Integrating biological HLA-DPB1 mismatch models to predict survival after unrelated hematopoietic cell transplantation

Relapse and graft-*versus*-host disease (GvHD) are the main impediments to the clinical success of allogeneic hematopoietic cell transplantation (HCT) in curing malignant blood disorders. Alloreactive donor T cells are important mediators of both relapse control by graft-*versus*-leukemia (GvL) effects, and of GvHD.[1] In unrelated donor (UD)-HCT, frequent human leukocyte antigen (HLA)-DPB1 disparity is the target of T-cell alloreactivity, contributing to both leukemia control and GvHD.[2] We have previously shown that two biological models of HLA-DPB1 mismatching, namely permissiveness according to T-cell epitope (TCE) groups and genetically determined high-expression levels, are individually associated with the risks of non-relapse mortality and GvHD/relapse, respectively.[3,4] This led us to hypothesize that combined TCE-permissive and high-expression (TPHE) HLA-DPB1 mismatches might synergize for best outcomes. We tested this novel hypothesis in over 6,000 HCT from 8/8 HLA-matched UD reported to the European Group for Blood and Marrow Transplantation (EBMT), to demonstrate that HLA-DPB1 non-TPHE mismatches were associated with worse relapse-free survival and overall survival than TPHE mismatches, present in 21.7% of single HLA-DPB1 disparate pairs. Our work provides a synthesis of previous algorithms, mechanistically based on HLA-DPB1 immunopeptidome divergence[5] and expression by residual leukemia cells,[6,7] respectively, into a new and integrative model for intelligent mismatching in UD-HCT, to improve survival for future patients.

Alloreactive donor T cells recognizing patient-specific genetic polymorphisms, including mismatched HLA allotypes, play a major role in both beneficial GvL and severe GvHD after UD-HCT. One of the best examples of these two contrasting aspects of T-cell alloreactivity is donor-recipient HLA-DPB1 disparity, present in over 80% of transplants from UD.[3] HLA-DPB1 disparity has been extensively explored for biological models apt to tease out clinically permissive mismatch combinations.[2] These include sharing of alloreactive TCE groups between mismatched HLA-DPB1 alleles (TCE-permissiveness), mainly associated with non-relapse mortality,[3,8] and high or low expression levels determined by a specific single nucleotide polymorphism in the HLA-DPB1 3' untranslated region (expression-permissiveness), mainly associated with acute GvHD.[4,9] Numerous studies have since investigated the clinical role of these two models in different national and international cohorts from the USA and Europe, both individually and in direct comparison.[10-13] However, it is unclear whether the two models can be integrated, and whether their integration improves prediction of survival. These two questions were addressed in the present study. We investigated a previously unexplored cohort of 6,627 HLA-A, -B, -C, -DRB1-matched (HLA-8/8) first UD-HCT for adult patients with hematologic malignancies, reported by 160 EBMT centers between 2005 and 2017 (Table 1). Reflecting the increasing numbers of available six-loci HLA-typed UD in worldwide registries, and mounting recognition of the relevance of HLA-DPB1 matching for outcome, the percentage of HLA-DPB1 allele-matched pairs was higher in later years compared to earlier years (Table 1). Informed consent was obtained from all patients according to the Declaration of Helsinki, and protocols were approved by the institutional review boards of the participating institutions. Patients had received mainly peripheral blood stem cells under reduced intensity conditioning and cyclosporine-based GvHD prophylaxis with *in vivo* T-cell depletion by anti-thymocyte globulin; use of post-transplant cyclophosphamide was excluded. The cohort was stratified by HLA-DPB1 allele matches or mismatches, by TCE-permissiveness or TCE-nonpermissiveness according to the three-group model,[3] or in the single HLA-DPB1 graft-*versus*-host (GvH) mismatched group by high expression or low expression according to the rs9277534 G/A single nucleotide polymorphism[4] and/or TCE-permissiveness, for the discrimination between TPHE mismatches and others (*Online Supplementary Figure S1A*). The primary study endpoint was relapse-free survival; secondary endpoints included non-relapse mortality, relapse, acute GvHD, chronic GvHD, GvHD-free relapse-free survival (GRFS) and overall survival. Univariable and multivariable analyses by the log-rank test, cumulative-incidence functions and (cause-specific) Cox-regression models were adjusted for non-HLA-DPB1 factors (*Online Supplementary Table S1*). For this hypothesis-testing analysis, *P*-values <0.05 were considered statistically significant.

