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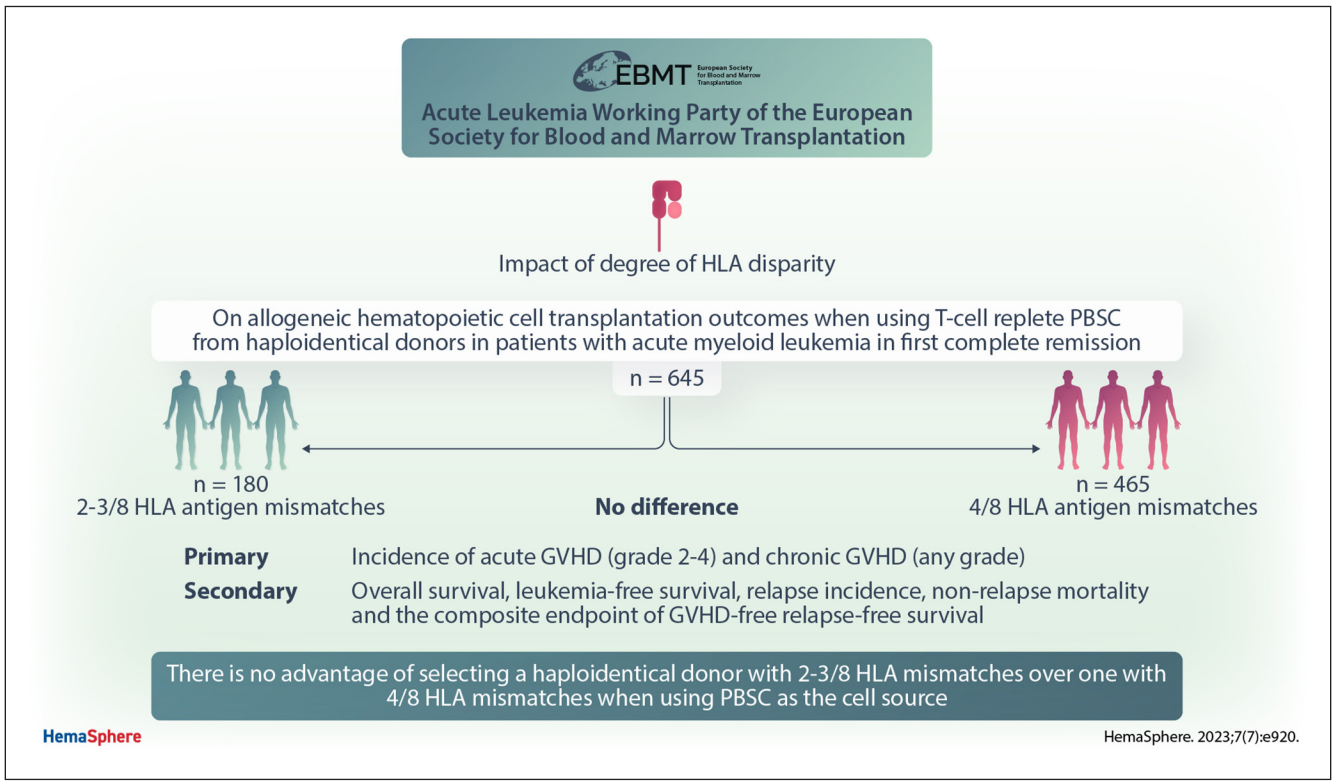
Significance of Degree of HLA Disparity Using T-cell Replete Peripheral Blood Stem Cells From Haploidentical Donors With Posttransplantation Cyclophosphamide in AML in First Complete Hematologic Remission: A Study of the Acute Leukemia Working Party of the EBMT

Mohamed A. Kharfan-Dabaja[1], Myriam Labopin[2,3], Ernesto Ayala[1], Ali Bazarbachi[4], Didier Blaise[5], Jan Vydra[6], Stefania Bramanti[7], Maija Itälä-Remes[8], Christoph Schmid[9], Alessandro Busca[10], Edouard Forcade[11], Werner Rabitsch[12], Marco Zecca[13], Nicolaus Kröger[14], Claude-Eric Bulabois[15], