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ABSTRACT

PURPOSE Human leukocyte antigen (HLA) mismatching can reduce survival of patients with blood cancer after hematopoietic cell transplantation (HCT). How recent advances in HCT practice, in particular graft-versus-host disease (GVHD) prophylaxis by post-transplantation cyclophosphamide (PTCy), influence HLA risk associations is unknown.

PATIENTS AND METHODS The study included 17,292 unrelated HCTs with 6-locus high-resolution HLA typing, performed mainly for acute leukemia or related myeloid neoplasms between 2016 and 2020, including 1,523 transplants with PTCy. HLA risk associations were evaluated by multivariable Cox regression models, with overall survival (OS) as primary end point.

RESULTS OS was lower in HLA mismatched compared with fully matched transplants (hazard ratio [HR], 1.23 [99% CI, 1.14 to 1.33]; $P < .001$). This was driven by class I HLA-A, HLA-B, HLA-C (HR, 1.29 [99% CI, 1.19 to 1.41]; $P < .001$) but not class II HLA-DRB1 and HLA-DQB1 (HR, 1.07 [99% CI, 0.93 to 1.23]; $P = .19$). Class I antigen-level mismatches were associated with worse OS than allele-level mismatches (HR, 1.36 [99% CI, 1.24 to 1.49]; $P < .001$), as were class I graft-versus-host peptide-binding motif (PBM) mismatches compared with matches (HR, 1.42 [99% CI, 1.28 to 1.59]; $P < .001$). The use of PTCy improved GVHD, relapse-free survival compared with conventional prophylaxis in HLA-matched transplants (HR, 0.77 [0.66 to 0.9]; $P < .001$). HLA mismatching increased mortality in PTCy transplants (HR, 1.32 [1.04 to 1.68]; $P = .003$) similarly as in non-PTCy transplants (interaction $P = .43$).

CONCLUSION Class I but not class II HLA mismatches, especially at the antigen and PBM level, are associated with inferior survival in contemporary unrelated HCT. These effects are not significantly different between non-PTCy compared with PTCy transplants. Optimized HLA matching should still be considered in modern HCT.

ACCOMPANYING CONTENT

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Data Supplement

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative treatment option for many patients with high-risk blood cancers.[1-3] Owing to important advances in transplant procedures, including high-accuracy human leukocyte antigen (HLA) tissue typing, pharmacological approaches to combat infection, new conditioning regimens, and new protocols for graft-versus-host disease (GVHD) prophylaxis and treatment, HCT outcomes have improved consistently over the past decades.[4-8] However, donor-recipient HLA mismatching can significantly impair patient survival.[9,10] Hence, clinically tolerable HLA mismatches are sought and may include class- or locus-specific risks,[9,11-13] B-leader disparity,[14,15] or the divergence between the repertoire of antigenic peptides, that is, the immunopeptidome, of mismatched HLA-DPB1 or HLA class I molecules.[16-19] These models have been developed in the

CONTEXT

Key Objective

This study investigates the role of human leukocyte antigen (HLA) mismatching in contemporary unrelated hematopoietic cell transplantation (HCT), in particular under post-transplant cyclophosphamide (PTCy)–based graft-versus-host disease (GVHD) prophylaxis.

Knowledge Generated

Class I but not class II HLA mismatches, especially at the antigen and peptide-binding motif level, are associated with inferior survival after contemporary unrelated HCT. This effect is not significantly different between transplants under conventional GVHD prophylaxis compared with PTCy. On the basis of this, optimized HLA matching should still be considered in modern HCT.

Relevance *(C.F. Craddock)*

This large registry study confirms the adverse impact of HLA mismatch on outcome in patients transplanted from an unrelated donor which, in this study, is not mitigated by the use of PTCy as a GVHD prophylaxis regimen. Ongoing prospective randomized trials will be of importance in definitively addressing the potential of PTCy to improve outcomes after mismatched HCT.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

setting of GVHD prophylaxis mainly based on calcineurin inhibitors, with or without in vivo T-cell depletion (TCD) by anti-thymocyte globulin (ATG) or alemtuzumab. The introduction of post-transplantation cyclophosphamide (PTCy) has markedly improved outcomes of allogeneic HCT across HLA mismatches, with similar survival rates after HLA-matched HCT under conventional GVHD prophylaxis and full-haplotype mismatched HCT under PTCy.[6,20-22] Recently, the use of PTCy has been reported to improve GVHD, relapse-free survival (GRFS) also in unrelated HLA-matched HCT.[23,24] If and how the HLA risk associations observed under conventional GVHD prophylaxis apply to PTCy-based transplant platforms is currently unknown.

Here, we investigated the impact of HLA in contemporary unrelated HCT, leveraging a cohort of over 17,000 recent transplants with 6-locus, high-resolution HLA typing collected through the European Society for Blood and Marrow Transplantation (EBMT) and performed under conventional or PTCy-based GVHD prophylaxis. This allowed us to study the potential interaction between HLA matching and the type of GVHD prophylaxis to comprehensively address the role of HLA in recent HCT for hematologic malignancies.

PATIENTS AND METHODS

Study Population and Design

The study included 17,292 adult patients with hematologic malignancies who underwent a first unrelated HCT from bone marrow or peripheral blood stem cells between 2005 and 2020 and had available 6-locus, high-resolution HLA typing for both donors and recipients (Table 1). Patients transplanted with cord blood units and those receiving grafts with ex-vivo TCD were excluded. Clinical data were collected and stored by the EBMT Registry. Transplant centers reporting to the Registry commit to obtain informed consent in agreement with the principles of the Declaration of Helsinki and according to the local regulations applicable at the time to report pseudonymized data. The study was approved by the Cellular Therapy and Immunobiology Working Party of the EBMT.