HLA-DPB1 allele mismatches were associated with lower risks of relapse, and increased risks of acute GvHD and non-relapse mortality without improved relapse-free survival, compared to matches (Figure 1, *Online Supplementary Table S2*). When considered individually, TCE-nonpermissive and high-expression HLA-DPB1 single GvH-mismatches were each associated with lower relapse but higher acute

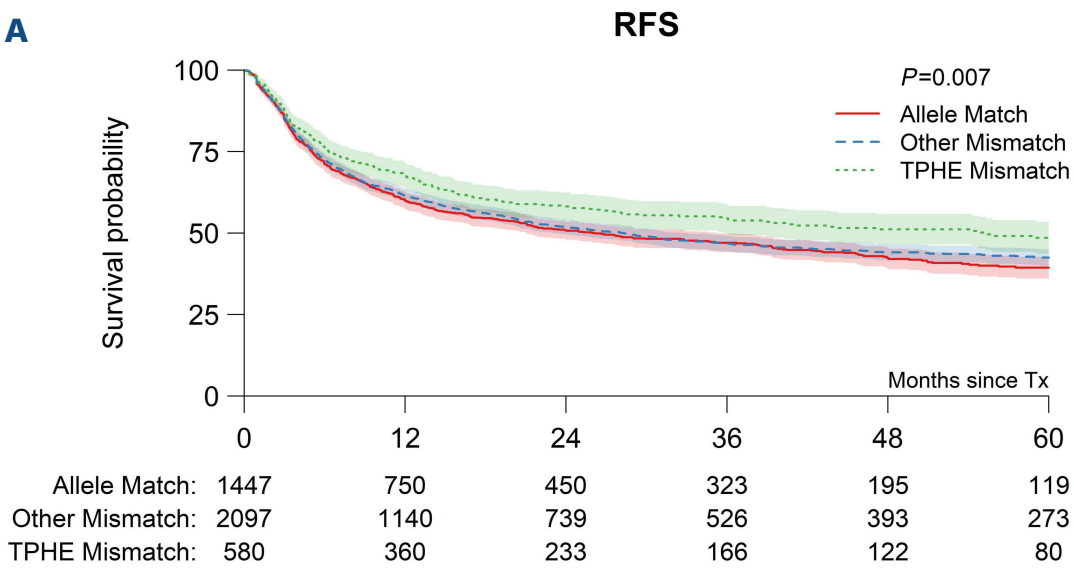
Table 1. Patient, donor and transplant characteristics.

