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Does matched unrelated donor transplantation have the same outcome as matched sibling transplantation in unselected patients?

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Abstract

Outcome differences by donor type for allogeneic hematopoietic stem cell transplantation vary based on disease and recipient age. The following paper summarizes analyses of transplant outcome among adults with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who received transplants from HLA-identical siblings, fully (8/8) matched unrelated donors (MUD), or mismatched (7/8) unrelated donors. The paper also reviews transplantation outcomes for children with leukemia who had genotypically matched sibling donors, mismatched (7/8) or phenotypically matched related donors or matched (8/8) unrelated donors. Morbidity is higher after unrelated donor vs HLA-matched sibling transplants due to higher rates of acute graft-vs-host disease (GVHD). However, survival is similar or within 10%–15% with all studies donor type, with disease-specific differences probably reflecting differences in underlying population risk for treatment-related mortality.

Keywords

acute myeloid leukemia; allogeneic transplant; HLA-identical sibling; matched unrelated donor; myelodysplastic syndrome (MDS); pediatric

Introduction

According to the Center for International Blood and Marrow Transplant Research (CIBMTR), between 7000 and 8000 allogeneic transplantations are performed each year in the United States. Most of these are for hematologic malignancies, particularly acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) [1]. Although historically allogeneic transplants were limited to those patients who had human leukocyte antigen (HLA)-identical siblings, over the past 5–6 years, for the first time, the number of alternative donor (mismatched related or unrelated) transplants now exceeds the number of HLA-identical sibling transplants. This is in part driven by the fact that donors can be found for more people, but also by the fact that

Conflict of interest statement

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substantial reductions in transplant-related mortality in the unrelated donor setting make it a more attractive therapeutic choice.

Data from the National Marrow Donor Program (NMDP) and CIBMTR on the outcome of unrelated vs HLA-identical sibling transplantation in patients with leukemia or MDS show that 1 year survival rates have come very close together since the late 1980s [1].

When median age at diagnosis of hematologic malignancies was compared with median ages of those receiving HLA-identical sibling donor and unrelated donor transplants 5 years ago, the median age of transplant recipients was much lower, indicating that many patients were not considered transplant candidates on the basis of age (Table 1a). Updated data (Table 1b) show that the median age of transplant recipients with both related and unrelated donors has increased, indicating that transplantation is being offered to a much broader range of patients with these diseases.

Comparison of donor type in adults with AML

A cohort study of 2223 patients with AML [2] analyzed transplant outcomes by donor type in adults transplanted in US centers from 2002 to 2006. All of the unrelated donor recipient pairs had high resolution typing for HLA A, B, C, and DRB1. All patients were older than 21 years and received T-cell replete transplants. The primary endpoint was 3-year survival. Multivariate analysis considered age, race, sex, performance score at transplant, cytomegalovirus status, leukemia status or stage, disease duration, cytogenetics and white blood cell count at diagnosis, therapy-related AML/MDS, extramedullary presentation, stem cell source, conditioning regimen, and graft-vs-host disease (GVHD) prophylaxis.

Of the 2223 patients [2], 624 received HLA-identical sibling transplants, 1193 received 8/8 HLA-matched unrelated donor (MUD) transplants, and 406 received 7/8 HLA-MUD transplants. Median age at transplant was around 51 years for HLA-matched sibling and 8/8 MUD transplant recipients, while the 7/8 MUD transplant recipients were younger, with a median age of 48 years. The HLA-identical sibling transplant recipients tended to have better performance scores. Median follow-up was sufficient in all groups for the analysis.

Analysis of disease characteristics reveals that 6% of patients in all groups had therapy-related AML [2]. Patients were most likely to be in first complete remission at time of transplant, especially if they received an HLA-identical sibling transplant. A higher proportion of patients with poor risk based on cytogenetics received MUD transplants.

Characteristics of the transplantation regimen also varied between the groups. The source of stem cells was more likely to be bone marrow for unrelated donor than HLA-identical sibling transplants. There was more use of reduced-intensity conditioning regimens and a higher use of tacrolimus vs cyclosporine for GVHD prophylaxis in the unrelated donor setting.

When outcomes were adjusted for patient characteristics in a multivariate regression [2], there was a higher risk of grade 2–4 acute GVHD with unrelated donors (~50%) vs HLA-identical sibling donors (~30%). There was also a higher risk of grade 3–4 acute GVHD

with unrelated donor transplants that was statistically significant, but the risk of chronic GVHD was ~45% with all donor types. The risk of treatment-related mortality was significantly higher with a mismatched (7/8 MUD) transplant but not with an 8/8 MUD transplant compared to an HLA-identical sibling transplant. There was no significant difference in the risk of relapse by donor type. Probability of overall survival at 3 years after transplant was virtually the same (~40%) with all donor types after adjusting for differences in patient characteristics. However, there was a statistically significant difference in early mortality with the 7/8 MUD transplants. Three-year leukemia-free survival rates were also similar among the 3 donor types.