HLA Matching

The number of allele (ie, second field) mismatches at HLA-A, HLA-B, HLA-C, HLA-DRB1, and/or HLA-DQB1 (henceforth referred to as the five main HLA loci) was used to classify transplants as fully matched (ie, 10 of 10) or 9 of 10 and eight of 10 matched, respectively (Table 1). Single HLA mismatches in the 9 of 10 pairs were further classified according to (1) their class (ie, HLA class I *v* HLA class II), (2) their locus (ie, any of the five main HLA loci), and (3) their resolution (ie, second-field allelic or first-field antigenic).[26] Single mismatches at HLA-B were also classified as B-leader[15] matched or mismatched. Moreover, single mismatches at HLA-A, HLA-B, or HLA-C were classified as peptide-binding motif (PBM)–matched or mismatched in the GVH vector, as previously described.[19] Finally, mismatches at HLA-DPB1 were divided into permissive or nonpermissive in both 9 of 10 and 10 of 10 pairs according to the functional distance-based, bidirectional T-cell epitope (TCE) model.[16,18,27-30]

Clinical Outcomes and Statistical Analysis

Clinical outcome was studied in the full cohort and in subgroups according to the aforementioned models. The

TABLE 1. Patient-, Disease-, and Transplant-Related Characteristics of the Cohort

Variable	Groups	PTCy No (n = 15,630)	PTCy Yes (n = 1,523)
Age, years, median (IQR)	Patients	56 (44-63)	55 (43-63)
	Donors	29 (24-37)	28 (24-36)
	Missing,[a] No. (%)	1,182 (7)	51 (3)
Disease at transplant, No. (%)	AML	5,706 (37)	522 (34)
	MDS	2,137 (14)	204 (13)
	MPN	1,096 (7)	78 (5)
	ALL	1,656 (11)	178 (12)
	Other[b]	5,035 (31)	541 (36)
Disease risk index,[c] No. (%)	Low	861 (5)	77 (5)
	Intermediate	11,405 (74)	1,109 (73)
	High	2,888 (18)	290 (19)
	Very high	476 (3)	47 (3)
Recipient-donor sex match, No. (%)	Male-male	7,154 (46)	713 (47)
	Male-female	1,974 (13)	210 (14)
	Female-male	3,971 (26)	371 (24)
	Female-female	2,396 (15)	222 (15)
	Missing	135 (<1)	7 (<1)
Recipient-donor CMV match, No. (%)	−/−	4,769 (31)	390 (26)
	−/+	1,364 (9)	105 (7)
	+/−	3,985 (25)	436 (28)
	+/+	5,332 (34)	577 (38)
	Missing	180 (1)	15 (1)
KPS, No. (%)	≥90	10,579 (68)	997 (65)
	80	3,315 (21)	407 (27)
	<80	736 (5)	74 (5)
	Missing	1,000 (6)	45 (3)
HCT-CI, No. (%)	Low risk (0)	6,230 (40)	728 (48)
	Intermediate risk (1-2)	2,815 (18)	299 (19)
	High risk (≥3)	3,010 (19)	360 (24)
	Missing	3,575 (23)	136 (9)
Graft source, No. (%)	BM	1,411 (9)	75 (5)
	PBSC	14,219 (91)	1,448 (95)
Conditioning regimen, No. (%)	MAC	4,600 (30)	593 (39)
	MAC + TBI	2,024 (13)	243 (16)
	RIC	7,377 (47)	492 (32)
	RIC + TBI	1,537 (9.9)	178 (12)
	Missing	92 (<1)	17 (1)
T-cell depletion,[d] No. (%)	No	3,026 (19)	1,159 (76)
	Yes	12,604 (81)	364 (24)
Conventional GVHD prophylaxis, No. (%)	CsA + MTX	5,495 (35)	0 (0)
	CsA + MMF	3,928 (25)	0 (0)
	CsA	1,491 (10)	0 (0)
	TAC-based	1,639 (10)	495 (33)
	Other	3,077 (20)	1,028 (67)
Transplant year, No. (%)	2005-2010	1,631 (10)	3 (<1)
	2011-2015	4,000 (26)	171 (11)
	2016-2020	9,999 (64)	1,349 (89)

(continued on following page)

TABLE 1. Patient-, Disease-, and Transplant-Related Characteristics of the Cohort (continued)

Variable	Groups	PTCy No (n = 15,630)	PTCy Yes (n = 1,523)
HLA matching status, No. (%)	10 of 10	12,210 (78)	924 (61)
	9 of 10	3,004 (19)	522 (34)
	8 of 10	416 (3)	77 (5)
HLA class mM,[e] No. (%)	Class I	2,117 (72)	418 (80)
	Class II	827 (28)	104 (20)
HLA class I PBM status,[f] No. (%)	PBM-GVH match	672 (31)	132 (32)
	PBM-GVH mM	1,182 (54)	219 (52)
	Not informative	323 (15)	67 (16)
HLA class I mM resolution,[g] No. (%)	Low-res match	530 (24)	68 (16)
	Low-res mM	1,647 (76)	350 (84)
HLA-DPB1 matching status, No. (%)	Allele-matched	3,998 (26)	360 (24)
	Permissive	6,462 (41)	619 (41)
	Nonpermissive	5,170 (33)	544 (36)

NOTE. 139 pairs with missing data for PTCy use are not included in the table.
Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CMV, cytomegalovirus; CsA, cyclosporin A; GVH, graft-verus-host; GVHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; KPS, Karnofsky Performance Score; Low-res, low resolution; MDS, myelodysplastic neoplasm; mM; mismatch; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm; MTX, methotrexate; PBM, peptide binding motif group; PBSC, peripheral blood stem cells; PTCy, post-transplantation cyclophosphamide; RIC, reduced intensity conditioning; TAC, tacrolimus; TBI, total body irradiation.
[a]Missing data refer to donor age only.
[b]Includes non-Hodgkin lymphoma (n = 1,509), chronic lymphocytic leukemia (n = 446), chronic myeloid leukemia (n = 481), Hodgkin lymphoma (n = 371), multiple myeloma (n = 643), MDS/MPN including chronic myelomonocytic leukemia (n = 1,377), and other acute leukemia (n = 793).
[c]Disease risk index calculated as described.[25]
[d]In vivo T-cell depletion by antithymocyte globulin, anti–T-lymphocyte globulin, or alemtuzumab.
[e]Referring to the 9 of 10 group.
[f]Referring to the HLA class I mismatched 9 of 10 group.
[g]Low-res match, allelic mismatch at the second field. Low-res mismatch, antigenic mismatch at the first field. Numbers and percentages refer to the HLA class I mismatched 9 of 10 group.

primary end point was overall survival (OS). GRFS, RFS, nonrelapse mortality (NRM), disease relapse or progression, and grades 2 to 4 and 3 to 4 aGVHD and chronic (c)GVHD were secondary end points. End point definitions were as follows: OS, time from transplant to death from any cause; GRFS, time to aGVHD grades 3 to 4, extensive cGVHD, relapse/progression (henceforth referred to jointly as relapse), or death, whichever occurred first[31]; RFS, time to relapse or death; NRM, time to death without relapse.

