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What are the most important donor and recipient factors affecting the outcome of related and unrelated allogeneic transplantation?

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Abstract

Several recipient and donor risk factors affect outcome after transplantation with allogeneic hematopoietic stem cells. The most important recipient risk factors are patient age, comorbidity, performance status, cytomegalovirus (CMV) status, and disease considerations, such as diagnosis, stage, and cytogenetic risk. Prior chemotherapy regimens, patient race, and IL10 promoter polymorphism also appear to have some impact, but to a lesser extent. The most important donor factor is the level of HLA mismatch. Donor gender, relation, age, and KIR genotype also affect outcome. Donor CMV serology, parity, and race do not appear to affect outcome. These factors must all be considered in relation to one another when selecting whether to recommend patients for transplant.

Keywords

transplant; acute leukemia; patient; recipient; donor; risk factors; HLA mismatch; comorbidity; related; unrelated

INTRODUCTION

Several recipient and donor factors predict outcome after allogeneic hematopoietic stem cell transplantation, and some factors have a more profound impact than others. Some recipient factors not only predict outcome in transplantation, but also in nontransplant therapies. Therefore, risk factors must be considered in the context of the benefit ratio for transplant vs nontransplant therapy. Risk factors must also be considered in relation to each other, and all of this information must be considered when selecting donors and patients for transplant.

RECIPIENT RISK FACTORS

Patient disease

A patient's diagnosis is the foremost predictor of outcome (Table 1). Different disease types and characteristics have dissimilar prognoses related to transplant outcome. For example, patients with myelodysplastic syndromes (MDS) have a better prognosis overall than

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patients with acute myeloid leukemia (AML). Patients with disease in stage CR1 have a better prognosis than those in CR2, and patients with active, detectable disease with a low level of tumor burden do better than those who have extensive disease.

Cytogenetic risk

Intrinsic risk, defined by the International Prognostic Scoring System (IPSS), is a major predictive factor. For example, patients with core binding factor translocations (t(8;21)) do better than patients with del 7 or complex cytogenetics. Allogeneic sibling transplant in first remission is associated with worse outcome in poor-risk AML than in good-risk or intermediate-risk AML, as shown by a meta-analysis from the Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research (HOVON-SAKK).¹ However, looking at the benefit of transplant vs nontransplant therapies according to risk, patients with poor-risk disease actually have more of an advantage with transplant. Good-risk patients do not benefit from transplant overall in a significant way because they have higher transplant-related mortality, although they have lower relapse rates after allografting.

Transplantation delay

In general, patients who are transplanted shortly after diagnosis fare better than those who are transplanted a long time after diagnosis. A decision analysis² in MDS based on cumulative data from the International Bone Marrow Transplant Registry (IBMTR) and other sources showed that patients with low-risk or intermediate-1 disease did better when transplanted at the time of disease progression rather than at the time of diagnosis. However, transplantation at a fixed interval after diagnosis (but before transformation to AML) maximized overall discounted life expectancy. Intermediate-2 or high-risk patients did better if transplanted at the time of diagnosis. However, patients with intermediate-2 risk suffered the largest decline in life expectancy with transplantation delay because these patients have the highest rate of disease progression. Patients with high-risk disease showed a small gain of life expectancy with transplant compared to nontransplant therapy. With transplantation delay, high-risk patients suffered only a moderate loss in already low life expectancy.

Patient age

The effect of patient age on outcome has been studied for as long as risk factors associated with transplantation have been studied. The HOVON-SAKK donor analysis showed that patients under the age of 40 years obtain a substantial benefit from transplant when compared to patients over 40 years, who do not benefit from transplant.¹ Similar data were obtained from the acute lymphoblastic leukemia (ALL) treatment trial that was conducted by the Eastern Cooperative Oncology Group (ECOG) and the Medical Research Council (MRC).³ ALL patients older than 35 years did not benefit from transplant because of increased transplant-related mortality. It is still unknown whether reduced-intensity regimens or improved control of graft-versus-host disease will offset this transplant-related mortality risk.

