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DONOR CHARACTERISTICS AS RISK FACTORS IN RECIPIENTS AFTER TRANSPLANTATION OF BONE MARROW FROM UNRELATED DONORS: THE EFFECT OF DONOR AGE

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ABSTRACT

INTRODUCTION

Utilizing marrow from unrelated volunteer donors is an established method of treatment for individuals requiring an allogeneic stem cell transplant but lacking a sibling donor with matching HLA. The aim of present study is to "assess the donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors & to report associations between outcome & donor age".

MATERIAL & METHODS

The present retrospective study was conducted at a tertiary care centre among patients who required bone marrow transplantation during the duration of study (2 years).

Through convenient sampling a total 100 patients who underwent bone marrow transplantation from an unrelated donor were selected on the basis of inclusion & exclusion criteria. The evaluation addressed possible effects of cytomegalovirus serologic status, donor age, sex & ABO compatibility on overall & disease free survival.

RESULTS

The recipient characteristics according to age with respect to gender, mean age, mean time, diseases, CMMV status, match status & GVHD prophylaxis was tabulated. Age was the only donor trait significantly associated with overall & disease-free survival.

All the patient of transplantation survived (100) whereas those who survived disease free were 90. Only the age & HLA matching of the donors were shown to be substantially linked with overall or disease-free survival ($P < .0001$).

CONCLUSION
Utilizing younger donors has the potential to decrease the occurrence of illness & enhance the likelihood of survival following bone marrow transplantation. Age should be taken into account when choosing from a pool of volunteer donors that have similar HLA compatibility.

KEYWORDS
Age, Bone Marrow, Donor, Recipient, Transplantation

INTRODUCTION

Haematopoietic stem cell transplant (HPSCT), often known as bone marrow transplant, is the process of giving healthy haematopoietic stem cells to patients who have bone marrow that is not functioning properly or has been depleted. This technique offers numerous advantages. It aids in enhancing the function of bone marrow. Furthermore, depending on the specific ailment being addressed, it has the potential to facilitate the eradication of cancerous tumour cells. Additionally, it has the ability to produce functional cells that can replace malfunctioning cells in conditions such as immune deficiency syndromes, hemoglobinopathies, & other ailments.[1,2]

Utilising marrow from unrelated volunteer donors is an established method of treating patients who require an allogeneic stem cell transplant but lack a sibling donor with a matching HLA.[3-9] The National Marrow Donor Program (NMDP) was founded in 1986 with the purpose of enlisting & performing HLA typing on a significant number of unrelated volunteer donors for the benefit of patients in need.[10-12]

When searching the NMDP Registry, it is common to find many matches for a patient's HLA-A, HLA-B, & DRB1. The selection strategies for an unrelated donor differ. Transplant physicians typically prioritise donors who are male, CMV seronegative, younger than other potential donors or racially matched with the patient. Preference may also be given to donors who are HLA-DQ–, DP–, HLA-& C-matched, ABO-compatible or to female donors who have never been pregnant.[13-15] If there is apprehension over the acquisition of a sufficient quantity of stem cells, it may be preferable to select a donor with a bigger supply.

The aim of present study is “to assess the donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors & to report associations between outcome & donor age”.

MATERIAL & METHODS

The present retrospective study was conducted at a tertiary care centre among patients who required bone marrow transplantation during the duration of study (2 years). Ethical clearance was taken from institutional ethics committee before commencement of study.Through convenient sampling a total 100 patients who underwent bone marrow transplantation from an unrelated donor were selected on the basis of inclusion & exclusion criteria.

Inclusion Criteria

- Patients who had not underwent any kind of transplantation in past
- Patients willing to participate in the research

Exclusion Criteria

- Mobilized peripheral blood transplants
- Patients undergone transplantation of allogeneic or autologous stem cells

The occurrence of acute GVHD was documented through the application of standardised criteria to assess the extent of skin, liver, & intestine involvement. A severity grade was determined by applying conventional criteria to these stages. The occurrence of haematologic relapse was documented for individuals diagnosed with leukaemia, lymphoma, & myelodysplastic syndromes & other malignant diseases.