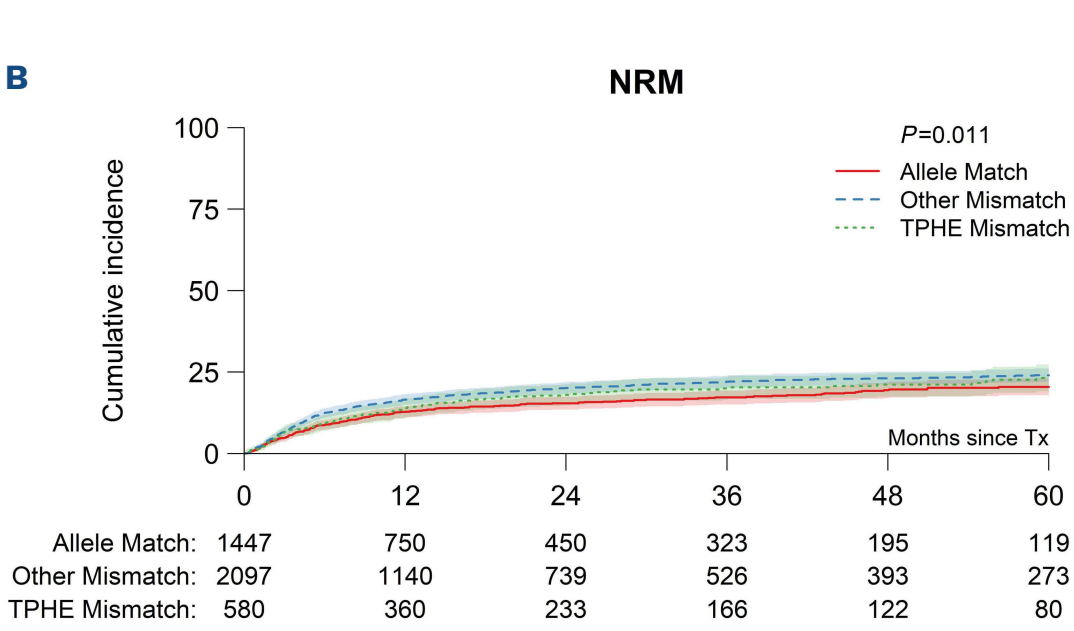
Characteristic[a]	Total N (%) / Missing N (%)[b]	Match N (%)[c]	Mismatch N (%)[d]	*P*[e]
Patients Age in years, median (range)	6,627 (100) / 0 (0)	1,480 (22.3) 55.1 (18-77)	5,147 (77.7) 54.1 (18-77)	0.06
Diagnosis AML/ALL MDS/MPN Other	6,627 (100) / 0 (0)	 759 (51.3) 379 (25.6) 342 (23.1)	 2,667 (51.8) 1,236 (24.0) 1,244 (24.2)	0.41
Disease stage Early Intermediate Advanced	6,552 (98.9) / 75 (1.1)	 664 (45.4) 408 (27.9) 391 (26.7)	 2,298 (45.2) 1,493 (29.3) 1,298 (25.5)	0.47
Karnofsky Index ≥90 <90	6,088 (91.9) / 539 (8.1)	 1,301 (95.5) 62 (4.5)	 4,513 (95.5) 212 (4.5)	0.44
Donor age Median (range)	5,788 (87.3) / 839 (12.7)	1,306 (19.7) 28.6 (18-60)	4,482 (67.6) 30.8 (18-61)	**<0.001**
Donor sex Female Male	6,567 (99.1) / 60 (0.9)	 408 (27.9) 1,053 (72.1)	 1,421 (27.8) 3,685 (72.2)	0.97
Cytomegalovirus match Negative/negative Other	6,555 (98.9) / 72 (1.1)	 459 (31.5) 1,000 (68.5)	 1,682 (33.0) 3,414 (67.0)	0.28
DQB1 Match Mismatch	6,627 (100) / 0 (0)	 1,436 (97.0) 44 (3.0)	 4,850 (94.2) 297 (5.8)	**<0.001**
Year 2005-2011 2012-2017	6,627 (100) / 0 (0)	 276 (18.6) 1,204 (81.4)	 1,462 (28.4) 3,685 (71.6)	**<0.001**
Stem cell source Bone marrow Peripheral blood stem cells	6,627 (100) / 0 (0.0)	 168 (11.4) 1,312 (88.6)	 713 (13.9) 4,434 (86.1)	**0.01**
Conditioning Reduced intensity conditioning Myeloablative conditioning	6,598 (99.6) / 29 (0.4)	 859 (58.6) 607 (41.4)	 3,093 (60.3) 2,039 (39.7)	0.261
GvHD prophylaxis CSA-MTX CSA-MMF Tacrolimus-based Other	6,627 (100) / 0 (0)	 894 (60.4) 423 (28.6) 131 (8.9) 32 (2.2)	 2,922 (56.8) 1,585 (30.8) 503 (9.8) 137 (2.7)	0.08
In vivo T-cell depletion No Yes	6,620 (99.9) / 7 (0.1)	 385 (26.0) 1,093 (74.0)	 1,376 (26.8) 3,766 (73.2)	0.61
HLA-DPB1 T-cell epitope-mismatch Permissive Nonpermissive	5,147 (77.7) / 1,480 (22.3)	 NA NA	 2,875 (55.9) 2,272 (44.1)	NA
Single HLA-DPB1 GvH expression-mismatch Low High	2,745 (41.4) / 3,882 (58.6)	 NA NA	 1,463 (53.3) 1,282 (46.7)	NA
Combined HLA-DPB1 TCE and expression mismatch TPHE Other	2,745 (41.4) / 3,882 (58.6)	 NA NA	 597 (21.7) 2,184 (78.3)	NA

