to isolate highly purified CD56+ hematopoietic cells from unstimulated leukapheresis products from healthy donors, allowing for posttransplant infusions of NK cells to further decrease relapse risks [63].

Investigators demonstrated that prior exposure to noninherited maternal antigens (NIMA) during pregnancy may lead to fetomaternal microchimerism with the induction of tolerance [64]. Published studies have demonstrated acceptable engraftment with lower rates of aGVHD in recipients of sibling or haploidentical T cell replete grafts in which the donor and recipient are mismatched for NIMA compared to those mismatched for noninherited paternal antigen (NIPA) [65-70]. An IBMTR analysis demonstrated that recipients of grafts from NIMA mismatched siblings result in a lower rate of aGVHD and cGVHD with similar rates of graft failure compared to NIPA mismatched siblings; when compared to parental donor HSCT, TRM was significantly lower for haploidentical sibling HSCT, mismatched for NIMA [71].

Haploidentical HSCT is a promising alternative treatment for patients requiring transplantation. Recent advances have resulted in rapid neutrophil and platelet engraftment, tolerable GVHD rates, and the potential to induce an alloreactive GVL effect in KIR mismatched donor-recipient pairs. However, delayed immune reconstitution and disease recurrence remain challenges. Future research in this field must define a safe platform for haploidentical HSCT while hastening immune reconstitution and reducing relapse. With improvements in graft engineering methodologies and the refinement of posttransplant immunotherapies, haploidentical HSCT may be increasingly used with near-universal donor availability allowing nearly all patients to undergo transplantation.

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