Outcomes from hematopoietic cell transplantation from unrelated donors continue to improve.

Outcomes From Unrelated Donor Hematopoietic Stem Cell Transplantation
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Background: Allogeneic hematopoietic cell transplantation (HCT) offers a curative treatment option for management of a variety of hematologic malignancies. While sibling donors have been the gold standard for adult patients in need of an HCT, not all patients have a suitable family donor. The availability of unrelated volunteer donor registries and alternative stem cell sources has expanded the wide application of this procedure. Methods: PubMed and MEDLINE were searched for human trials and the English language from 2001 to 2011. Factors influencing transplantation outcomes involving unrelated donors over the last decade are discussed, and feasible alternative stem cell sources when a matched unrelated donor is not available are reviewed. Results: HCT using a matched unrelated donor offers outcomes comparable to sibling HCT due to current molecular-based HLA typing and improvements in conditioning regimens and/or supportive care. The primary factor that contributes to improved outcome is the degree of donor-to-recipient HLA matching. The selection of younger unrelated donors has also been associated with improved outcomes in HCT. Evidence supports the universal application of matched unrelated donors even in high-risk leukemia and/or older patients. In adult patients without a matched related donor, other promising options as stem cell source include mismatched unrelated donors, umbilical cord blood units, and haploidentical donors. Conclusions: With current methodologies for molecular HLA typing and supportive care tools, outcomes of transplants with matched unrelated donors are comparable to those achieved with sibling donors. Alternative stem cell donors when a matched unrelated donor is not available are feasible expanding the stem cell donor pool.
Unrelated donor transplants account for 41% of the allogeneic transplants performed by the European Group for Blood and Marrow Transplantation (EBMT). More importantly, several clinical studies have shown similar results when comparing unrelated donors with sibling donors, regardless of malignancy diagnosis. These results are encouraging since not all patients have a matched related donor.

The universal application of allogeneic transplantation is limited by the cost of the procedure, which increases with the use of unrelated donors. The donor search and the inpatient care during the first 100 days following a transplant account for the majority of the costs, and severe complications post-transplant also increase costs. However, the high degree of effectiveness in certain patients results in a cost-effectiveness ratio that is comparable to that of other accepted complex medical interventions, and its role should be examined in the context of emerging pharmacological interventions.

This review of the literature examines the evidence supporting the use of unrelated donor as a viable and comparable option to treat hematologic conditions.

Methods
PubMed and MEDLINE were searched for human trials and the English language from 2001 to 2011. Factors influencing better outcomes reported over the last decade are discussed herein. This review also summarizes feasible alternative stem cell sources when a matched unrelated donor is not available to proceed with an allogeneic transplant.

Matched Unrelated vs Related Donor Transplantation
Early evidence has shown that transplantation in early chronic phase chronic myelogenous leukemia (CML) using an unrelated donor resulted in overall and disease-free survival approaching that of matched related transplants. A retrospective study by the Australasian Bone Marrow Transplant Recipient Registry between 1992 and 2002, involving a relatively small (n = 105) and uniform patient cohort with acute myelogenous leukemia (AML), showed equivalent 5-year disease-free survival, transplant-related mortality at 100 days, and cumulative incidence of acute GVHD for matched related and unrelated donor transplants. Additional studies in AML have also shown similar results despite intrinsic limitations of protocol design and/or the use of novel myeloablative regimens.