Survival probabilities and cumulative incidence estimates were calculated using the Kaplan-Meier and the Aalen-Johansen method, respectively. Competing risks models were used to calculate the cumulative incidences of NRM and aGVHD/cGVHD, for which relapse and death or second allogeneic HCT were considered as competing risks, respectively. Univariable comparisons were performed with the log-rank and Gray tests. Regression analyses were performed using multivariable Cox proportional hazards models, including a gamma-distributed frailty term for transplant center.[32] For outcomes with competing risks, cause-specific hazard models were fitted. To analyze the differential effects of HLA mismatch models in the subgroups with conventional or PTCy-based GVHD prophylaxis, interaction analyses were implemented. Complete-case analysis was used to deal with missing data in baseline covariates other than HCT-CI, Karnofsky Performance Score, and donor age, where the missing indicator method was used instead.[33,34] To account for multiple testing, a predefined threshold of $P < .01$ was used to determine statistical significance. All statistical analyses were performed using R Statistical Software (version 4.3.1).[35]

Further details on the clinical outcomes and statistical methods can be found in the Data Supplement (online only).

RESULTS

Overall Outcomes

The median follow-up time in the overall cohort was 39.7 (95% CI, 38.8 to 40.8) months. At 60 months post-transplant, the OS was 50.8% (95% CI, 49.9 to 51.7) while GRFS and RFS were 21.4% (95% CI, 20.7 to 22.2) and 44.2% (95% CI, 43.3 to 45.1), respectively. The overall cumulative incidences of relapse, NRM, and cGVHD at 60 months were

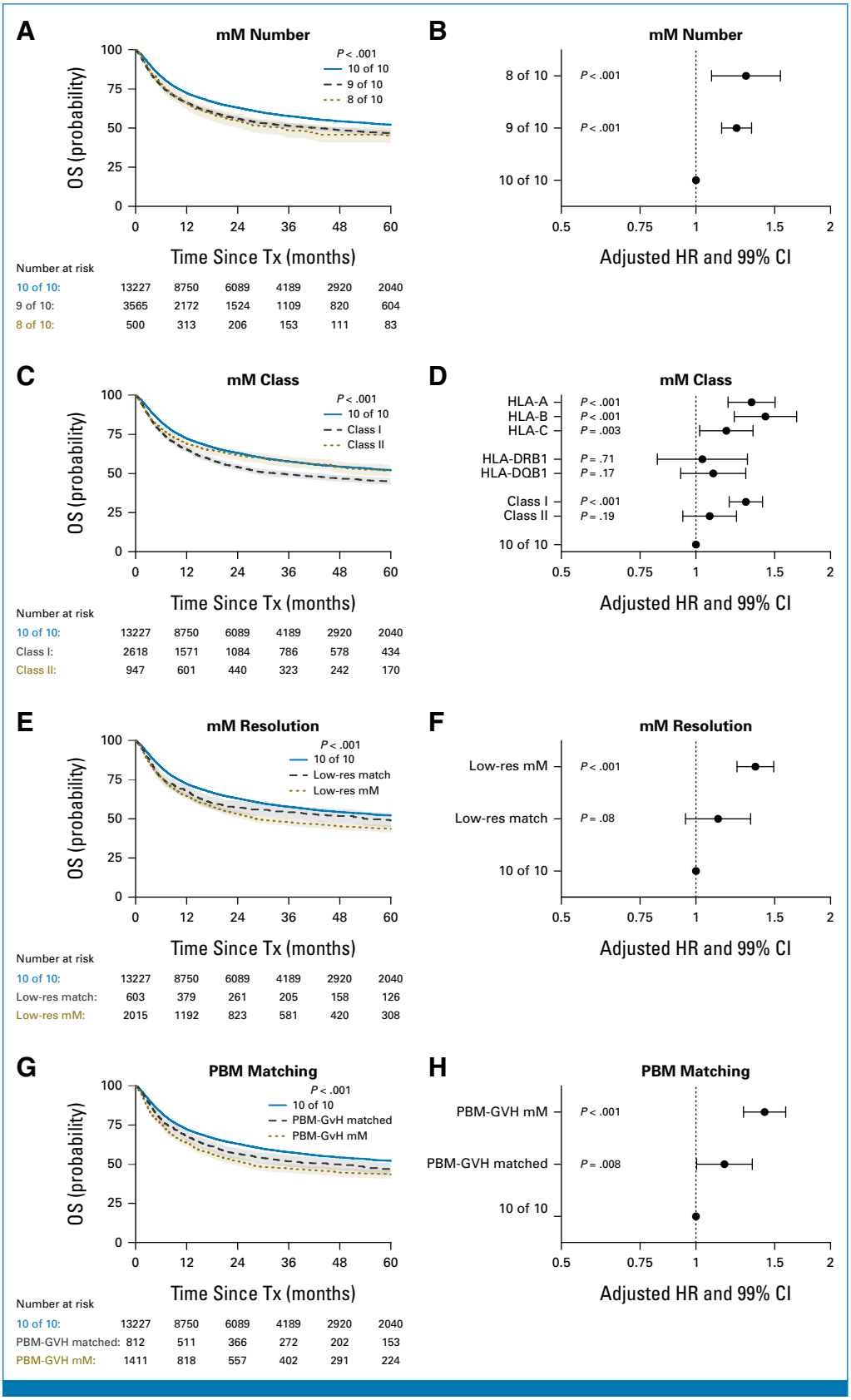

FIG 1. Survival after contemporary HCT according to HLA mismatching. Kaplan-Meier and forest plots show overall survival (OS) probabilities (shaded areas) and adjusted HR estimates and their 99% CI for the entire cohort stratified according to (A, B) the number of mismatches (mM) at HLA-A, HLA-B, HLA-C, HLA-DRB1, or HLA-DQB1; (C, D) the specific mismatched HLA locus and class among the 9 of 10 pairs; (E, F) the typing resolution for HLA class I mM in the 9 of 10 pairs; and (G, H) PBM GVH (continued on following page)

FIG 1. (Continued). matching for HLA class I mM in the 9 of 10 pairs. The fully matched 10 of 10 pairs are used as reference in the HR estimates (vertical lines). The numbers below the Kaplan-Meier plots correspond to the number of individuals at risk at the different time points according to the groups indicated in the legend from top to bottom. HR and *P* values in the forest plots are derived from multivariable analyses shown in Table 2. GVH, graft-versus-host; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HR, hazard ratio; Low-res, low resolution (ie, antigen level); OS, overall survival; PBM, peptide-binding motif.