[a]*Diagnosis*. AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; Other: includes chronic myeloid or lymphatic leukemia, malignant plasma cell disorders and lymphoma. *Disease stage*. Early: first complete remission, first chronic phase, refractory anemia with or without ring sideroblasts, deletion 5q; Intermediate: second complete remission, chronic phase (not first), refractory anemia with excess blasts-1, refractory anemia with excess blasts-2; Advanced: refractory anemia with excess blasts in transformation, MDS transformed to AML, accelerated phase, blast crisis, partial remission, very good partial remission, refractory, untreated, progression, relapse. *GvHD prophylaxis*: CSA: cyclosporine A, MTX: methotrexate, MMF: mycophenolate mofetil. *In vivo T-cell depletion*. Use of anti-thymocyte globulin, anti-T-lymphocyte globulin or Campath. TCE: T-cell epitope, *Combined HLA-DPB1 TCE and expression mismatch*. TPHE: single graft-*versus*-host (GvH) mismatches that are both TCE-permissive and high expression; Other: all single GvH mismatches that are not TPHE (for explanations see text). [b]For HLA-DPB1 TCE-mismatch, Missing N (%) refer to allele-matched pairs. For Single HLA-DPB1 GvH expression-mismatch and combined HLA-DPB1 TCE and expression mismatch, Missing N (%) refer to the sum of allele-matched pairs and pairs that did not have a single DPB1 mismatch in the GvH direction. [c]NA not applicable. [d]Mismatch refers to allele-level (i.e., 2-digit) mismatch. [e]*P*-values were obtained by the χ^2 test for categorical variables, and by the Kruskal-Wallis test for continuous variables (i.e. patient and donor age). Statistically significant *P*-values <0.05 are indicated in bold.

GvHD and non-relapse mortality, compared to allele matches (*Online Supplementary Table S2*). In contrast, the risk of non-relapse mortality was not higher in TCE-permissive or low-expression HLA-DPB1 single GvH-mismatches compared to allele matches. Importantly, TCE-permissive but not low-expression HLA-DPB1 single GvH-mismatches were associated with lower relapse risks compared to allele matches, albeit with higher GvHD. Neither permissive or nonpermissive TCE-mismatches *nor* high- or low-expression, were individually associated with relapse-free survival (*Online Supplementary Table S2*) or overall survival (*data not shown*).

Reflecting the strong linkage disequilibrium between exon variation of HLA-DPB1 determining TCE groups and the rs9277534 single nucleotide polymorphism determining expression levels,[14] there was some overlap between the TCE-model and the expression-model, with 65% of single HLA-DPB1 GvH-mismatches being TCE-nonpermissive and high expression (685/2,745, 25%) or TCE-permissive and low expression (1,100/2,745, 40%) (*Online Supplementary*