The analyses of recurrence & disease-free survival were limited to these specific disorders. Neutrophil engraftment was determined by seeing a consistent neutrophil count of at least 0.5 x 10^9/L in three consecutive laboratory assays. A minor ABO mismatch is characterised by the transplantation of bone marrow from a donor with type O blood into a recipient with a blood type that is not O, or from a donor with type A or B blood into a recipient with type AB blood. A bidirectional mismatch is defined as the transplantation of bone marrow from a type A donor to a type B recipient, or the reverse.
The lowest criterion for HLA matching was a 5-of-6 antigen match for HLA-B, HLA-A, & DR. Transplant centers may have established more rigorous matching criteria according to their transplant protocols or patient characteristics. HLA typing was performed utilizing several methodologies throughout the course of this study. HLA serologic typing was conducted according to the criteria set forth by the World Health Organization HLA nomenclature committee. The typing of HLA-B, HLA-A, & DRB1 via molecular technologies was conducted through various ways with varying degrees of precision. This research defined potential matches as instances categorized using serologic evidence or low-resolution molecular techniques, without an identified allele-level DRB1 mismatch. HLA-A & HLA-B locus matching was established according to serologic antigen levels, irrespective of whether molecular or serologic typing methods were employed.

The donor characteristics were evaluated for associations using the chi-square test for categorical variables, Spearman's rank correlation test for continuous data, & the Wilcoxon rank sum test for comparing a categorical variable with a continuous variable. The survival & disease-free survival rates were calculated using the Kaplan-Meier method & compared employing the log-rank statistic. Each model included illness & stage, donor age, sex, parity, CMV serologic status, & race, without assessing their significance. Additional factors were included in the model if they exhibited a statistically significant connection with the outcome ($P < .05$).

The model considered parameters like HLA-B, HLA-A, & DRB1 matching, cell dose, transplant center, year of transplantation, interval from diagnosis to transplantation, recipient age, CMV serologic status, sex, & race. A distinct model was developed for each disease category to estimate the interval between diagnosis & transplantation.

Owing to nonlinear effects, the continuous variables of recipient age & time from diagnosis to transplantation were categorized into distinct groups. The influence of the donor's CMV serologic status was examined independently for recipients who were CMV-seropositive & CMV-seronegative. The impact of the donor's race was analyzed independently for receivers who were white & those from minority backgrounds. The impact of cell dosage was analyzed solely in instances where T-cell repletion occurred.

RESULTS

The recipient characteristics according to age with respect to gender, mean age, mean time, diseases, CMMV status, match status & GVHD prophylaxis is shown in table 1.

Characteristic		**Age (years)**			**Total**	**P value**
		18-30	**31-45**	**>46**		
Gender	Male	21	18	17	56	0.28
	Female	15	14	15	44	
Disease CML	Chronic	10	8	4	22	0.65
	Accelerated	4	3	2	9	
	Blast	1	0	1	2	
AML	1st remission	8	5	6	19	
	2nd	4	3	3	10	

	3rd	3	2	1	6	
ALL	1st	7	4	3	14	
	2nd	6	1	1	8	
	3rd	1	1	0	2	
MDS		2	1	0	3	
NHL		1	1	0	2	
Other disease		1	1	1	3	
CMMV seropositive		16	14	18	48	0.64
Match status	HLA-A, B, DRB 1 match	32	22	15	69	0.21
	Potential match	5	3	2	10	
	HLA-A mismatch	7	2	2	11	
	HLA-B mismatch	6	1	1	8	
	HLA-DRB 1 mismatch	1	1	0	2	
GVHD prophylaxis	T cell depletion	12	7	4	23	<0.001
	MTX+CsA	13	8	7	28	
	MTX+ CsA+prednisone	7	7	5	19	
	MTX± other	8	7	5	20	
	other	5	4	1	10	
Mean age		28.5	29.3	26.5	27.8	0.11
Mean time from diagnosis to transplant		15.1	14.2	14.3	15	0.03

Table 1: Recipient characteristics according to age

Donor characteristics according to age with respect to total number of donors, Gender, CMMV positivity & match status are shown in table 2.

Characteristic		**Age (years)**			**Total**	**P value**
		18-30	**31-45**	**>46**		
Number of donors		36	32	32	100	
Gender	Male	21	18	17	56	<0.001
	Female	15	14	15	44	
CMMV seropositive		15	`12	9	36	<0.001
Match status	ABO match	20	12	8	40	0.53
	Minor ABO mismatch	11	10	4	25	
	Bidirectional ABO mismatching	3	2	1	6	
	Other ABO mismatch	8	7	5	20	
	ABO unknown	4	2	3	9	

Table 2: Donor characteristics according to age

All the patient of transplantation survived (100) whereas those who survived disease free were 90 as shown in figure 1.