32.5% (95% CI, 31.7 to 33.3), 23.3% (95% CI, 22.6 to 24), and 40.7% (95% CI, 39.9 to 41.5) while those of grades 2 to 4 and grades 3 to 4 aGVHD at 4 months were 30.5% (95% CI, 29.8 to 31.2) and 11.5% (95% CI, 11 to 12), respectively.

TABLE 2. Multivariable Cox Proportional Hazards Models of HLA Associations in the Full Cohort

End Point	Subgroups	No. (events)	99% CI	*P*
OS	10 of 10	12,841 (5,143)	1	
	9 of 10	3,435 (1,603)	1.23 (1.14 to 1.33)	<.001
	8 of 10	473 (234)	1.29 (1.08 to 1.54)	<.001
	10 of 10	12,841 (5,143)	1	
	Class I mM	2,525 (1,218)	1.29 (1.19 to 1.41)	<.001
	Class II mM	910 (385)	1.07 (0.93 to 1.23)	.19
	10 of 10	12,841 (5,143)	1	
	Low-res[a] match	579 (257)	1.12 (0.95 to 1.33)	.08
	Low-res[a] mM	1,946 (961)	1.36 (1.24 to 1.49)	<.001
	10 of 10	12,841 (5,143)	1	
	PBM-GvH[b] match	776 (362)	1.16 (1 to 1.34)	.008
	PBM-GvH[b] mM	1,367 (679)	1.42 (1.28-1.59)	<.001
GRFS	10 of 10	11,992 (6,879)	1	
	9 of 10	3,131 (1,942)	1.17 (1.09 to 1.25)	<.001
	8 of 10	425 (261)	1.19 (1.01 to 1.4)	.007
	10 of 10	11,992 (6,879)	1	
	Class I mM	2,301 (1,466)	1.23 (1.14 to 1.33)	<.001
	Class II mM	830 (476)	1 (0.88 to 1.13)	.98
	10 of 10	11,992 (6,879)	1	
	Low-res[a] match	528 (315)	1.06 (0.91 to 1.24)	.30
	Low-res[a] mM	1,773 (1,151)	1.3 (1.19 to 1.41)	<.001
	10 of 10	11,992 (6,879)	1	
	PBM-GVH[b] match	711 (450)	1.15 (1.01 to 1.31)	.004
	PBM-GVH[b] mM	1,234 (799)	1.33 (1.2 to 1.46)	<.001

NOTE. Multivariable models were adjusted for patient and donor age, sex (mis)matching, CMV serostatus matching, comorbidity score (HCT-CI),[36] Karnofsky Performance Score, disease at transplant, disease risk index,[25] year of HCT, stem cell source, conditioning regimen and use of total-body irradiation, use of in vivo T-cell depletion, PTCy use, and HLA-DPB1 TCE matching status, and include a gamma-distributed frailty term for transplant center.

Abbreviations: GRFS, graft-versus-host disease, relapse-free survival; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HR, hazard ratio; mM, mismatch; OS, overall survival; PBM-GVH, peptide-binding motif graft-versus-host; TCE, T-cell epitope.

[a]Low-resolution (Low-res).

[b]PBM-GVH matching for HLA class I mM.

HLA Mismatching and HCT Outcome

We first examined the effect of the number of mismatches at any of the five main HLA loci on HCT outcome in the overall cohort. The presence of one or two mismatches significantly reduced the 5-year probability of OS from 52.2% (95% CI, 51.1 to 53.2) in the 10 of 10 pairs to 46.7% (95% CI, 44.8 to 48.6) and 45.3% (95% CI, 40.4 to 50.1) in the 9 of 10 and 8 of 10 pairs, respectively ($P < .001$; Fig 1). In multivariable analysis, one or two mismatches were associated with higher risk of mortality (both OS and GRFS) compared with full matches (Fig 1, Table 2). Similar significant associations were observed for RFS, NRM, and aGVHD II-IV and III-IV but not for relapse or cGVHD (Data Supplement, Table S1 and Fig S1). Additional covariates also significantly associated with OS included patient and donor age and disease- and performance status-related factors (Data Supplement, Table S2).

Next, we performed a more granular risk evaluation in 9 of 10 transplants according to HLA mismatch class, locus, or resolution. Five-year OS was significantly worse for single HLA class I but not HLA class II mismatches, both in univariable and multivariable analysis (Fig 1, Table 2). Of note, there was evidence for time dependency of these associations, apparently driven by strong nonproportionality in the HLA class II effect (Data Supplement, Fig S2). Among mismatched class I loci, HLA-A (hazard ratio [HR], 1.33 [95% CI, 1.18 to 1.50], $P < .001$) and HLA-B (HR, 1.43 [95% CI, 1.22 to 1.68], $P < .001$) conferred higher adjusted risks than HLA-C (HR, 1.17 [95% CI, 1.02 to 1.34], $P = .003$) compared with the 10 of 10 reference (Fig 1). Instead, the adjusted risks for HLA-DRB1 (HR, 1.03 [95% CI, 0.82 to 1.29], $P = .71$) and DQB1 (HR, 1.09 [95% CI, 0.92 to 1.29], $P = .17$) mismatches were similar and not significantly different from the 10 of 10 reference (Fig 1). HLA class I low-resolution mismatches (ie, at the first field or antigen level) were associated with worse OS compared with high-resolution mismatches (ie, at the second field or allele level), both in univariable and multivariable analysis (HR, 1.21 [95% CI, 1.01 to 1.46]; $P = .007$; Fig 1, Table 2). Class- and locus-specific associations with lower OS were mirrored by lower GRFS (Table 2), RFS, and higher NRM and aGVHD and cGVHD, whereas no significant associations were observed with relapse (Data Supplement, Table S1).

