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 MM 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 an 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
reduced intensity conditioning, TBI syndrome, MMF—detail reviewed by Wang et al. [9].

**Table 1**

| Disease          | 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%)                   | p < 0.001 |
| Donor type       |                                  |                                   |                               |         |
| 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%)                   |         |
| Sternum cell source | 2 (0.7%)                        | 0                                 | 2 (0.7%)                      |         |
| BM               | 16 (5.9%)                        | 3 (9.7%)                          | 19 (6.3%)                     | p = 0.412 |
| PBSC             | 255 (94.1%)                      | 28 (90.3%)                        | 283 (93.7%)                   |         |
| Conditioning regimen |                                  |                                   |                               | p = 0.927 |
| RIC              | 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        | 3 (1.1%)                         | 0                                 | 3 (1.0%)                      |         |
| CyA + MTX no     | 193 (67.5%)                      | 26 (83.9%)                        | 209 (69.2%)                   |         |
| sirolimus        | 1 (0.4%)                         | 0                                 | 1 (0.3%)                      |         |
| ATG used         | 127 (46.8%)                      | 24 (77.4%)                        | 151 (50%)                     | p = 0.635 |
| aGVHD ≥ grade 2  | 130 (47.9%)                      | 14 (45.1%)                        | 144 (47.7%)                   | p = 0.884 |
| cGVHD            | 116 (42.8%)                      | 13 (41.9%)                        | 129 (42.7%)                   | p = 0.981 |
| Cause of Death   |                                  |                                   |                               |         |
| 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%)                     |         |

**Table 2**

| Outcome          | 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              | 1.21 [0.62, 3.65]      | 0.23        |         |

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

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 HLA 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 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 a study by Lorentino 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 marker of GvHD, showing no difference in the incidence of aGvHD, as well as no significant effects on OS [7, 16]. Shah et al. showed even a significant lower incidence of aGvHD [8].

In the course 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 DBP1 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, DBP1 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 DBP1 mismatch must be considered on the individual situation of the underlying disease, disease stage, conditioning regimen, and T-cell depletion taking into account the patient’s risk for relapse and GVHD.
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Declaration of Competing Interest
The authors declare no conflict of interest.

Supplementary materials
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