Patient comorbidities

The number of patient comorbidities is related to age. With advancing age, the proportion of patients with 0 comorbidities decreases and the proportion of patients with 1 or more comorbidities increases.⁴ In their earlier analysis of approximately 1000 patients transplanted with either nonablative or ablative therapy at the Fred Hutchinson Cancer Research Center in Seattle, Sorror et al found that the Charlson Comorbidity Index (CCI), which is used to predict survival in the general population, is as good a predictor of outcome in transplant populations as it is in nontransplant patients.^{5,6}

To make the Index more sensitive, Sorror et al modified the CCI to include comorbidity definitions that are specific for the transplant population, resulting in an index (HCT-CCI) with improved predictive value for hematopoietic cell transplant (HCT) patients.⁴ In the HCT-CCI, 4 parameters (lung injury, liver injury, heart valve, and prior solid tumor) are assigned a score between 1 and 3, according to their degree of abnormality. Kidney, peptic ulcer, and rheumatologic comorbidities are given an HCT-CI score of 2. Other comorbidities, such as active infection, coronary artery or cerebrovascular disease, inflammatory bowel disease, obesity, diabetes, and psychiatric history, have a lower impact on outcome. The study found that HCT-CI predicts patient survival after transplantation at all scores. At MD Anderson Cancer Center in Houston, the same scoring system was also predictive for outcome, but the MD Anderson series had many patients that received higher-intensity therapy, not the minimal-intensity therapy that was used in Seattle. It is still unclear whether these risks can be overcome with a reduced-intensity regimen or a regimen with intensity adjusted to the patient's age or comorbidity.

A recent multivariate analysis of survival showed that HCT-CI risk score is independent of age and Karnofsky performance status.⁷ Older patients probably have inferior outcomes because they are more susceptible to complications and die more of graft-versus-host disease. Age, HCT-CI score, and Karnofsky performance status must all be considered when selecting patients for transplant therapies and when designing prospective trials to compare transplant therapies to nontransplant therapies.

Other factors

Other recipient factors, such as number of prior chemotherapy regimens,⁸ patient race, and IL-10 promoter polymorphism, have been studied extensively. The difference between racial or ethnic minorities, such as Hispanics and African Americans, has been well-documented.^{9–12} The IL-10 promoter polymorphism or other immune response genes also appear to predict outcome.^{13,14} Though cytomegalovirus (CMV) status was important before the era of the anti-CMV drugs, that effect has almost been completely neutralized in the patients with low-risk disease. The same is not true for patients with high-risk MDS or AML who are transplanted from an unrelated donor, but it is possible that a newer anti-CMV drug, like maribavir, may actually help the higher-risk patient population.

DONOR FACTORS

Several factors are considered in the selection of donors for patients receiving transplant (Table 2). These donor factors include human leukocyte antigen (HLA) mismatch, sibling gender, relation, age, KIR genotype, CMV serology, parity, and donor race. CMV serology does not appear to confer risk significantly even to CMV-negative patients. Donor parity and donor race also do not appear to confer additional risk once other variables are taken into account.

Sibling gender

An analysis of 4000 transplant patients in Seattle showed that sibling gender affected survival when a female sibling donated to a male transplant patient.¹⁵ In these female to male transplants, the risk of relapse is decreased, but the risk of mortality from a transplant-related complication, such as graft-versus-host-disease, is increased, thus decreasing survival overall. In female recipients, the sibling donor's gender does not have a significant effect. The findings were similar for patients with chronic myeloid leukemia (CML), AML, and ALL.

Donor relation and HLA matching

HLA mismatch was the first donor factor to be identified that predicted mortality for transplant patients. This discovery led to the practice of using HLA-identical siblings for transplants rather than donors with HLA mismatch. Furthermore, for many years, it has been felt that unrelated-donor transplants are more complicated than related-donor transplants. Because of this, the use of unrelated donors is mostly restricted to patients with increased disease risk. This makes assessing the increment of risk more difficult when using an unrelated donor.

In patients with chronic phase CML who were transplanted within 1 year of diagnosis, there was a 10% drop in disease-free survival when using a matched unrelated donor compared to rates for transplants using a matched sibling donor.¹⁶ However, that study did not type at HLA-C, and mismatch at this antigen may account for the increased risk in the unrelated-donor transplants.¹⁷ Mismatches at HLA-DQ or -DP did not appear to affect outcome. It has recently been suggested that HLA-DP mismatch may pose a significant risk factor for graft-versus-host disease and transplant-related mortality but may protect against relapse.¹⁸ Therefore, the net effect of HLA-DP matching on survival may be null.

