PIRCHE-II in *HLA-DPB1* mismatches conferred risk for Acute Graft-versus-Host Disease in a cohort of unrelated Hematopoietic Stem Cell Transplantation

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Abstract

Acute graft-versus-host disease (aGvHD) remains a major complication following allogeneic hematopoietic stem cell transplantation (aHSCT). While donor-recipient pairs matching have included *HLA-A, -B, -C, -DRB1* and *-DQB1 Loci* (10 alleles), mismatches in HLA-DPB1 have emerged as an independent risk factor for aGvHD. Additionally, polymorphisms in certain regions of DPB1 may affect the expression of these molecules, although some findings from previous studies have been contradictory. Therefore, the aim of this study was to compare aGvHD incidence and overall survive outcomes between permissive and non-permissive *HLA-DPB1* mismatches as well as their expression levels in unrelated-donor aHSCT. The results indicated that the *HLA-DPB1* T cell epitope (TCE-1) group, as well as the combination of non-permissive *HLA-DPB1* mismatches and high expression levels of these molecules, were associated with an increased risk of aGvHD. The *Predicted Indirectly Re Cognizable HLA Epitopes* (PIRCHE) model was also evaluated. PIRCHE-I score greater than 5.00 and PIRCHE-II score greater than 10.00 were both associated with a higher risk of aGvHD. Furthermore, survival analysis suggested increased risk of overall mortality in cases with two *HLA-DPB1* mismatches and high scores for PIRCHE-I and II grouped. In conclusion, HLA mismatches between recipient/donor pairs should be carefully analyzed before selecting the most suitable donor for unrelated aHSCT.

Introduction

Although the use of HLA-matched unrelated donors can reduce the risk of aGvHD, this approach is not always achievable. Notably, up to 80% of 10/10 HLA-matched donor–recipient pairs may exhibit mismatches at the *HLA-DPB1 locus*. *HLA-DPB1* mismatches may be clinically better tolerated due to reduced alloreactivity associated with shared T-cell epitopes, with the TCE-3 group being the most tolerated (permissive) and the TCE-1/2 groups the least tolerated (non-permissive). Additionally, a single nucleotide exchange from adenine to guanine in the 3'UTR gene region can lead to increased expression of these molecules. Still, mismatched HLA antigens may be indirectly recognized by donor T cells, potentially triggering aGvHD. Therefore, this retrospective study aimed to investigate the association between permissive *HLA-DPB1* mismatches and the incidence of aGvHD following unrelated aHSCT for the treatment of hematologic malignancies.

Methods and Materials

Next generation sequencing was performed for high-resolution HLA typing of the DPB1 *locus* in samples from 74 donors–recipient pairs who initially underwent HLA 10x10 matched transplantation at our center between 2010 to 2023. Post-transplant, cyclophosphamide was administered for aGvHD prophylaxis. aGvHD was classified according to the criteria of National Institutes of Health as grades I, II, III, and IV. The classification of permissive/non-permissive HLA-DPB1 mismatches was based on three biological models (TCE, PIRCHE and Expression) and was determined using the IPD-IMGT/HLA, PIRCHE databases and the SNP rs9277534A/G, respectively. Statistical analysis was performed using RStudio v4.4.1. Incidence of aGvHD was performed using Logistic Regression Model. For univariate analysis of overall survival (OS), the Kaplan-Meyer and Log-rank Models were used. Multivariate analysis of OS was performed using Cox Regression Model.

Results

The median (range) recipient age was 22 (2–68) y, and 47 (64%) of the recipients were male. Patients were most frequently transplanted for ALL (49%), AML (28%), CML (11%), MDS (9%), and NHL (3%). Ten (14%) recipients developed grade I aGvHD, 19 (26%) had grade II, four (5%) had grade III, and 41 (55%) did not develop aGvHD. No grade IV cases were observed. Among the 74 donor-recipient pairs, 20 (26,5%) were HLA 12/12 matched, 41 (55%) had one *HLA-DPB1* mismatch and 14 (18,5%) had two *HLA-DPB1* mismatches. However, among the 20 recipients with HLA 12/12 matched aHSCT, only four (20%) developed grade II-III aGvHD. Regarding the TCE model, 12 pairs had TCE-1 and 16 pairs had TCE-2 non-permissive mismatches while 11 pairs had TCE-3 core and 15 pairs TCE-3 noncore permissive mismatches. Analyses revealed a greater risk non-permissive TCE-1 mismatches for grade II-III aGvHD (OR=5.60; p=0,033). For the PIRCHE model, *DPB1* mismatches had PIRCHE-I scores ranging from 0.00 to 9.00 and PIRCHE-II scores ranging from 0.00 to 19.00. Analyses indicated an increased risk when the PIRCHE-I score exceeded 5.00 and PIRCHE-II score exceeded 10.00 for grade II-III aGvHD (OR=4.80; p=0,057 and OR=5,60; p=0,033, respectively). The presence of non-permissive *DPB1* combined with rs9277534GG alleles and a PIRCHE-II score above 10.00 suggested an increased risk of grade II-III aGvHD (OR=8,00; p=0,032), Table 1. Survival analyses indicated increased risk of overall mortality for *HLA-DPB1* 10/12 match (OR=3,86; p=0,04) and *HLA-DPB1* PIRCHE I and II grouped (OR=3,62; p=0,06), Figure 3.

