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Impact of HLA class I high-resolution mismatches on chronic graft-versus-host disease and survival of patients given hematopoietic stem cell grafts from unrelated donors

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Summary:

There is consensus that matching of unrelated donors (URD) and patients for HLA class II alleles improves the outcome of hematopoietic stem cell transplantation (HSCT). However, the significance of HLA class I allelic mismatches for transplant outcome is under discussion and reports on long-term effects like chronic graft-versus-host disease (GVHD) are rare. Thus, we investigated the association of human leukocyte antigen (HLA) class I allele mismatches and outcome in 144 patients given HSCT from URD who were matched for HLA-DRB1, DRB3/4/5, and DQB1 alleles. The risk of chronic GVHD was significantly increased in patients with class I mismatched donors, the mismatch either detected by low- or high-resolution typing. A single HLA class I allele mismatch significantly increased the risk of chronic GVHD in multivariate analysis. Overall survival was significantly reduced in patient/donor pairs with more than one-allele class I mismatch. Thus, selection of unrelated donors for transplantation should be based on high-resolution HLA class I typing.
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Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established curative therapy for lymphohematopoietic and congenital metabolic disorders.[1,2] Since a genotypically matched sibling donor is available for only 20–30% of the patients in need of a transplant, an increasing number of HSCT from human leukocyte antigen (HLA)-matched unrelated donors (URD) has been performed during the last years.[3,4] URD transplants are usually associated with a higher incidence of posttransplant complications compared to HLA-genoidentical transplants.[3,5–10] This is mainly due to unresolved HLA incompatibilities or to mismatched loci not tested for by conventional tissue typing. The use of molecular typing techniques for all HLA loci has demonstrated that serological matching is insufficient to ensure an allelic match.[8] High-resolution DNA-based typing for both HLA class I and class II alleles has greatly improved accuracy of donor selection resulting in improved outcome of HSCT in HLA-identical donor/patient pairs.[6–9,11–16]

Controversies remain as to whether mismatches which can only be detected using high-resolution (allele level) nucleic acid techniques are more permissive of clinical success than those mismatches which can be detected using serology or comparable low-resolution (antigen level) typing approaches.

Especially, reports on the impact of HLA allelic disparities on incidence and severity of chronic graft-versus-host disease (GVHD) are rare.[17,18] Here, we report a single center study with long follow-up on 144 patients given HSCT from URD all matched for DRB1, DRB3, DRB4, DRB5, and DQB1 alleles typed at the high-resolution level. We show that HLA class I allelic mismatches significantly increase the risk of chronic GVHD and thus, should be taken into account when searching for an unrelated donor.

Patients and methods

Patients

We performed a retrospective analysis of 144 consecutive patients transplanted from URD at the Medical University of Vienna from September 1994 until July 2003. Pretransplant characteristics of the patients are shown in Table 1. All except three patients were conditioned for transplantation with cyclophosphamide and fractionated total body irradiation. For GVHD prophylaxis, all except five received cyclosporine A (CSA) and methotrexate. A total of 100

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Table 1 Characteristics of donors and patients

	All	*Allelic match*	*Allelic mismatch*	*Antigen mismatch*
No. of patients	144	82	23	39
Median age of patients (years)	37	38	36	35
Range	18–55	18–55	22–54	21–50
Median age of donors (years)	37	36	38	37
Range	18–53	18–52	24–49	20–53
Gender (donor/patient)				
M/M	67	36	13	18
M/F	28	16	4	8
F/F	33	20	4	9
F/M	16	10	2	4
Donor pregnancy[a]	30	24	1	5
Diagnosis				
CML	53	31	10	12
AML	40	20	7	13
ALL + AL	31	18	3	10
SAA	2	2	0	0
NHL	7	6	1	0
MDS	10	5	2	3
MM	1	0	0	1
Disease risk				
Standard[b]	80	44	13	23
High	64	38	10	16
CMV (donor/patient)[c]				
Pos/Pos	26	20	4	2
Pos/Neg	27	14	5	8
Neg/Neg	44	24	7	13
Neg/Pos	42	22	5	15
ABO incompatibility[d]	87	47	13	27
Rhesus incompatibility[d]	46	32	5	9