Comparison of donor type in adults with MDS

A similar study is underway in 701 patients who received allogeneic transplants for MDS, 176 from HLA-identical sibling donors, 413 from 8/8 MUD, and 112 from 7/8 MUD. Baseline characteristics of the MDS patients are similar among the different donor types, except for a substantially longer time from diagnosis to transplant in the patients who received a MUD transplant (8 months for 8/8 MUD and 10 months for 7/8 MUD vs 6 months for HLA-identical sibling donor recipients). Preliminary data indicate higher acute GVHD and treatment-related mortality rates with unrelated vs HLA-identical sibling donors. Overall survival rates are somewhat lower with both matched and mismatched unrelated donors but within 10%–20% of rates seen with HLA-identical sibling donors. One limitation of this study is the limited information about therapies pretransplant and response to those therapies, so outcomes could not be adequately adjusted for those things.

A recent review of unpublished CIBMTR data showed that survival rates after unrelated (matched and mismatched) donor transplants and HLA-identical sibling transplants for adults with ALL transplanted between 2000 and 2009 were similar. Regardless of donor type, outcomes are better when transplantation is done earlier in the course of the disease.

Comparison of donor type in pediatric patients with leukemia and MDS

In a study in a pediatric population [3], transplantation outcomes were analyzed in patients younger than 18 years old with diagnoses of AML, ALL, chronic myeloid leukemia (CML), or MDS. This study included unrelated donor transplants as well as related transplants that were either phenotypically identical (a parent or a cousin who was phenotypically matched but not a genotypically HLA-identical sibling) or a single locus mismatched transplant. When split by donor type, 1208 received an HLA-identical matched sibling donor transplant, 151 received a 1-antigen mismatched or phenotypically matched related donor transplant, and 266 received an 8/8 MUD transplant.

When the distribution of patient and disease characteristics was analyzed [3], median age by donor type was similar (~9 years old); there was a higher frequency of AML in the matched sibling cohort; there was a higher proportion of patients in first remission in both related donor cohorts vs the unrelated donor cohorts; and there was a shorter interval between diagnosis and transplant in the related donor cohorts vs unrelated donor cohorts. Median follow-up was more than 5 years in all cohorts.

Analysis of transplant outcomes revealed a higher risk of acute GVHD with either the mismatched related or the unrelated alternative donors vs the HLA-matched sibling donors. There was also a higher risk of chronic GVHD and a higher risk of treatment-related mortality among those with mismatched related or unrelated matched donor recipients vs HLA-identical sibling donor recipients, but there was no difference in relapse among the cohorts. There was not a significant difference in acute or chronic GVHD, treatment-related mortality, or relapse between the fully matched unrelated donor and the minimally mismatched related donor cohorts. There was a survival advantage for the matched sibling cohort vs the unrelated donor and mismatched related donor cohorts at 3 years (61% vs ~50%, respectively).

Differences in outcomes between the types of donors in the matched sibling cohort vs the alternative donors for children may be explained by research that shows that children who have HLA-identical sibling donors have younger donors than those who receive transplants from alternative donors. A recent study shows a significant adverse impact of older donor age, which can really only be studied in the unrelated donor setting, since donor and recipient age are highly correlated in the related donor setting [4]. Therefore, children who receive an alternative donor transplant are receiving a transplant not only from a donor who is more genetically dissimilar, but also from a donor who is likely older than if they had a sibling donor.

Conclusions

Morbidity as measured by the risk of GVHD is higher with unrelated vs HLA-matched sibling transplants, primarily due to more acute GVHD. Importantly, however, 3–5 year survival rates are very close (within 10%–15%) with unrelated, matched or minimally mismatched, and HLA-identical sibling donors. Disease-specific differences between AML and MDS and between adults and children likely reflect the underlying risk for treatment-related mortality of the population and differences in pretransplant therapies. These data suggest that transplantation should be pursued for patients who have diseases for which it is the best therapy, even if a matched donor cannot be found in the family. Given the current size of unrelated donor registries, 8/8 or 7/8 matched donors can be found for more than 70% of patients, providing effective therapy for a large proportion of these patients who may have few other effective treatment options.

References

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Table 1.

Median age of patients with hematologic malignancies at time of diagnosis and time of transplant. (a) Data from 2007. (b) Most recent data.

	All patients*(% >65 y)	HLA-identical sibling donor (% >65 y)	Unrelated donor (% >65 y)
a.			
NHL	65 y (50%)	46 y (1%)	43 y (1%)
Myeloma	70 y (60%)	49 y (1%)	47 y (0%)
AML	50 y (23%)	40 y (2%)	35 y (1%)
Hodgkin	35 y (10%)	34 y (0%)	32 y (2%)
MDS	72 y (71%)	53 y (3%)	50 y (0%)
CML	55 y (35%)	38 y (1%)	35 y (1%)
ALL	15 y (2%)	22 y (1%)	18 y (1%)
b.			
NHL	65 y (50%)	53 y (7%)	53 y (9%)
Myeloma	70 y (60%)	55 y (11%)	52 y (2%)
AML	50 y (23%)	51 y (10%)	49 y (12%)
Hodgkin	35 y (10%)	32 y (0%)	34 y (5%)
MDS	71 y (80%)	57 y (14%)	57 y (19%)
CML	55 y (35%)	47 y (4%)	42 y (3%)
ALL	15 y (2%)	32 y (2%)	27 y (2%)