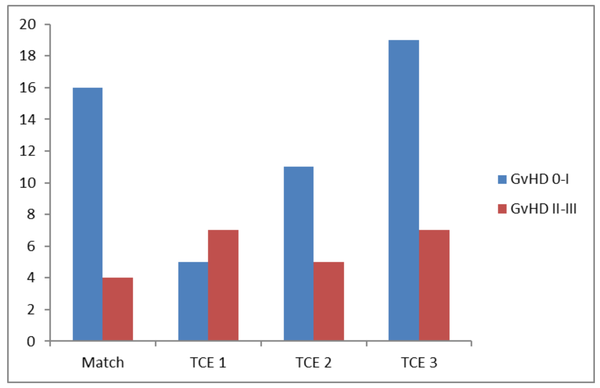

Figure 1. Incidence of acute GvHD degrees between HLA match, HLA-DPB1 TCE-1, TCE-2 non-permissive and TCE-3 permissive mismatches donor-recipient pairs.

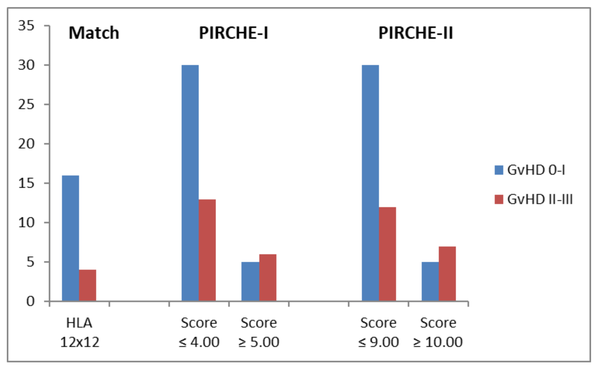

Figure 2. Incidence of acute GvHD degrees between HLA match, HLA-DPB1 PIRCHE-I and PIRCHE-II mismatches donor-recipient pairs.

Table 1. Effect of *HLA-DPB1* mismatch permissiveness, expression levels, and PIRCHE scores on the incidence of aGvHD.