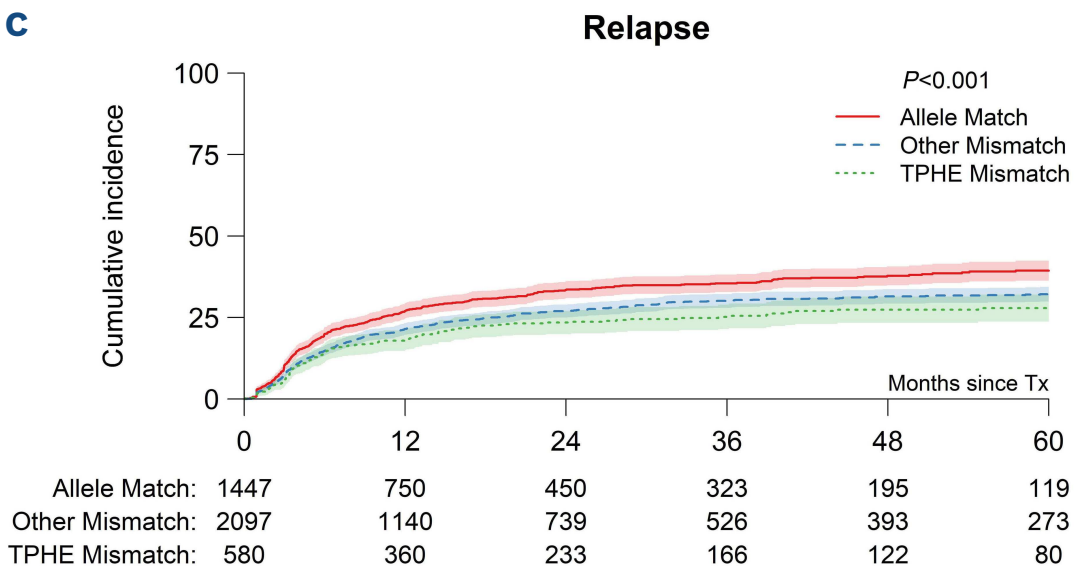


Figure 1. Univariable associations between combined HLA-DPB1 T-cell epitope and expression matching and outcome after 8/8 HLA-matched unrelated donor hematopoietic cell transplantation. Five-year outcome probabilities (A,B) or (C) 5-year cumulative incidence are shown for HLA-DPB1 T-cell epitope (TCE)-permissive and high expression (TPHE) mismatches, other (i.e. non-TPHE) mismatches or allele matches. (A) Relapse-free survival (RFS) (49% [95% CI: 44-53%], 42% [95% CI: 40-45%] or 39% [95% CI: 36-43%], *P*=0.007), (B) non-relapse mortality (NRM) (23% [95% CI: 19-27%], 24% [95% CI: 22-26%], 20% [95% CI: 18-23%], *P*=0.01), (C) relapse (28% [95% CI: 24-32%], 32% [95% CI: 30-34%], 39% [95% CI: 36-42%], *P*<0.001). Overall survival and relapse-free survival were assessed using the Kaplan-Meier (KM) method, with reverse KM for determination of median follow-up. Univariable comparisons were performed using the log-rank test. Outcomes with competing risks were assessed using cumulative incidence curves and univariable comparisons for these outcomes were performed using the Gray test. For each of relapse, acute GvHD, and chronic GvHD, death without the event of interest was a competing event, as was second transplantation.

Figure S1A). In contrast, the remaining 35% of single HLA-DPB1 GvH-mismatches were TCE-nonpermissive and low-expression (363/2,745, 13.3%) or TCE-permissive and high expression (TPHE; 597/2,745, 21.7%). We developed and tested the novel hypothesis that the latter group might identify pairs with best outcomes, given that both TCE-permissive and high-expression mismatches were individually associated with reduced relapse risks, but at the same time, TCE-permissive pairs did not have increased risks of non-relapse mortality (*Online Supplementary Table S2*). Univariable associations with relapse-free survival were better for TPHE-mismatches than for non-TPHE-mismatches or allele-matches, reflecting lower non-relapse mortality and lower relapse (Figure 1, *Online Supplementary Figure S1B*). Multivariable analysis adjusted for non-HLA-DPB1 factors (*Online Supplementary Table S1*) confirmed the association between non-TPHE mismatches or allele matches with lower relapse-free survival, compared to TPHE mismatches (hazard ratio [HR]=1.21, 95% confidence interval [95% CI]: 1.04-1.41, *P*=0.01) (Table 2). With TPHE mismatches as the reference, overall survival was worse for non-TPHE mismatches but not for allele matches (HR=1.18, 95% CI: 1.01-1.39, *P*=0.04), while there were no differences in GRFS (Table 2). To confirm the observation that the association of high-expression mismatches with acute GvHD and non-relapse mortality was dependent on the TCE status, we performed interaction analyses. We found a significant interaction between high expression and TCE permissiveness in opposing directions for acute GvHD (interaction HR=0.62; 95% CI: 0.45-0.85, *P*=0.003) and non-relapse mortality (interaction HR=1.64; 95% CI: 1.09-2.48, *P*=0.018), with lower mortality associated with TCE permissiveness in the high-expression group despite increased acute GvHD.