Models for Tolerable HLA Mismatches

In the 3,526 patients transplanted from 9 of 10 donors, we tested three models of tolerable HLA mismatches, that is,

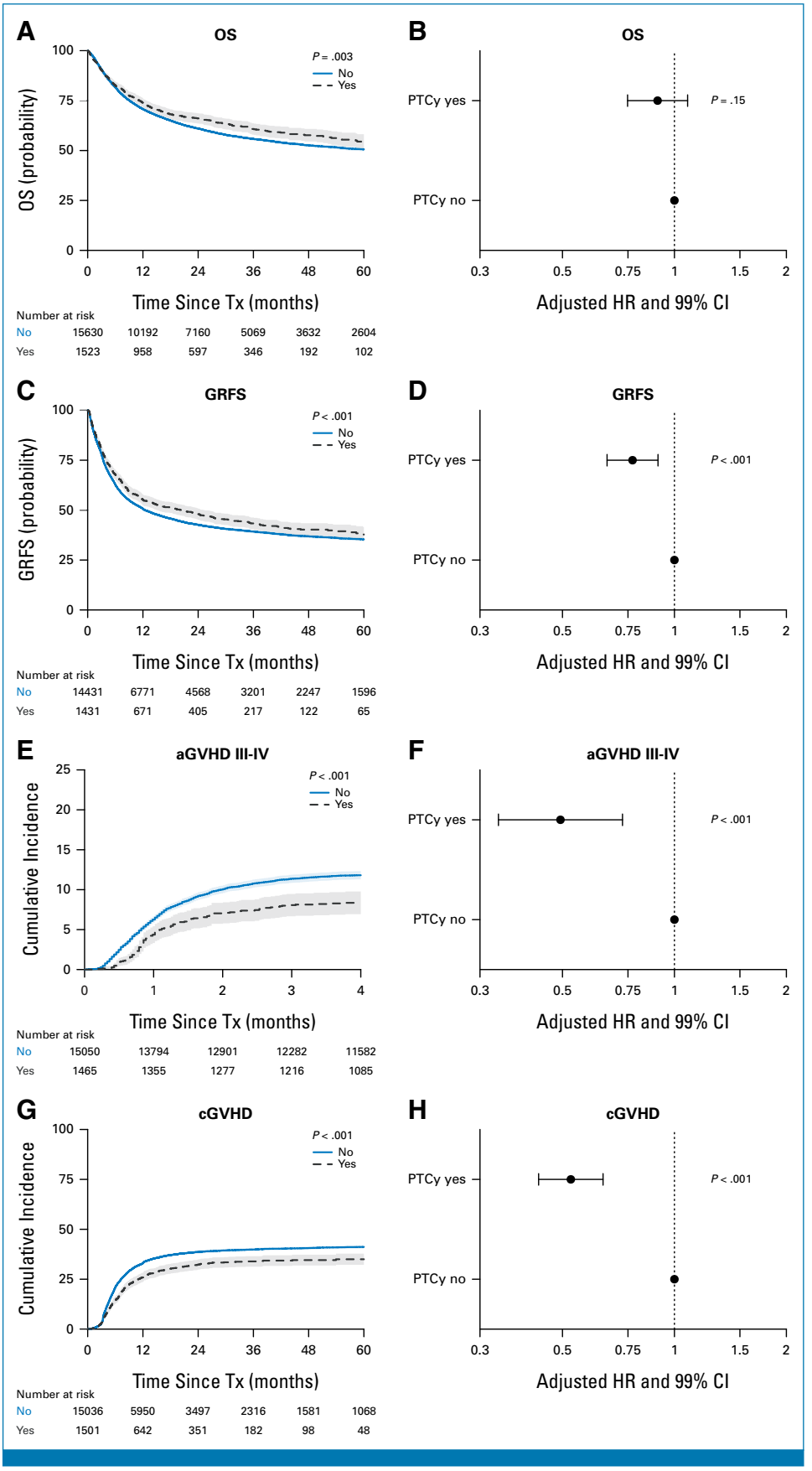

FIG 2. HCT outcome in the full cohort according to the use of PTCy. Kaplan-Meier/cumulative incidence and forest plots show probabilities and adjusted (continued on following page)

FIG 2. (Continued). HR estimates and their 99% CI stratified according to the use of PTCy-based or conventional GVHD prophylaxis. (A, B) OS; (C, D) GRFS; (E, F) aGVHD III-IV; and (G, H) cGVHD. *P* values in the Kaplan-Meier/cumulative incidence plots correspond to the results of univariable comparisons in the overall cohort using log-rank or Gray tests, as appropriate. Individuals at risk at different time points post-transplant are shown underneath each plot (top row: transplants without PTCy; bottom row: transplants with PTCy). HR and *P* values in the forest plots are derived from multivariable analyses for the fully 10 of 10 matched pairs shown in Data Supplement, Table S5 with conventional GVHD prophylaxis as reference (vertical lines). GRFS, graft-versus-host disease, relapse-free survival; (a/c)GVHD, (acute/chronic) graft-versus-host disease. GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HR, hazard ratio; OS, overall survival; PBM, peptide-binding motif; PTCy, post-transplant cyclophosphamide.