Risk analysis for permissiveness HLA-DPB1	aGvHD Degree 0-I N	aGvHD Degree 0-I %	aGvHD Degree II-III N	aGvHD Degree II-III %	Overall N	Overall %	OR	CI (95%)	*p*
Match HLA 12/12	**16**	**31.4**	**4**	**17.4**	**20**	**27.0**		**reference**	
TCE Model									
Permissive mismatch	20	39.2	7	30.4	27	36.5	1.40	(0.35 - 6.14)	0.636
Non permissive mismatch	15	29.4	12	52.2	27	36.5	3.20	(0.89 - 13.50)	0.087
TCE Group									
TCE 1	5	9.8	7	30.4	12	16.2	5.60	(1.21 - 30.30)	**0.033**
TCE 2	11	21.6	5	21.7	16	21.6	1.82	(0.39 - 8.87)	0.442
TCE 3 - Core/Core	8	15.7	3	13.0	11	14.9	1.50	(0.25 - 8.52)	0.644
TCE 3 - Core/nonCore	11	21.6	4	17.4	15	20.3	1.45	(0.28 - 7.41)	0.643
PIRCHE Class I									
Score 0.00 - 4.00	30	58.8	13	56.5	43	58.1	1.73	(0.51- 6.94)	0.398
Score 5.00 - 9.00	5	9.8	6	26.1	11	14.9	4.80	(0.99 - 26.50)	**0.057**
PIRCHE Class II									
Score 0.00 - 9.00	30	58.8	12	52.2	42	56.8	1.60	(0.47 - 6.45)	0.473
Score 10.00 - 19.00	5	9.8	7	30.4	12	16.2	5.60	(1.21 - 30.30)	**0.033**
TCE + rs9277534A/G									
permissive + AA	8	15.7	6	26.1	14	18.9	4.00	(0.93 - 13.90)	0.109
permissive + GA	12	23.5	1	4.3	13	17.6	0.92	(0.20 - 3.97)	0.742
non-permissive + AA	3	5.9	2	8.7	5	6.8	5.00	(0.77 - 27.95)	0.139
non-permissive + GA	9	17.6	4	17.4	13	17.6	1.78	(0.42 - 7.22)	0.681
non-permissive + GG	3	5.9	6	26.1	9	12.2	8.00	(1.32 - 36.56)	**0.032**
TCE + PIRCHE I									
permissive + score 0-4	19	37.3	6	26.1	25	33.8	1.26	(0.34 - 4.50)	0.968
permissive + score 5-9	1	2.0	1	4.3	2	2.7	4.00	(0.17 - 73.97)	0.936
non-permissive + score 0-4	11	21.6	7	30.4	18	24.3	2.54	(0.63 - 9.06)	0.355
non-permissive + score 5-9	4	7.8	5	21.7	9	12.2	5.00	(0.77 - 27.95)	0.138
TCE + PIRCHE II									
permissive + score 0-9	18	35.3	6	31.6	24	32.4	1.33	(0.36 - 4.76)	0.974
permissive + score 10-19	2	3.9	1	5.3	3	4.1	2.00	(0.12 - 20.10)	0.819
non-permissive + score 0-9	12	23.5	6	31.6	18	24.3	2.00	(0.51 - 7.28)	0.573
non-permissive + score 10-19	3	5.9	6	31.6	9	12.2	8.00	(1.30 - 36.51)	**0.032**

All statistical analyses were performed using the HLA 12/12 match as the reference group.

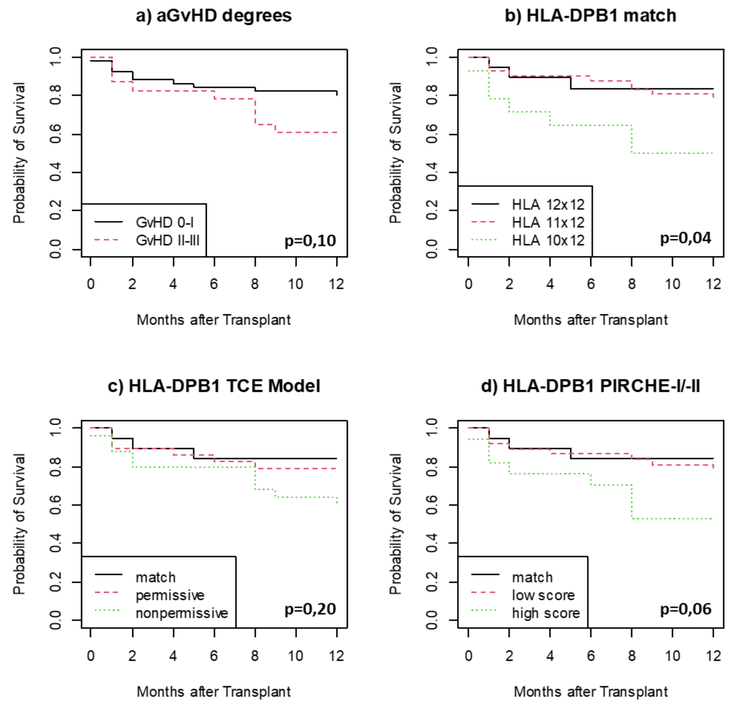

Figure 3. Kaplan-Meyer survival curves for the 74 recipients analyzed. Overall survival according transplant characteristics: a) incidence of aGvHD; b) HLA match; c) *HLA-DPB1* mismatch TCE Model; d) *HLA-DPB1* mismatch PIRCHE-I and PIRCHE-II grouped.

Conclusions

This study suggests a possible association between non-permissive *HLA-DPB1* alleles (TCE-1) and PIRCHE-II scores with an increased risk of grade II–III acute graft-versus-host disease (aGvHD), as well as a higher risk of mortality following unrelated-donor *HLA-DPB1* mismatched aHSCT.

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