Our study is the first to investigate the combined effects of the biological HLA-DPB1 TCE and expression models in HLA-8/8-matched transplantation for association with survival. The results provide a synthesis of both biological algorithms into a new and integrative model for intelligent mismatching in UD-HCT. Mechanistically, HLA-DPB1 TCE permissiveness reflects limited immunopeptidome diver-

Table 2. Multivariable analysis of associations between combined HLA-DPB1 T-cell epitope and expression status and clinical endpoints.

		TPHE mismatch[a]	Other mismatch[a]	Allele match
Overall survival[b]	HR	1.0	1.18	1.08
	95% CI		1.01-1.39	0.91-1.28
	P		**0.04**	0.36
Relapse-free survival[b]	HR	1.0	1.21	1.23
	95% CI		1.04-1.41	1.05-1.44
	P		**0.01**	**0.01**
GvHD-free, relapse free survival[b]	HR	1.0	1.05	1.14
	95% CI		0.91-1.20	0.99-1.32
	P		0.50	0.07
Non-relapse mortality[b]	HR	1.0	1.17	0.91
	95% CI		0.93-1.47	0.71-1.17
	P		0.18	0.47
Relapse[b]	HR	1.0	1.21	1.47
	95% CI		0.98-1.48	1.20-1.81
	P		0.07	**<0.001**
Acute GvHD 2-4[b]	HR	1.0	0.74	0.66
	95% CI		0.62-0.97	0.55-0.80
	P		**<0.001**	**<0.001**
Acute GvHD 3-4[b]	HR	1.0	0.80	0.76
	95% CI		0.61-1.07	0.57-1.03
	P		0.13	0.08
Chronic GvHD[b]	HR	1.0	0.77	0.89
	95% CI		0.66-0.91	0.75-1.05
	P		**0.002**	0.16

[a]TPHE: combined T-cell epitope (TCE)-permissive and high expression; Other: other single HLA-DPB1 graft-*versus*-host (GvH)-mismatches, [b]Adjustment was made for non-HLA-DPB1 variables as in *Online Supplementary Table S1*. Overall survival: time from transplant to death, Relapse-free survival: time from transplant to first of relapse or progression, second transplant or death; Graft-*versus*-host disease (GvHD)-free relapse-free survival: time from transplant to first of acute GvHD grades 3-4, extensive chronic GvHD, relapse, second transplant or death; HR: hazard ratio; 95% CI: 95% confidence interval. Patients without the relevant event were censored at last available follow-up. Multivariable analysis was performed using Cox proportional hazards models for overall survival, relapse-free survival, and GvHD relapse-free survival, and cause-specific hazards models for all other outcomes. All analyses were adjusted for the same clinically relevant non-HLA-DPB1 variables of interest (*Online Supplementary Table S1*). Interactions between HLA-DPB1 allele, TCE or expression matching status and disease stage or T-cell depletion were considered for all endpoints, and found only between T-cell depletion and expression matching for acute GvHD grades 2-4 and between disease stage and expression matching for chronic GvHD. All statistical analysis were performed in R version 3.6.3, using the packages survival (version 3.1-12), cmprsk (version 2.2-9) and prodlim (version 2019.11.13). Statistically significant *P*-values <0.05 are indicated in bold.