More recently, with the development of reduced-intensity chemotherapy conditioning and improved supportive care, allogeneic transplantation options have been extended for patients older than 55 years of age. The cooperative German Transplant Study Group reported the results of matched related or unrelated donors in the era of high-resolution DNA-based HLA typing in 368 patients older than 50 years with standard- or high-risk AML. In transplants performed from 1995 to 2005, overall and event-free survival in patients with a matched unrelated donor were similar to those with a matched related donor. Event-free survival rates in matched related vs matched unrelated donor transplants were 45% vs 51% at 1 year, 57% vs 57% at 2 years, and 35% at 30% at 5 years. In a multivariate model, the adjusted relative risk of overall and event-free survival following allogeneic hematopoietic cell transplantation in AML was 0.7 (95% confidence interval [CI], 0.4–1.1) in matched unrelated donors and 0.8 (95% CI, 0.5–1.3) in matched related donors, suggesting that matched unrelated donor transplants are permissible in the older population and are safer compared to a decade ago. A recent retrospective analysis of 1,448 patients from a single institution compared the outcome of patients with high- vs intermediate-risk AML who were transplanted with matched related or unrelated donors, excluding patients with acute leukemia in first remission without high-risk features or CML. Previous retrospective studies included patients with CML who are no longer transplanted front-line with the introduction of tyrosine kinase inhibitors. In patients with high-risk disease, no statistically significant differences occurred in disease-free survival or in nonrelapse mortality if transplanted with a matched unrelated vs related donor. For intermediate-risk disease, matched unrelated donor transplantation was associated with a modest lower survival compared with matched related donor transplantation. This study solidifies our understanding of the comparable relative outcomes between matched unrelated vs related donors in patients with high-risk disease.

There is clear evidence of the graft-vs-leukemia effect in acute lymphoblastic leukemia (ALL), resulting in prolonged leukemia-free survival. An international collaboration (MRC UKALL XII/ECOG E2993) established matched related donor allogeneic transplantation as the treatment of choice for patients up to 55 years of age with standard-risk ALL in remission, providing the best chance of preventing relapse and improving long-term survival. In this study, high-risk patients benefited less from having a donor than the standard-risk patients had in terms of overall survival. For high-risk patients, the donor-vs-no-donor comparison showed a 5-year overall survival rate of 41% vs 35%, which was not significantly superior. The relapse rate for high-risk patients was still substantially reduced; therefore, the transplant toxicity was thought to be responsible for similar overall survival in this population. In young adults between 16 and 21 years of age, intensive “pediatric-type” chemotherapy confers a 5-year event-free survival rate of approximately 70%. Allogeneic transplantation should be reserved for CR2 patients. A systematic, evidence-based review of publications reported in early 2000 comparing matched related to matched unrelated donors supported the use of unrelated donors for high-risk ALL in CR1 but not for...
Factors Influencing Unrelated Donor Transplantation Outcomes

A recent evaluation of 38,060 transplants performed in the United States and Canadian centers and reported to the CIBMTR shows a significant improvement for transplants performed from 2004 to 2005 compared with those performed from 1994 to 1995.27 Day 100 and 1-year overall survival was significantly improved by most factors, regardless of disease diagnosis and/or stem cell source (matched related vs unrelated donor). Improvement in outcome over the past decade is attributed to multiple factors, primarily donor selection and better supportive care. The primary criterion for outcome of unrelated donor transplants depends on the degree of HLA matching between the donor and recipient. The development of DNA-based tissue typing that enables typing at higher resolution has significantly improved our ability to identify the ideal matched donor. Current techniques provide the ability to discriminate between allelic differences at the HLA class I (A, B, C) and II (DQ, DR, DP) antigens. HLA-A, -B, -C, or DRB1 must be typed at high resolution by DNA-based methods. Several studies have documented the importance of HLA matching in transplantation outcomes (graft failure, GVHD, and death), although HLA disparity and survival differ among these studies.28-31 Data from the National Marrow Donor Program (NMDP) from 3,857 transplants performed from 1988 to 2003 with myeloablative conditioning showed that high-resolution DNA matching for HLA-A, -B, -C, or -DRB1 (8/8 match) was the minimum level of matching associated with the highest survival as HLA-DQ or HLA-DP mismatch was not associated with adverse transplantation outcomes. Most transplants were T-cell replete with calcineurin inhibitor containing GVHD prophylaxis (78%) and using bone marrow (94%) as the stem cell source.31 The NMDP has provided guidelines for optimal donor-recipient matching criteria.32

“Be the Match Registry,” operated by the NMDP program, currently has 9 million potential donors and nearly 150,000 cord blood units. Through searches via the NMDP, the global availability of donors can be expanded to almost 20 million potential donors. The NMDP matching algorithm HapLogicSM, which uses advanced logic to predict a donor’s high resolution match and utilizes mathematical formulas to predict HLA-DR match in HLA-A,-B-typed donors, has facilitated the identification of donors. As the donor population is mobile through time, donor location and medical-social conditions may delay the transplant process from the original plan. The current goal of the NMDP is to optimize the donor search process in order to expand donor availability.