immunopeptidome divergence between HLA-A, HLA-B, HLA-C or HLA-DPB1 mismatches as classified by PBM or TCE groups, respectively,[16,19] and B-Leader mismatches.[15] The 5-year probabilities of OS dropped from 52.2% (95% CI, 51.1 to 53.2) in the 10 of 10 reference to 46.7% (95% CI, 42.7 to 50.6) and 43.5% (95% CI, 40.5 to 46.4) in the HLA class I PBM-GVH matched and mismatched groups, respectively ($P < .001$, Fig 1). In multivariable analysis, the hazards of OS, NRM, and aGVHD II-IV were significantly worse both in HLA class I PBM-GVH matched and mismatched pairs compared with the 10 of 10 reference; however, this difference was more marked for HLA class I PBM-GVH mismatches (Fig 1, Table 2 and Data Supplement, Table S1). Of note, HLA class I PBM-GVH mismatched pairs had significantly worse OS than HLA class I PBM-GVH matched pairs in direct comparison (HR, 1.23 [95% CI, 1.04 to 1.46], $P = .002$). This was mirrored by significantly worse GRFS, RFS, aGVHD III-IV, and cGVHD compared with the 10 of 10 reference for HLA class I PBM-GVH mismatches but not for matches (Table 2 and Data Supplement, Table S1). Significant associations with nonpermissive but not permissive HLA-DPB1 TCE mismatches were observed in the 9 of 10 cohort only for aGVHD II-IV, whereas in the 10 of 10 group nonpermissive mismatches were associated with worse NRM and aGVHD III-IV (Data Supplement, Table S3). In the 10 of 10, the hazards of relapse were significantly reduced while those of aGVHD II-IV were significantly increased for both permissive and nonpermissive HLA-DPB1 mismatches. Single B-Leader matches were associated with significantly worse OS, GRFS, RFS and NRM compared with the 10 of 10 reference, whereas B-leader mismatches were significantly associated only with NRM (Data Supplement, Table S4). However, we did not observe significant differences between B-leader matched and mismatched pairs for any of the outcomes tested (HR, 0.89 [95% CI, 0.60 to 1.34], $P = .47$ for OS; not shown for the other end points).

Effects of PTCy on the Role of HLA Mismatching in HCT Outcome

To investigate the effects of PTCy on transplant outcome, we studied the 1,523 patients who received PTCy-based GVHD prophylaxis. The median follow-up time in this group of patients was 28.9 (95% CI, 27.1 to 31.1) months. Overall, the use of PTCy improved the 5-year probability of OS from 50.5% (95% CI, 49.6 to 51.5) under conventional prophylaxis to 54.5% (95% CI, 50.6 to 58.2%; $P = .003$). This was mirrored by significantly better GRFS and reduced aGVHD and cGVHD compared with conventional prophylaxis (Fig 2). Multivariable models for the 10 of 10 matched transplants confirmed these findings for GRFS and GVHD, whereas no significant differences were observed for other end points (Fig 2 and Data Supplement, Table S5).

To better understand the impact of PTCy on the role of a mismatch at any of the five main HLA loci, we comparatively analyzed outcomes in patients that had received a 9 of 10 or a 10 of 10 matched transplant under conventional or PTCy-based GVHD prophylaxis. The effects of a single HLA mismatch were similar regardless of PTCy use (nonsignificant interaction; $P = .22$), conferring significantly increased risks of mortality (both OS and GRFS) in the presence and absence of PTCy (Fig 3, Table 3 and Data Supplement, Fig S3). Similar findings were obtained when excluding the 364 patients who had received in vivo TCD in addition to PTCy (Table 1) from the analysis (not shown). We did not find significant differences in the effects of HLA class I mismatches, low-resolution mismatches, and PBM-GVH mismatches between the groups that did or did not receive PTCy (nonsignificant interactions; $P \geq .42$; Fig 3, Table 3, and Data Supplement, Fig S3). Similar data were also found for the other end points studied (Data Supplement, Table S6). Risk associations between permissive or nonpermissive HLA-DPB1 TCE mismatches observed in 10 of 10 transplants under conventional GVHD prophylaxis appeared to be less pronounced when PTCy was used, although the relevant interaction tests were not significant (Data Supplement, Table S7).

DISCUSSION

HLA matching between donor and recipient has been considered a mainstay for the clinical success of unrelated HCT[1,2,37] on the basis of compelling evidence from numerous independent retrospective studies.[9,12,13,15] Consequently, the ideal unrelated donor should be fully matched at the allelic level for these loci and, if possible, carry a tolerable HLA-DPB1 mismatch according to the TCE model.[16,18,27,28,38-40]