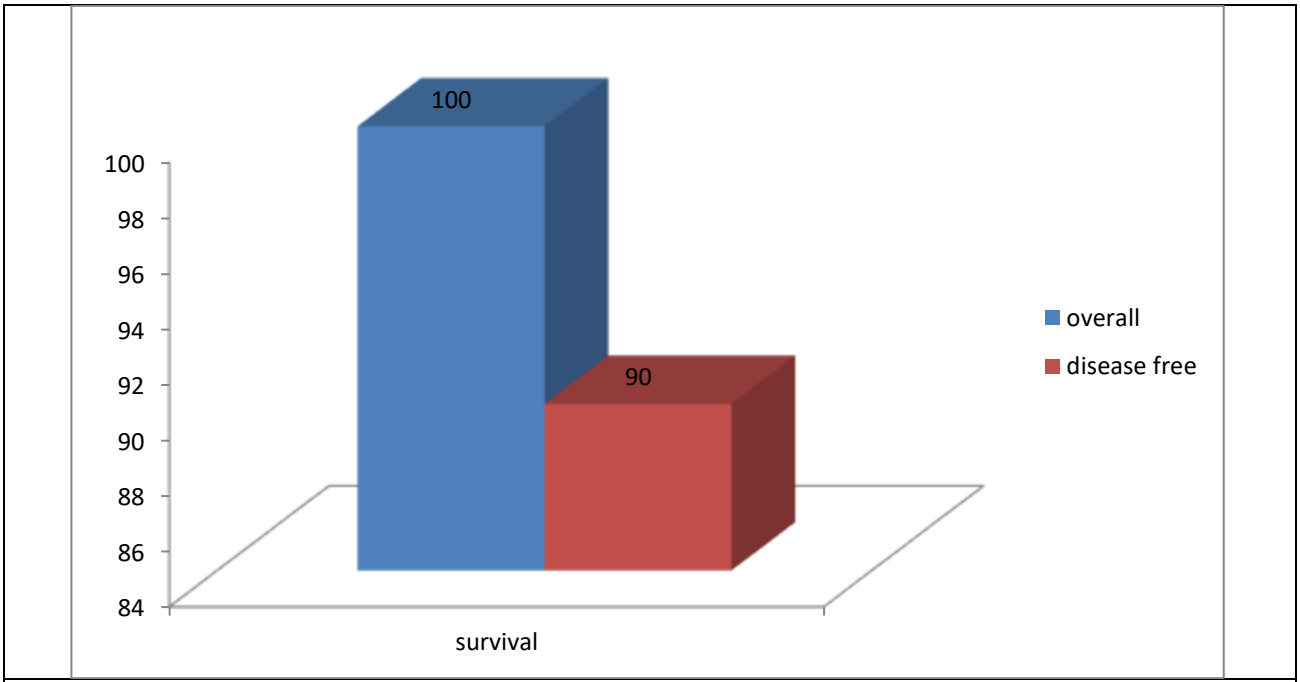

Figure 1: Outcome of patients

The multivariate analysis considered the primary factors of disease, transplant center, HLA matching, cell dose, time from diagnosis to transplantation (in instances of chronic-phase chronic myelogenous leukemia [CML] & severe aplastic anemia), along with recipient age & sex. Only the age & HLA compatibility of the donors were significantly associated with overall or disease-free survival (P < .0001). The study found no significant effects of the donor's CMV serologic status or gender. The influence of donor age on overall survival was constant in cases of HLA mismatch (P value of 0.01). No substantial relationships between donor age & recipient diagnosis or recipient age were seen, as illustrated in Table 3.

Factor	**RR**	**Overall Survival**			**Disease-free Survival**			
		95% CI	**P**	**Favorable**	**RR**	**95% CI**	**P**	**Favorable**
Donor age (per decade)	1.11	(1.05,1.13)	< 0.0001	Younger	1.08	(1.04,1.03)	< 0.0001	Younger
Donor CMV positive (CMV negative recipient)*	0.84	(0.85,1.03)	0.28	NS	0.94	(0.85, 1.03)	0.17	NS
Donor CMV positive (CMV positive recipient)	1.02	(0.94, 1.02	0.51	NS	1.03	(0.94,1.12)	0.58	NS
Male donor	1.01				1.00			
Female donor	1.03	(0.95. 1.23)	0.23	NS	1.04	(0.94, 1.18)	0.30	NS
ABO match	1.00				1.00			
ABO minor mismatch	0.76	(0.90. 1.02)	0.55	NS	1.00	(0.93. 1.08)	0.86	NS
ABO major mismatch	1.02	(0.91. 1.04)	0.75	NS	1.02	(0.95, 1.04)	0.81	NS
HLA-A,B,DRB1 match$	1.00			Matched	1.00			Matched
HLA-A mismatch	1.20	(1.26,1.53)	<		1.24	(1.23,	<	

			0.0001			1.33)	0.0001	
HLA-B mismatch	1.27	(1.31,1.64)	< 0.0001		1.21	(1.18. 1.52)	< 0.0001	
HLA-DRB1 mismatch	1.13	(1.13,1.38)	< 0.0001		1.78	(1.05, 1.23)	0.0007	