Killer immunoglobulin-like receptor (KIR) ligand incompatibility in the graft-vs-host direction in haplo-type-mismatched transplants suggests a possible clinical benefit as it may allow early recovery of donor alloreactive natural killer cells with enhanced anti-leukemia activity in AML.33 Farag et al34 investigated the effect of KIR ligand mismatching on the outcome of unrelated donor hematopoietic cell transplantation in the T-replete setting. This study did not support the choice of selection of unrelated donor based on KIR ligand mismatch determined by HLA typing. More recently, Cooley et al35,36 analyzed the outcomes of 1,409 patients, taking into account the role for KIR gene variability. Donor KIR genotype influenced transplantation outcomes for patients with AML but not for those with ALL. KIR genotyping of several best HLA-matched potential unrelated donors should result in superior disease-free survival for patients with AML and may change clinical practice in the future.

When patients have multiple similar HLA-matched donors, a prioritization tree should be established to choose the best donor. Non-HLA factors considered in donor selection of unrelated donors include donor and recipient age, sex, parity, cytomegalovirus (CMV) serostatus, and ABO blood type. The evidence supporting these non-HLA factors remains conflicting.31,37-39 In a retrospective review of 6,878 transplants, the NMDP found that
donor age was the only trait significantly associated with overall and disease-free survival and also that the use of younger donors may lower the incidence of GVHD and improve hematopoietic cell transplantation survival.37 Kröger et al40 confirmed these findings in a multivariate analysis reported in abstract form in 2010. In contrast, Lee et al31 found in a multivariate analysis that there was no association between donor age and survival.

Other historical non-HLA factors that have shown no impact in transplant survival include CMV serostatus, donor parity, donor race, and/or ABO blood type. In CMV-negative patients, CMV-positive donors led to a higher risk of CMV infection. For CMV-positive patients, a CMV-positive donor may be preferable.38 Randolph et al41 analyzed donor-patient sex matching in more than 3,000 matched related donor transplants. Male recipients of female transplants had the lowest risk for relapse and the greatest risk for GVHD, suggesting a potential beneficial role for female into male pairs in matched related donors; this finding should be explored in the unrelated donor setting. Stem cell source could potentially affect allogeneic transplantation outcome as well.18 Extensive studies have compared bone marrow vs peripheral blood stem cells in the matched related donor setting.42 The BMT Clinical Trials Network (BMT-CTN) recently completed accrual to a United States randomized trial (NCT00075816) to determine if there is a difference in outcome depending on stem cell source in the unrelated setting. Due to an ongoing evolution of clinical practice in conditioning regimens, graft sources, GVHD prophylaxis, and supportive care, recommendations for the best donor should be based on the best available evidence to date.43 Recommendations for identifying the ideal donor are available at http://marrow.org/ and at http://bioinformatics.nmdp.org/.32,44

Alternative Stem Cell Sources in Unrelated Donor Transplantation

When a matched unrelated donor is not identified, alternative stem cell donors include mismatched unrelated donors, UCB units, or haploidentical donors. The choice of donor selection in adults depends on availability, cell dose, urgency of the transplant, and potential need for donor lymphocyte infusions. No prospective randomized study has been performed to determine which alternative stem cell source is preferable. Donor selection ultimately depends on availability, transplant urgency, and expertise at the transplant center. Studies comparing UCB to mismatched unrelated donors have shown that neither source is superior. Reported comparable results have been encouraging, concluding that UCB is an acceptable stem cell source for adults.45,46 A recent CIBMTR report supports improved transplant-related mortality using a matched unrelated donor compared to UCB and a mismatched unrelated donor; with comparable leukemia-free survival and a reduced incidence of GVHD with the use of UCB.47 The low cell dose in a UCB graft has markedly restricted the use of UCB since the majority of adults cannot find a UCB unit that provides the recommended nucleated cell dose of 2.5 × 10^7/kg. The concept of double UCB grafts to overcome the cell dose barrier has shown encouraging results in adults.48 The use of UCB is reviewed in detail elsewhere in this journal edition [Claudio G. Brunstein; pp 222-236]. Haploidentical donors are immediately available and are available following transplant for cellular immunotherapy. This procedure is complicated by GVHD and infections due to poor immune reconstitution as a result of T-cell depletion.49,50