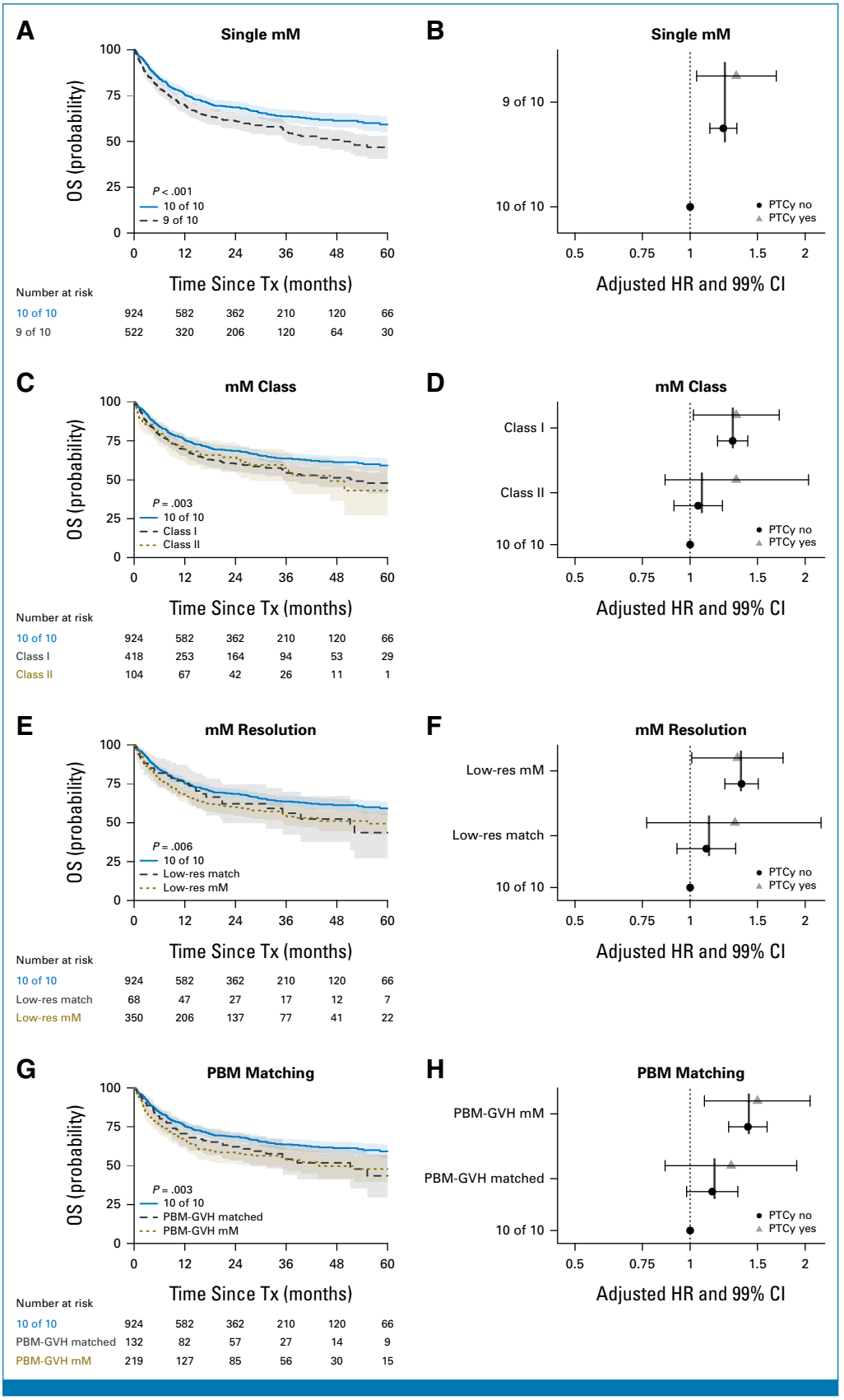

FIG 3. Survival after HCT according to HLA mismatching and GVHD prophylaxis. Kaplan-Meier and forest plots show overall survival (OS) probabilities and adjusted HR estimates and their 99% CI stratified according to (A, B) the presence (9 of 10) or absence (10 of 10) of a mismatch (mM) at HLA-A, HLA-B, HLA-C, HLA-DRB1, or HLA-DQB1, (C, D) the specific mismatched HLA class, (E, F) the typing (continued on following page)

FIG 3. (Continued). resolution for HLA class I mM, and (G, H) PBM GVH matching for HLA class I mM. The Kaplan-Meier plots and relevant *P* values correspond to the results of univariable comparisons in the subgroup of patients who received PTCy-based GVHD prophylaxis, using log-rank tests. Individuals at risk at different time points post-transplant are shown underneath each plot, according to the groups indicated in the legend from top to bottom. HR and 99% CI in the forest plots are derived from multivariable analyses shown in Table 3, separately for the conventional and PTCy-based GVHD prophylaxis, using the 10 of 10 pairs from each PTCy subgroup as reference. Interaction tests were nonsignificant in all cases ($P \geq .15$). The thick vertical lines correspond to the HR estimates for single (ie, 9 of 10), class I/class II, Low-res, and PBM-GVH matched/mismatched pairs in the full cohort. Low-res, low resolution (ie, antigen level). GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HR, hazard ratio; PBM, peptide-binding motif; PTCy, post-transplant cyclophosphamide.

Nevertheless, the studies at the basis for the current practice in donor selection originate mainly from the beginning of the century, and it is unknown if and how they have been affected by the developments in transplantation and histocompatibility since that time. In particular, high-accuracy next-generation sequencing–based HLA typing has been established in most tissue typing laboratories around the world within the past decade.[5,41,42] This has led to a dramatic increase in the number of unrelated donors with high-quality HLA data in the worldwide registries, allowing for granular selection of well-matched donors for increasing numbers of patients.[43-45] Perhaps the most important change in transplantation protocols over the past decade, regards the introduction of PTCy-based regimens for GVHD prophylaxis.[6,22,46-48] Similar survival probabilities after HLA-matched HCT under conventional immune prophylaxis and after HLA-mismatched HCT under PTCy have suggested that its use can overcome the HLA barrier.[21,49] However, this notion is at least partly challenged by observations that HLA mismatches are still relevant when their role is evaluated within the PTCy platforms[50,51] and that tolerable mismatches can be identified also in the setting of haploidentical HCT under PTCy.[52,53]

In this study, we reassessed the role of HLA mismatches in contemporary unrelated HCT, leveraging a data set of more than 17,000 transplants, including over 1,500 under PTCy-based GVHD prophylaxis, collected through the EBMT Registry mainly within the past decade. Our results show that HLA disparity remains an important factor determining mortality risks also to date, but that this role is driven by HLA-A, HLA-B, HLA-C and not by HLA-DRB1, HLA-DQB1 mismatches, a finding in line with a recent independent international study.[15] Of note, the HLA class II effects were time-dependent, that is, an impact on OS could be appreciated in the first months after transplantation but not at longer follow-up, possibly mirroring a protective effect on cGVHD, although this was not accompanied by a lower incidence of relapse.

Toxicity by HLA class I mismatches resulted in increased severe aGVHD and NRM, without a concomitant decrease in relapse incidence. This underlines the importance of continuing endeavors to prevent and treat GVHD[7,8] for improved transplant outcomes. We also find that high-resolution HLA class I mismatches are less deleterious than low-resolution mismatches. This might at least partly mirror the advantageous effect we demonstrated for HLA class I PBM-GVH matches compared with mismatches, the former being more likely between alleles that are matched at the low-resolution level.[26] Again, toxicity from PBM-GVH mismatches resulted in higher risks of severe aGVHD and NRM, validating our previous observations made in an independent, mainly North American cohort.[19] Together, these findings provide further compelling evidence for the role of immunopeptidome divergence between mismatched HLA molecules as biomarker for risk stratification in allogeneic HCT and provide a means for intelligent mismatched unrelated donor selection to improve transplant outcome. This notion is also at the basis of the risk associations between nonpermissive HLA-DPB1 TCE mismatches and clinical outcome that have been repeatedly validated.[17,54] These findings were confirmed in the 10 of 10 and extended to the 9 of 10 setting in this study.

