Influence of HLA-DPB1 mismatches on outcome after allogeneic hematopoietic stem cell transplantation

Dear Editor,

The success of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is limited by early and late complications like acute and chronic graft-versus-host disease (GvHD), infectious complications and relapse [1]. The donor–recipient HLA match is an important factor affecting the transplant outcome. The gold standard is a genotypically identical sibling. However, since 70% of the patients are lacking a genotypically identical sibling, a 10/10 matched unrelated donor is the preferred alternative [2,3]. This 10/10 match means that five HLA loci are the same in the donor and the recipient. These five HLA loci are HLA-A, -B, -C, -DRB1 and -DQB1, because their impact on the outcome in allo-HSCT is well known [4,5].

The high-resolution typing for a 12/12 match with the additional matching of HLA-DPB1 is still controversial [6]. Existing studies showed no influence of HLA-DPB1 mismatches on transplant outcomes like acute GvHD, disease-free survival, overall survival (OS) and disease relapse rate [7,8]. Other studies showed the contrary when having a HLA-DPB1 mismatch; like increase of aGvHD incidence, lower relapse rate and lower OS [9,10]. The decision whether a HLA-DPB1 mismatch is of relevance should be made individual for each patient, his disease stage and possible survival advantages with a mild form of acute GvHD. The aim of this study was to find out, whether HLA-DPB1 affects different clinical outcomes.

In this retrospective single-center study, we analyzed data from 302 consecutive patients receiving an allo-HSCT in the period from 2012 to 2016 at the University Hospital Basel. Haplo-identical HSCT was excluded. The study was performed according to the regulations of the local ethics committee. The first step was to determine whether the patient and their donor were HLA-DPB1-matched or mismatched (MM). Secondary analyses examined the following: mismatch at HLA-DPB1 and HLA-DPB1 permissive vs non-permissive mismatches according to T-cell epitope grouping, as previously reported [11,12]. An online calculator is also available (http://www.ebi.ac.uk). The effect of HLA-DPB1 match and HLA-DPB1 permissive/nonpermissive MMs on HSCT outcome were estimated. We determined the incidence rates of HLA-DPB1 mismatches and their association with recipient age, underlying disease, conditioning regimen, stem cell source and graft-versus-host disease (GvHD). Furthermore, the effect of DPB1 mismatches on clinical outcome after allo-HSCT, such as overall survival (OS) and non-replase mortality (NRM), was examined. Categorical variables were presented as absolute counts and percentages. Continuous variables were described by median, mean, and range of values, as appropriate. Differences in demographic, clinical and transplantation parameters were assessed using the Chi-square- or Fisher's exact test for categorical variables and Student's *t*-, Mann–Whitney *U*-, or Kruskal–Wallis test for continuous variables, depending on data distributions. For each patient, OS was calculated from allo-HSCT until death from any cause or last follow-up, with censoring of survivors. NRM were calculated as the time from allo-HSCT to death from any cause excluding relapsing disease. Logistic regression analysis was performed to explore the effect of major clinical variables (patient age at transplantation, disease, source of stem cells, conditioning regimen, T-cell depletion) with HSCT outcome. The likelihood ratio and significance values are presented as Odds Ratio (OR) with a 95% Confidence Interval (CI) and the *p*-value for each variable. All *p*-values were two-sided and statistical significance was determined by a *p*-value <0.05. The Kaplan–Meier estimator and the log–rank test were used for OS. Statistical analysis was performed using SPSS (version 22; IBM, Chicago, IL, USA).