No = number; M = male; F = female; CML = chronic myelogenous leukemia; AML = acute myelogenous leukemia; ALL = acute lymphoid leukemia; AL = acute biphenotypic leukemia; SAA = severe aplastic anemia; NHL = non-Hodgkin's lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; CMV = cytomegalovirus; pos = positive; neg = negative.
[a]Four results missing.
[b]Complete remission and chronic phase.
[c]Five results missing.
[d]One result missing.

patients were given unmanipulated bone marrow (BM) and 44 unmanipulated peripheral blood stem cells (PBSC). The clinical diagnosis of GVHD was confirmed by histopathology and graded as published.[19,20]

The protocols used had been approved by the ethical committee of the University of Vienna. Informed consent was obtained from all patients.

HLA typing and strategy for the selection of donors

Low-resolution typing for HLA-A, B, C, and DR was performed with a standard two-stage complement-dependent test of microtoxicity[21] or by ligation-based typing.[22] For high-resolution typing, sequencing analyses of exons 1–3 of HLA class I alleles and exons 2 of HLA class II alleles were performed.[23]

We aimed at comprehensive matching of HLA-DRB1, DRB3/4/5, and DQB1 alleles as assessed by high-resolution typing and matching of HLA-A, B, or C antigens as assessed by low-resolution typing. High-resolution typing, of HLA class I alleles was performed prospectively.

Statistical analysis

Data were analyzed as of February 1, 2004. Patients were considered evaluable for engraftment if they survived 21 days after transplant and evaluable for chronic GVHD if they survived at least 80 days. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, whereas relapse, transplant-related mortality (TRM), acute and chronic GVHD were calculated as cumulative incidence[24] to adjust the analysis for competing risks. For the analysis on acute and chronic GVHD, both relapse and death in remission in the absence of GVHD were considered competing events; for the analysis on relapse incidence, death was the competing event, whereas relapse was the competing event for the analysis on TRM. Comparisons of cumulative incidences between different groups were made by k-sample Gray

Table 2 Number and types of HLA class I mismatches observed in 144 donor/patient pairs matched for HLA-DRB1, DRB3/4/5, and DQB1

Mismatches by locus						
Locus	*Low resolution*		*High resolution*			
	Match	*Mismatch*	*Match*	*Mismatch*		
HLA-A	132	12	125	19		
HLA-B	139	5	123	21		
HLA-C	122	22	110	34		
Details of HLA class I allelic mismatching in HLA-DRB1, DRB3/4/5, and DQB1 matched pairs						
	A	*B*	*C*	*A and B*	*A and C*	*B and C*
One mismatch	14	10	22			
Two mismatches	1		3	3	1	6
Three mismatches						1
Four mismatches						1

test.[24] Log-rank test statistics were used to evaluate the univariate effects of HLA class I antigen and allele incompatibility on outcome. For HLA-A, B, and C, donor/recipient matching was considered in three categories: high-resolution match, low-resolution match/high-resolution mismatch, and low-resolution mismatch.

Additionally, other factors, namely patient and donor age, patient and donor sex, diagnosis, disease status at HSCT, and stem cell source were tested in univariate analysis. Multivariate analyses were carried out by Cox proportional hazards regression modelling of OS and relapse. The median observation time of surviving patients is 45 (range, 6–114) months.

Results

Degree of HLA class I disparity

Number and types of HLA class I mismatches observed are shown in Table 2. In total, 105 donor/patient pairs (73%) had no HLA class I antigen level mismatches, whereas 39 were mismatched for one antigen (12 for HLA-A, five for HLA-B, and 22 for HLA-C). High-resolution typing reduced the number of HLA class I identical donor/patient pairs to 82 (57%). A single class I allelic mismatch was present in 46 (32%), more than one mismatch was observed in 16 (11%) donor/patient pairs. Overall, high-resolution typing revealed HLA class I mismatches not detected by low-resolution typing in 35 (24%) donor/patient pairs.