There is a significant increase of 20% in the relative risk of death in patients who are receiving transplants with 1 sequence mismatch at HLA-A, -B, -C, or -DRB1 when compared to those receiving matched unrelated donor transplants.¹⁹ In addition, the risk from sequence mismatch for 1 single allele (of 8) is the same as for 1 single serotype. Transplant patients have an incremental decrease in survival estimates of approximately 10% for each additional donor locus mismatch at HLA-A, -B, -C, or -DR. If DNA sequence matching is used to select available donors, overall patient survival could be improved by as much as 10%. Though there are no prospective data to confirm which patients should receive mismatched transplants, high-risk patients in first remission, patients who fail primary induction, and patients with relapsed leukemia may be acceptable candidates for unrelated-donor transplants with 1 HLA mismatch. These patients are unlikely to achieve a superior outcome with current chemotherapy.

KIR genotype

On chromosome 19, a complex of killing immunoglobulin-like receptors (KIR) are expressed, some of which are inhibitor receptors. There are 6 genes for activating KIRs (2DS2, 2DS3, 3DS1, 2DS4, 2DS5, and 2DS1).²⁰ Individuals differ for the number of activating KIRs in their genome. Those with B haplotypes have 1 or more of the activating KIRs, while those with A haplotypes, about 25% of the population, have no activating KIRs. In a study of 400 transplants in AML patients, the survival rate was doubled when the donor had a B haplotype,²¹ because of the decreased relapse rate and the decreased transplant-related mortality. These findings need to be validated in future work.

Other factors

Donor age is the only other donor factor that appears to be as important as HLA mismatching for unrelated-donor transplants.²² Donor CMV positivity, female donor with pregnancy, ABO compatibility, and donor race do not matter for recipient survival.

CONCLUSION

Though there are several recipient and donor factors that predict outcome in hematopoietic stem cell transplantation, the most important factors for recipients appear to be patient disease factors, patient age, patient comorbidity, performance status, and patient CMV status. The most important donor factor is level of HLA mismatch, but sibling gender, donor

relation, age, and KIR genotype also affect outcome. Several factors must be taken into account when selecting donors and patients for transplantation. Some of these factors may become less important as our understanding and technology advance.

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Table 1

Recipient risk factors for transplantation

Risk factor	Impact
Diagnosis	Patients with AML have worse prognosis than those with MDS
Stage	Patients in CR2 do worse than those in CR1
Tumor load	Patients with active, detectable disease and a low level of tumor burden do better than those who have extensive disease
Time to transplant	Patients who have been transplanted shortly after diagnosis do better than those transplanted a long time after diagnosis
Intrinsic risk	Patients with core binding factor translocations (t[8;21]) do better than patients with del 7 or complex cytogenetics
Age	Patients < 40 years obtain a substantial benefit from transplant when compared to patients > 40
Comorbidity	The predictive value of the CCI was refined when hematopoietic cell transplantation-specific measures were incorporated (HCT-CI)
CMV status	Does not affect low-risk patients but negatively impacts high-risk patients or those with unrelated-donor transplants
Prior chemotherapy regimens	Outcomes were similar in patients with de novo disease and previously treated disease
Patient race	Hispanics have lower 1-year and 3-year survival than Caucasians
IL-10 promoter polymorphism	Appears to predict outcome

AML, acute myeloid leukemia; CCI, Charlson Comorbidity Index; CR, complete remission; del, deletion; HCT, hematopoietic cell transplant; IL, interleukin; MDS, myelodysplastic syndromes

Table 2

Donor risk factors for transplantation

Risk factor	Impact
HLA mismatch	Most important factor; each mismatch decreases disease- free survival by 10%
Sibling gender	Female donor to male recipient decreases survival
Relation	Difficult to determine because used mostly in high-risk patients for whom related-transplant is not an option
Age	Appears to be as important as HLA mismatching for unrelated-donor transplants
KIR genotype	B haplotype doubles survival rates
CMV serology	Does not appear to affect outcome
Parity	Does not appear to affect outcome
Donor race	Does not appear to affect outcome

CMV, cytomegalovirus; HLA, human leukocyte antigen; KIR, killing immunoglobulin-like receptor