Our data set provided the important opportunity to investigate the impact of PTCy on HCT outcome overall and on the role of HLA mismatches. PTCy improved GRFS compared with conventional GVHD prophylaxis as previously described[23,24] and reduced severe acute and chronic GVHD without a significant increase in the hazard of relapse. There were no significant differences in the detrimental effects of mismatches at the five main HLA loci on outcome between conventional and PTCy-based regimen. In particular, although the numbers in each subgroup are still limited, our findings suggest that the negative effect of HLA class I disparity at the low-resolution and PBM-GVH level may apply also to transplantation under PTCy-based immune prophylaxis. Of note, PTCy effects seemed to be more pronounced for HLA-DPB1 mismatches. If confirmed, this might suggest different impacts of PTCy on alloreactive CD4+ compared with CD8+ T-cell responses, as previously suggested.[55,56] Further investigations are warranted to test this intriguing hypothesis.

Our study has limitations, in particular regarding its retrospective nature and potential underlying sources of heterogeneity related to the use of registry data. It should be

TABLE 3. Multivariable Cox Proportional Hazards Models of HLA Associations by PTCy Use

		PTCy No			PTCy Yes			
End Point	Subgroups	No. (events)	HR (99% CI)	*P*	No. (events)	HR (99% CI)	*P*	Interaction *P*[a]
OS	10 of 10	11,943 (4,867)	1		898 (276)	1		.43
	9 of 10	2,924 (1,393)	1.22 (1.13 to 1.33)	<.001	511 (210)	1.32 (1.04 to 1.68)	.003	
	10 of 10	11,943 (4,867)	1		898 (276)	1		.42
	Class I mM	2,117 (1,050)	1.29 (1.18 to 1.41)	<.001	408 (168)	1.32 (1.02 to 1.71)	.006	
	Class II mM	807 (343)	1.05 (0.91 to 1.21)	.39	103 (42)	1.32 (0.86 to 2.04)	.09	
	10 of 10	11,943 (4,867)	1		898 (276)	1		.69
	Low-res[b] match	515 (230)	1.1 (0.92 to 1.32)	.15	64 (27)	1.31 (0.77 to 2.2)	.19	
	Low-res[b] mM	1,602 (820)	1.36 (1.23 to 1.51)	<.001	344 (141)	1.33 (1.01 to 1.75)	.007	
	10 of 10	11,943 (4,867)	1		898 (276)	1		.75
	PBM-GVH[c] match	648 (310)	1.14 (0.98 to 1.33)	.03	128 (52)	1.28 (0.86 to 1.9)	.11	
	PBM-GVH[c] mM	1,153 (586)	1.42 (1.26 to 1.59)	<.001	214 (93)	1.5 (1.09 to 2.06)	<.001	
GRFS	10 of 10	11,147 (6,472)	1		845 (407)	1		.72
	9 of 10	2,645 (1,662)	1.16 (1.08 to 1.25)	<.001	486 (280)	1.2 (0.97 to 1.47)	.02	
	10 of 10	11,147 (6,472)	1		845 (407)	1		.74
	Class I mM	1,912 (1,240)	1.24 (1.14 to 1.34)	<.001	389 (226)	1.22 (0.98 to 1.52)	.02	
	Class II mM	733 (422)	0.99 (0.87 to 1.13)	.79	97 (54)	1.1 (0.76 to 1.61)	.50	
	10 of 10	11,147 (6,472)	1		845 (407)	1		.36
	Low-res[b] match	469 (287)	1.09 (0.93 to 1.28)	.14	59 (28)	0.82 (0.5 to 1.36)	.32	
	Low-res[b] mM	1,443 (953)	1.29 (1.18 to 1.42)	<.001	330 (198)	1.31 (1.04 to 1.65)	.002	
	10 of 10	11,147 (6,472)	1		845 (407)	1		.90
	PBM-GVH[c] match	589 (381)	1.15 (1 to 1.32)	.008	122 (69)	1.16 (0.83 to 1.63)	.26	
	PBM-GVH[c] mM	1,032 (676)	1.32 (1.18 to 1.47)	<.001	202 (123)	1.39 (1.06 to 1.82)	.002	

NOTE. Multivariable models were adjusted for patient and donor age, sex (mis)matching, CMV serostatus matching, comorbidity score (HCT-CI),[36] Karnofsky Performance Score, disease at transplant, disease risk index,[25] year of HCT, stem cell source, conditioning regimen and use of total-body irradiation, use of in vivo T-cell depletion, and HLA-DPB1 TCE matching status and include a gamma-distributed frailty term for transplant center.
Abbreviations: GRFS, graft-versus-host disease, relapse-free survival; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HR, hazard ratio; mM, mismatch; N, number; PBM, peptide-binding motif; OS, overall survival; PTCy, post-transplantation cyclophosphamide; TCE, T-cell epitope.
[a]Interaction analyses between the respective matching models and the use of PTCy.
[b]Low-resolution (Low-res).
[c]PBM matching for class I mM.

emphasized that, although, to our knowledge, our data set contains one of the largest numbers of unrelated transplants under PTCy-based GVHD prophylaxis with 6-locus HLA typing for patients and donors pairs analyzed so far, its size is still limited to draw any definitive conclusions on the role of HLA disparity in this setting. Compared with other recent studies from international registries,[57,58] ours has the distinct feature of including both PTCy and non-PTCy transplants, thereby enabling us to investigate the statistical interaction between HLA matching status and GVHD prophylaxis. The lack of evidence for such interaction in our data set suggests that optimal HLA matching should still be considered in the selection of stem cell donors for HCT also under PTCy-based GVHD prophylaxis. Nevertheless, the relative role of HLA compared with other relevant clinical variables such as donor age could not be addressed because of the limited size of the PTCy cohort and are hence warranted in future studies. Moreover, these investigations should also leverage the results from ongoing and future prospective clinical trials on HLA-matched and mismatched PTCy-based unrelated HCT.[59-61]

Taken together, our findings suggest that HLA class I, in particular at the antigen and PBM level, should be prioritized over class II matching in contemporary unrelated donor selection and that these recommendations still hold also for transplants performed under PTCy-based GVHD prophylaxis. However, compiling larger, preferentially multiregistry data and evidence from prospective clinical trials is highly needed to better understand the role of HLA in the era of PTCy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Human Leukocyte Antigen Mismatching and Survival in Contemporary Hematopoietic Cell Transplantation for Hematologic Malignancies

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