Table 3: Proportional hazards regression models for overall survival & disease-free survival

DISCUSSION

Unrelated donor bone marrow transplantation is a significant & increasingly common treatment option for patients without a related donor. Various factors, including patient, illness, & donor characteristics, all influence patient outcomes. Although patient features & disease biology are mostly unchangeable, donor characteristics can often be chosen & enhanced, particularly when there are several eligible donors for many patients. The objective of this study is to evaluate the donor features as potential risk factors in recipients who have bone marrow transplantation from unrelated donors. Additionally, this study aims to identify any correlations between the outcome of the transplantation & the age of the donor.

The impact of the age of the donor was noted in all recipients. The impact of donor age was similar to that observed in other subgroups, such as patients with patients with acute leukemia in first remission, chronic-phase CML, cases without T-cell depletion, T-cell–depleted cases, female donors, male donors, CMV-seronegative donors, multiparous donors & CMV-seropositive donors. The impact of donor age on “acute graft-versus-host disease (GVHD)” may only be significant in HLA-mismatched pairs. However, for chronic GVHD & overall survival, the impact is evident in both matched & mismatched pairs.

Surgeons favor donors who do not have cytomegalovirus (CMV) antibodies, particularly when the patient also does not have CMV antibodies. Less than 40% of donors in this study tested positive for CMV, while around half of the recipients were found to be CMV positive. Given the much lower survival rates of recipients who are CMV-seropositive, it is logical to consider that the potential transmission of the virus from a seropositive donor to a seronegative recipient provides an extra risk of mortality. Nevertheless, we observed no harmful consequences of seropositive donors on either seronegative or seropositive recipients. Upon accounting for other donor features & pertinent risk factors, the serologic status of the donor's cytomegalovirus (CMV) was found to have no correlation with survival.[16]

These findings align with a previous study that concluded that the presence of CMV antibodies in a donor does not indicate the likelihood of the recipient developing a CMV infection after transplantation.[17] Administering medications such as ganciclovir has proven to be highly effective in avoiding CMV infections in transplant recipients. An investigation into the utilization of “unrelated-donor transplantation” in patients with CML revealed that the use of ganciclovir in CMV-seropositive individuals was linked to a higher rate of survival.[18]

Previously, ABO mismatching was found to be a risk factor for higher mortality in a study conducted at a single site. The investigation focused on patients with “acute myelogenous leukemia (AML) & myelodysplastic syndrome (MDS)”.Several other investigations have concluded that there is no impact of ABO incompatibility on the result. Furthermore, we did not find any impact of ABO mismatching on either the entire dataset or the specific groups of transplantations in patients with AML or MDS.[19-21]

The average age of donors ranged from 20 to 30 years. This discovery implies that age is assigned a significantly lower level of importance in the process of selecting donors. Consequently, the likelihood of survival could be enhanced by prioritizing the selection of younger donors. Furthermore, these data indicate that utilizing younger donors may assist in reducing the detrimental consequences of a partial HLA mismatch. The probability of identifying a donor with a single mismatched HLA determinant is substantial, even for uncommon HLA phenotypes. Therefore,

numerous searches that fail to find a complete match for a patient result in multiple volunteers who are mismatched in only one specific factor. This usually provides the chance to choose a youthful donor who is not a perfect match. Utilizing younger donors in HLA-mismatched transplants can enhance the success rates for patients & enable a wider range of patients to access this treatment.[22] The underlying biological mechanisms responsible for the impact of donor age are not thoroughly comprehended. The rising prevalence of illnesses among older donors implies that tolerance may diminish over time due to increasing exposure of the resistant system to a wider range of distant antigens. This could be attributed to a higher prevalence of memory T cells replacing naive T cells as individual's age. Multiple studies have demonstrated age-related alterations in hematopoiesis. Further studies have revealed that younger individuals who donate bone marrow have a reduced likelihood of developing obstructive lung disease, B-cell lymphoproliferative diseases & secondary graft failure following transplantation.[23-25]

CONCLUSION

The study concluded that there is ongoing debate on the most effective technique for identifying an unrelated donor. The highest priority is to match the patient's HLA-A, HLA-B, & DRB1. Our study revealed that in unrelated transplantation, the age of the donor has a greater impact on overall mortality compared to the donor's CMV serologic status, sex, & ABO incompatibility. Nevertheless, the precise significance of risk variables such as the correlation at other HLA loci remains uncertain. Additional investigation is necessary to ascertain the comparative significance of the several risk variables that can be modified by the selection of a donor.

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