In mismatched unrelated donor transplants, GVHD remains the principal obstacle in achieving successful outcomes. Serious infections and impairment of generalized immune function are responsible for GVHD mortality. GVHD incidence and severity depend primarily on donor and recipient matching for HLA and the regimen used for postgrafting immune suppression. Lee et al31 reported an incidence of grade III-IV acute GVHD of 44% (95% CI, 40–48) in 653 transplants with two mismatches for HLA-A, -B, -C, or -DRB1 sequences, 37% (95% CI, 34–40) in 985 transplants with one mismatch, and 28% (95% CI, 26–30) in 1,840 matched related donor transplants. A single mismatch at HLA-A, -B, -C, or -DRB1 (7/8 match) was associated with higher mortality (relative risk, 1.25; 95% CI, 1.13–1.38; P < .001) and a 1-year survival rate of 43% compared with 52% for 8/8 matched pairs. Mismatching at two or more loci increased the risk of GVHD and mortality. This study was in contrast to a previous report that analyzed fewer patients (n = 1,874), although different statistical methods may explain the discrepant results.50 An additional analysis of 1,933 transplants performed between 1999 and 2006 with unrelated donor peripheral blood stem cells has shown that an 8/8 match at HLA-A, -B, -C, or -DRB1 resulted in an overall survival rate of 56% compared with 47% in 7/8 HLA-matched pairs. HLA-C antigen mismatches (n = 189) were associated with a worse outcome compared with HLA-C allele mismatches (n = 61). HLA-A antigen/allele (n = 136), HLA-DRB1 allele (n = 39), or HLA-DQ antigen/allele (n = 114) mismatches did not affect outcomes. While conclusive regarding HLA-C mismatches, the sample size of this study was too small to establish the role of other antigen/allele mismatches.51

GVHD prevention has been based largely on the use of pharmacological agents and, to a lesser degree, on the depletion of T cells from the stem cell graft.52,53 A phase III, multicenter, controlled trial established tacrolimus plus methotrexate as the state-of-the-art regimen for GVHD prophylaxis in the unrelated donor setting.54 An alternative option that utilized a combination of tacrolimus and sirolimus to avoid methotrexate toxicity has resulted in a comparable incidence of GVHD in matched related vs unrelated donors.56 There is a need for better
GVHD prevention after transplantation from unrelated grafts mismatched for 1 or 2 alleles for patients with an increased incidence of acute GVHD. Extensive study has focused on the use of antithymocyte globulin (ATG) for GVHD prophylaxis and therapy. Initially Bacigalupo et al reported a pilot study and two randomized studies showing that rabbit ATG at 15 mg/kg resulted in a significant reduction of acute and chronic GVHD but with an increase in serious infection. A variety of ATG doses and formulations have been tested over time with diverse results. Investigators have reported the use of ATG (1 mg/kg on day 3, 3, 25 mg/kg per day on day 2 and 1 before stem cell infusion) followed by tacrolimus plus methotrexate, a prophylaxis approach that effectively decreased the occurrence of grade III-IV acute and severe chronic GVHD in mismatched unrelated donors. A recent meta-analysis reported that ATG has a beneficial effect on the prevention of severe grade III-IV acute GVHD but has no significant affect on overall survival.

Conclusions
Unrelated donor transplantation is a feasible option when an HLA-matched sibling is not available. With current methodologies for molecular HLA typing and supportive care tools, patient outcomes are comparable to results achieved when a sibling donor is available. Evidence supports the universal application of unrelated donor transplantation for a variety of malignant hematologic conditions, including high-risk leukemia, and for its safety in older patients, who are mainly affected by these conditions. The primary factor that contributes to improved outcome is the degree of donor-to-recipient HLA matching. KIR genotyping could help to identify grafts with favorable KIR gene content that may result in superior disease-free survival for patients with AML. Selecting younger unrelated donors has resulted in improved hematopoietic cell transplantation outcomes. For adult patients without a matched unrelated donor, feasible options with promising results include use of mismatched unrelated donors, UCB sources, or haploidentical donors.

References