GVHD

Stable engraftment occurred in all patients. The cumulative incidence of acute GVHD was 66% (95% confidence interval (CI), 59–74%) for the whole cohort and was 67% (95% CI, 58–78%), 57% (95% CI, 39–81%), and 69% (95% CI, 56–85%) in the high-resolution match, low-resolution match/high-resolution mismatch and low-resolution mismatch, group and thus, not significantly different. The corresponding percentages for acute GVHD grades III–IV were with 22, 18, and 22%, also not significantly ($P=0.45$) different.

The cumulative incidence of chronic GVHD at 3 years was 32% (95% CI, 25–40%) for the whole group. It was

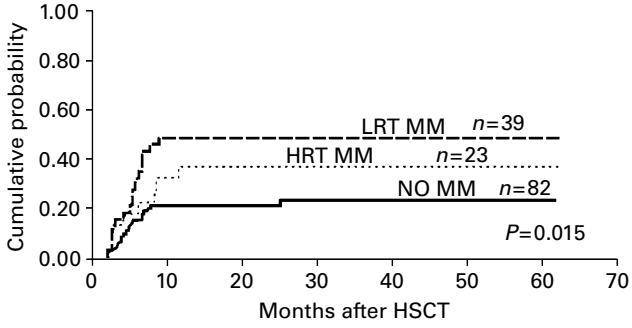

Figure 1 HLA class I disparities and incidence of chronic GVHD. Cumulative incidence of chronic GVHD at 3 years is shown according to the degree of HLA class I disparity between donor and recipient. Groups comprise patients with high-resolution match (thick solid line; HLA-A, B, and C antigen and allele match), low-resolution match/high-resolution mismatch (fine, broken line; antigen match but allele mismatch of HLA-A, B or C) and low-resolution mismatch (thick broken line; HLA-A, B, or C antigen mismatch) donors.

23% (95% CI, 15–34%), 37% (95% CI, 21–64%), and 48% (95% CI, 35–67%) for patients with high-resolution match, low-resolution match/high-resolution mismatch, and low-resolution mismatch donors. (Figure 1, $P=0.015$). The corresponding percentages for chronic extensive GVHD were 12, 13, and 23% and not significantly ($P=0.08$) different. A single HLA class I allele mismatch significantly increased the risk of chronic GVHD at 3 years from 21% (95% CI, 14–32%) to 44% (95% CI, 33–58%). In both univariate and multivariate analysis (Table 3), only HLA class I disparity significantly increased the risk of chronic GVHD ($P=0.0007$).

Outcome

A total of 24 patients died within 60 days after HSCT of infections ($n=6$), GVHD and infections ($n=3$), GVHD and multiorgan failure (MOF, $n=3$), MOF ($n=6$), veno-occlusive disease ($n=3$), bleeding ($n=1$), and relapse ($n=2$). The cumulative incidence of TRM at 3 years was 24% (95% CI, 16–35%), 26% (95% CI, 13–52%), and 34% (95% CI, 21–52%) for patients without HLA class I allelic disparities, low-resolution match/high-resolution

Table 3 Multivariate analysis of HLA compatibility/transplant outcome

	OS *P*	*DFS* *P*	*aGVHD* *P*	*cGVHD* *P*	*Rel* *P*
HLA compatibility					
HRT-M/HRT-MM/LRT MM	0.27	0.46	0.62	0.0007	0.49
Disease stage					
Standard/high risk	0.01	0.0003	0.19	0.29	<0.0001
Stem cell source					
BM/PBSC	0.39	0.62	0.73	0.36	0.15
Patient age					
<40/⩾40 years	0.37	0.68	0.53	0.12	0.78
Donor age					
<40/⩾40 years	0.74	0.33	0.72	0.44	0.42
Patient CMV status					
Positive/negative	0.69	0.58	0.79	0.74	0.55
Donor CMV status					
Positive/negative	0.75	0.74	0.55	0.85	0.72

OS = overall survival; DFS = disease-free survival; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; rel = relapse; HRT-M = high-resolution typing match; HRT-MM = high-resolution typing mismatch; LRT MM = low-resolution typing mismatch; BM = bone marrow; PBSC = peripheral blood stem cells; CMV = cytomegalovirus.

mismatch, and low-resolution mismatch donors and thus, not significantly different.