Patients' baseline characteristics are shown in Table 1. The median age was 55 years (range 20–72 years). Conditioning regimens were in the majority myeloablative (72.5%).Of the 302 transplant recipients, 230 (76.2%) were matched at HLA-A, -B, -C, -DRB1, and -DQB1 (HLA-10/10), whereas 72 patients (23.8%) had one antigen mismatch (HLA-9/10) (mismatch: A $n = 29$, B $n = 10$, C $n = 13$, DRB1 $n = 8$, DQB1 $n = 12$). Among 72 transplant recipients with one antigen mismatch at either HLA-A,-B, -C, -DRB1, or -DQB1 (HLA-9/10), 2 had one HLA-DPB1 mismatch. Among the patients matched at HLA-A, -B, -C, -DRB1, and -DQB1 (HLA-10/10), 29 had one HLA-DPB1 mismatch (HLA-11/12) Permissive MMs were present in 14/29 (48.3%) unrelated patient-donor pairs and non-permissive HLA-DPB1 MMs were detected in 15/29 (51.7%) pairs (5 HvG; 10 GvH direction). As shown in Table 1, acute GvHD ≥ grade 2 occurred in 144/302 patients (47.7%) and 129/302 (42.7%) had chronic GvHD. There was no significant difference in comparison of the groups with and without HLA-DPB1 mismatch ($p = 0.635$ and $p = 0.884$, respectively). In multivariable analysis (Table 2) of the whole cohort, HLA-DPB1 mismatching was not associated with increased risk of aGvHD ≥ grade 2 (hazard ratio [95% confidence interval]) (1.23 [0.92, 3.52]; $p = 0.83$) and cGvHD (1.15 [0.90, 1.53]; $p = 0.43$). There was no significant difference in OS between unrelated patient-donor pairs who were matched and those who were permissive/non-permissive mismatched for HLA-DPB1 alleles (1.03 [0.79, 2.20], $p = 0.63$), although there was a trend of worse OS for HLA-DPB1-matched pairs (supplementary Figure 1). The impact of HLA-DPB1 matched and permissive/non-permissive HLA-DPB1 mismatched unrelated patient-donor pairs had no worse impact on NRM (1.23 [0.82, 3.65], $p = 0.23$) (Table 2).

In our analysis on the outcome of HLA-DPB1 mismatches in HSCT, we found no difference in OS. We are in line with the studies by Lorentino et al., Gagne et al. and Shaw et al. who also found no significant difference in OS regarding DPB1 match [13–15]. In other studies, a lower relapse rate in HSCT with HLA-DPB1 mismatch was shown and in

Table 1
Comparison of patients with and without HLA-DPB1 mismatches.

	No DPB1 mismatch (n = 271; 89.7%)	With DPB1 mismatch (n = 31; 10.3%)	Total patients (n = 302, 100%)	*p*-value
Female	122 (45%)	15 (48.4%)	137 (45.4%)	p = 0.721
Male	149 (55%)	16 (51.6%)	165 (54.6%)	
Donor type				p<0.001
Identical sibling	118 (43.5%)	0	118 (39.1%)	
Matched related	2 (0.7%)	0	2 (0.6%)	
Mismatched related	2 (0.7%)	2 (6.5%)	4 (1.3%)	
Unrelated	147 (54.2%)	29 (93.5%)	176 (58.3%)	
Syngeneic	2 (0.7%)	0	2 (0.7%)	
Stem cell source				p = 0.412
BM	16 (5.9%)	3 (9.7%)	19 (6.3%)	
PBSC	255 (94.1%)	28 (90.3%)	283 (93.7%)	
Conditioning regimen				p = 0.927
MAC	196 (72.3%)	23 (74.3)	219 (72.5%)	
RIC	75 (27.7%)	8 (25.8%)	83 (27.5%)	
TBI	94 (34.7%)	7 (22.6%)	101 (33.4%)	p = 0.210
Underlying disease				p = 0.037
AML	100 (36.9%)	15 (48.4%)	115 (38.1%)	
ALL	29 (10.7%)	2 (6.5%)	31 (10.3%)	
CML	8 (3.0%)	1 (3.2%)	9 (3.0%)	
CLL	23 (8.5%)	0	23 (7.6%)	
MDS	34 (12.5%)	2 (6.5%)	36 (11.9%)	
MPN	18 (6.6%)	4 (12.9%)	22 (7.3%)	
Plasma cell disorder	34 (11.9%	0	33 (10.9%)	
Bone marrow failure	5 (1.8%)	3 (9.7%)	8 (2.6%)	
Hodgkin's disease	4 (1.5%)	0	4 (1.3%)	
Non-Hodgkin lymphoma	16 (5.9%)	4 (12.9%)	20 (6.6%)	
Autoimmune disease	1 (0.4%)	0	1 (0.3%)	
GvHD prophylaxis				p = 0.445
CyA + MMF	81 (29.9%)	5 (16.1%)	86 (28.5%)	
CyA	3 (1.1%)	0	3(1.0%)	
CyA + MTX	183 (67.5%)	26 (83.9%)	209 (69.2%)	
no	3 (1.1%)	0	3 (1.0%)	
sirolimus	1 (0.4%)	0	1 (0.3%)	
ATG used	127(46.8%)	24 (77.4%)	151 (50%)	
aGvHD ≥ grade 2	130 (47.9%)	14 (45.1%)	144 (47.7%)	p = 0.635
cGvHD	116 (42.8%)	13 (41.9%)	129 (42.7%)	p = 0.884
Cause of Death				p = 0.981
Infections	11 (4.1%)	1 (3.2%)	12 (4.0%)	
GvHD	19 (7.0%)	2 (6.5%)	21 (7.0%)	
Progressive disease	32 (11.8%)	2 (6.5%)	34 (11.3%)	
Relapse	18 (6.6%)	0	18 (6.0%)	
Others	19 (7.0%)	0	19 (6.3%)	