gence between mismatched allotypes, constraining the number and diversity of the alloreactive T-cell receptor repertoire.[5] HLA class II expression, on the other hand, is a hallmark of different hematologic malignancies, including acute myeloid leukemia, in which its downregulation is an established mechanism of immune escape after allogeneic HCT.[6,7] The favorable associations between HLA-DPB1 TPHE mismatches and survival observed in this study suggest that the GvL effect mediated by limited T-cell alloreactivity in the TCE-permissive setting might be most effective when HLA-DP expression levels on residual malignant cells are high. Concordantly, we found that in the high-expression group, the mean (± standard deviation) immunopeptidome overlap of the informative mismatched HLA-DPB1 alleles was 11% (± 13%) for TCE-permissive pairs, and 1.9% (± 0.8%) for TCE-nonpermissive pairs (P<0.0001 in the 2-tailed Mann-Whitney test). It should be noted that due to the aforementioned linkage disequilibrium within the HLA-DPB1 locus, TPHE mismatches mostly involve certain HLA-DP allotypes carrying the DEAV motif in the patient but not in the donor, whose immunoepeptidomes have only partly been explored.[5,15] Specific immunopeptidome characterization of the relevant TPHE mismatches will help to improve our understanding of the mechanisms underlying alloreactive T-cell-mediated GvL effects.

The present study confirmed previously described associations of HLA-DPB1 allele mismatches with relapse, and of the individual TCE and expression models with non-relapse mortality[3,8,12,13] and acute GvHD grade 2-4,[4,9,11] but also revealed some differences. Overall survival was not improved for TCE-permissive mismatches, and single HLA-DPB1 high-expression mismatches were not associated with severe acute GvHD grade 3-4 (*data not shown*). Patients in our study received more reduced-intensity/non-ablative conditioning regimens and peripheral blood stem cell products with T-cell depletion, compared to previous cohorts.[3,4,11] These transplant characteristics might explain why the GvL advantage for TPHE-mismatches was not negated by GvHD toxicity, resulting in the observed survival benefits in the current study.

Our study has limitations related to its retrospective nature and its current applicability only to patients with single GvH mismatches, resulting in a relatively limited number of patients in the TPHE subset of interest. Further studies are needed to explore the possibility that our observations apply to the entire set of HLA-DPB1 mismatched patients. Moreover and importantly, confirmation of our findings in additional, independent cohorts is clearly warranted. Nevertheless, our data suggest that the combined consideration of two biological mechanisms of T-cell alloreactivity, TCE and expression, can teach us new lessons regarding the mechanisms underlying cellular immunotherapy of malignant blood disorders, and help to improve survival after UD-HCT.

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An appendix with all contributing EBMT centers can be found at the end of the manuscript.

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https://doi.org/10.3324/haematol.2021.280055

Received: October 12, 2021.
Accepted: April 12, 2022.
Prepublished: May 12, 2022.

Disclosures

No conflicts of interest to disclose.

Contributions

AR, CC and KF designed the study and wrote the manuscript, LCdW and EFB performed statistical analyses and wrote the manuscript, PC and CRM stratified and validated HLA data, JDH provided data management, VD, JP, LW, SGM, and MB provided HLA types; GS, RN, IYY, JJC, TGD, EF, CRC, VG, ET, CEB, AH, GC, ED, MIR, SL, JEJ, and GvG provided clinical data, EWP, LV, CB and VR provided significant advice throughout the study.

Funding

This work was supported by grants from the Deutsche Forschungsgemeinschaft (DFG FL 843/1-1), the Deutsche José Carreras Leukämie Stiftung (DJCLS R 15-02; DJCLS 20R/2019), and the Joseph-Senker Stiftung to KF, and the DKMS (DKMS-SLS-MHG-2018-01) to PC.

Data-sharing statement

The final analysis dataset will be available upon specific request to the chair of the Working Party.

Appendix: EBMT members contributing to this study

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