At the end of study, 42 patients (31%) had experienced relapse including 14 (17.5%) with standard risk and 28 (44%) with high-risk disease prior to HSCT. The cumulative incidence of relapse at 3 years was 35% (95% CI, 26–48%), 27% (95% CI, 14–53%), and 27% (95% CI, 16–46%) for patients with high-resolution match, low-resolution match/high-resolution mismatch and low-resolution mismatch, donors and not significantly different. Only disease status at transplant ($P \leqslant 0.0001$) had a significant impact on relapse as shown in Table 3.

The Kaplan–Meier estimates for OS at 3 years were 49% (95% CI, 6–51%), 50% (95% CI, 11–50%), and 38% (95% CI, 8–62%) for patients with no detectable HLA class I allelic mismatch, low-resolution match/high-resolution mismatch, and low-resolution mismatch donors. Whereas OS was 49% (95% CI, 6–51%) in both allele matched and one-allele mismatched patient/donor pairs, it was only 25% (95% CI, 11–75%) in two and more allele mismatched pairs (Figure 2). Thus, multiple allelic mismatches of HLA class I significantly ($P = 0.03$) decreased survival. In this patient group, causes of death were TRM in two-thirds of patients and relapse in one-third, whereas half of deaths in patients with no detectable HLA class I allelic mismatch or one-allele mismatched donors were TRM and the other half relapse.

In multivariate analysis, HLA class I allelic disparity had no significant impact ($P = 0.18$) on OS whereas high-risk disease prior to HSCT had a significant ($P = 0.001$) negative impact on survival as shown in Table 3.

The Kaplan–Meier probability of DFS at 3 years was 41% (95% CI, 6–59%), 47% (95% CI, 11–53%), and 40% (95% CI, 8–60%) for patients with HLA class I allelic match, low-resolution match/high-resolution mismatch,

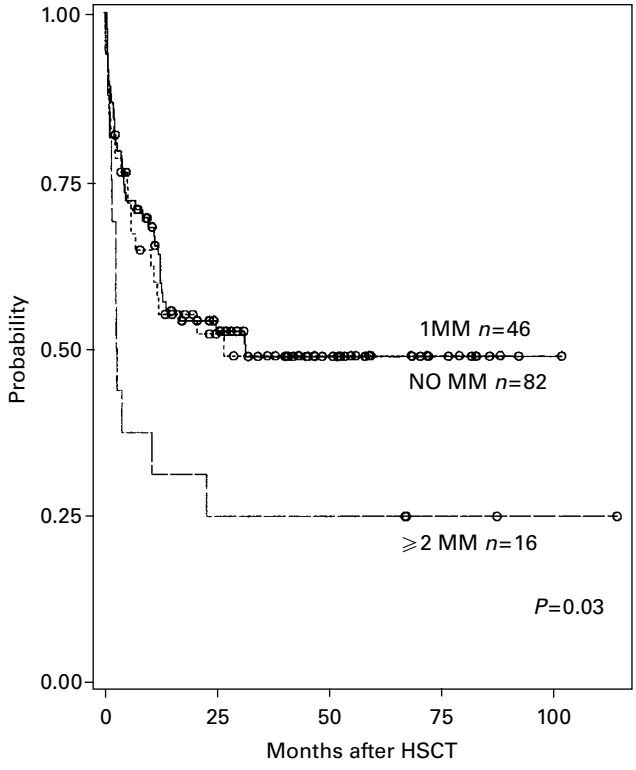

Figure 2 Impact of multiple HLA class I allelic disparities on OS. Probability of overall survival at 3 years is shown according to the number of HLA class I allele disparities between donor and recipient assessed by high-resolution typing. Groups comprise patients without allelic mismatches (thick solid line), with one allelic mismatch (including 29 with one antigen mismatch already detected by low-resolution typing, fine, broken line) and two or more allelic mismatches (including 16 with antigen mismatches already detected by low-resolution typing, thick broken line).

and low-resolution mismatch donors. Only disease stage had a significant impact on DFS in univariate ($P \leqslant 0.0001$) and multivariate analysis ($P = 0.0001$) as shown in Table 3.