Abbreviations: aGvHD = acute graft-versus-host disease, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, ATG = antithymocyte globulin, BM = bone marrow, cGvHD = chronic graft-versus-host disease, CLL = chronic lymphocytic leukemia, CML = chronic myeloid leukemia, CyA = cyclosporine A, MAC = myeloablative conditioning, MDS = myelodysplastic syndrome, MMF = mycophenolate mofetil, MPN = myeloproliferative neoplasm, MTX = methotrexate, PBSC = peripheral blood stem cells, RIC = reduced intensity conditioning, TBI = total body irradiation.

detail reviewed by Wang et al. [9].

We could not find a difference in the incidence of acute GvHD in HLA-DPB1 mismatched HSCT compared to HSCT without HLA-DPB1 mismatch. A reason for this could be the low patient number in our

Table 2
Multivariable analysis of associations between outcomes and HLA-DPB1 matching status (permissive/non-permissive mismatched versus matched).

Whole cohort (n = 302)	HR (95% CI)	*p*-value
aGvHD ≥ grade 2	1.23 [0.92, 3.52]	0.83
cGvHD	1.15 [0.90, 1.53]	0.43
OS	1.03 [0.79, 2.20]	0.63
NRM	1.23 [0.82, 3.65]	0.23

Abbreviations: aGvHD = acute graft-versus-host disease, cGvHD = chronic graft-versus-host disease, NRM = non-relapse mortality, OS = overall survival.

study. But, we are in line with the studies by Burek Kamenaric et al. and Petersdorf et al., which showed no difference in the incidence of aGvHD, as well as no significant effects on OS [7,16]. Shaw et al. showed even a significant lower incidence of aGvHD [8].

In a study byLorentino et al., DPB1 allele mismatches were also not associated with any significant difference in OS, and this was reflected by a balance between significantly higher risks of aGvHD, in the presence of a markedly though not significantly lower risks of relapse [13]. This was shown in many other studies as well [16–18].

In the case of chronic GvHD incidence, we did not find a difference in the compared groups. We are in line with the results from Gagne et al., which showed no impact of DPB1 mismatch on cGvHD, OS and relapse [14]. On the contrary, Moyer et al. showed an increase of cGvHD risk [19]. The reason could be the high rate of peripheral blood as stem cell source in our study, which was associated with higher cGvHD risk. Furthermore, DPB1 non-permissive and -permissive mismatched groups must be taken into account [9]. Our study has several drawbacks: a heterogeneous patient population with different diseases, disease stages, conditioning regimen, stem cell source, and GvHD prophylaxis. Nevertheless, permissive/non-permissive HLA-DPB1 mismatches were noted in about 10% of the patients in our cohort and did not have an impact on outcome of allo-HSCT.

In conclusion, in our population the overall survival was not negatively influenced by a HLA-DPB1 mismatch. Acute and chronic GvHD did not occur more often in HLA-DPB1 mismatched HSCT. The impact of mismatches may vary depending on the type and state of the underlying disease, the GvHD prophylaxis (T-cell depletion) used, and the conditioning regimen. In patients with an available 10/10 HLA-matched donor, the relevance of a DPB1 mismatch must be considered on the individual situation of the underlying disease, disease stage, conditioning regimen, and T-cell depletion taking into account the patients'risk for relapse and GvHD.

Compliance with ethical standards

Declarations

Ethics approval
The study was performed according to the regulations of the local ethics committee.

Patient consent to participate statement
The patients have consented to participate and the use of materials.

Consent for publication
The authors have provided the consent for publication.

Declaration of Competing Interest

All authors declare no conflict of interest regarding matters pertinent to the current manuscript.
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Mireille Hunziker: Writing – original draft, Data curation. **Jakob Passweg:** Data curation, Writing – review & editing. **Michael Medinger:** Conceptualization, Writing – original draft, Data curation.

Declaration of Competing Interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2021.100259.

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