Discussion

For patients without an HLA-identical sibling, transplantation with hematopoietic stem cells from an unrelated donor may be an alternative. Unfortunately, the morbidity and mortality associated with such transplants are usually higher. Matching of HLA-A, B, C, and DRB1 led to reduction of risk of acute GVHD and improvement of survival after transplantation with URD.[4,6,8,12,16–18] So far, few data on the impact of HLA class I and class II disparities on incidence and severity of chronic GVHD have been published.[17,18] In a multicentre study reported by Morishima *et al*,[17] HLA-A/B allele disparities were significantly correlated with chronic GVHD by both univariate and multivariate analysis and HLA-C mismatch had a tendency to increase the incidence of chronic GVHD. We confirm these findings in a smaller but with regards to conditioning and GVHD prophylaxis more homogenous patient population. In addition, all our patients were matched for HLA-DRB1, DRB3/4/5, and DQB1 alleles. In our study, a significantly increased incidence of chronic GVHD was seen in patients with HLA class I allelic and antigen level mismatched unrelated donors. Furthermore, a single HLA class I allele mismatch significantly increased the risk of chronic GVHD at 3 years after HSCT from 21 to 44%. In both univariate and multivariate analysis, only HLA class I disparity significantly increased the risk of chronic GVHD. Besides HLA disparity, age of recipient, type of GVHD prophylaxis and its duration, cytomegalovirus seropositivity, and prior acute GVHD are known risk factors for chronic GVHD.[25] Whereas Morishima *et al*[17] observed an effect of age on incidence of chronic GVHD, this was not seen in our study. However, the median age of their patient population was 23 years, 14 years less than ours. Furthermore, the power of the analysis may be compromised by the smaller number of patients in our study. Recently, Flomenberg *et al*[18] reported a significantly adverse effect of HLA-A mismatches on chronic GVHD whereby these were more evident in transplants with low-resolution *vs* only high-resolution mismatches.

In our study, survival probabilities were not significantly different in patients with no detectable HLA class I allelic mismatch donor and low-resolution match/high-resolution mismatched donors. We could confirm data published by Petersdorf *et al*[7] where single class I disparities were well tolerated, whereas a significantly lower survival was observed when more than one class I allelic mismatch was present. While no statistically significant difference in incidence of severe acute GVHD was observed in the later group, there was a trend towards increased chronic extensive GVHD and TRM. Similarly, Flomenberg *et al*[18] reported a progressively reduced survival with increased mismatches for HLA-A, B, and C.

Owing to small patient/donor pair numbers with HLA class I mismatches, no further analyses on the impact of various class I alleles on survival were performed in our study. Morishima *et al*[17] observed a reduced OS due to worse nonrelapse mortality in patients given HLA-A and/or HLA-B allele mismatch grafts, whereas the HLA-C mismatch or HLA class II (DRB1 and/or DQB1) mismatch did not. The favorable survival rate in single HLA-C mismatch graft recipients was mainly influenced by the low incidence of nonrelapse mortality, although relatively high incidence of severe GVHD occurred in HLA-C mismatch graft recipients compared with HLA matched ones. In contrast, Flomenberg *et al*[18] demonstrated significant adverse impact for HLA-A, B, or C mismatching on survival. There, transplants with low-resolution mismatches were associated with significantly worse survival than those with only high-resolution mismatches.

In our study, 73% of donor/patient pairs were matched for HLA-A, B, C antigens and DRB1. Based on previous findings[6,17,26] that HLA-C exerts significant effects on graft failure and survival, these HLA loci were included in our donor search algorithm. Recent publications confirm these findings.[18,27] High-resolution typing revealed mismatches not detected by low-resolution typing in 24% of donor/patient pairs reducing the percentage of fully matched pairs to 57%. In all, 80% of mismatches involved HLA-B or C and two-thirds of mismatches were observed as single allelic ones. Thus, our study population had fewer HLA disparities compared to other reports.[18] Nevertheless, HLA class I allelic mismatch was significantly associated with an increased risk for chronic GVHD. In view of the marked reduction of quality of life of patients with long-lasting chronic GVHD, their need of prolonged immunosuppressive therapy and the significant reduction in overall survival of our patients with more than one-allelic HLA class I mismatch donors, selection of unrelated donors for transplantation should be based on high-resolution class I typing for HLA-A, B, and C.

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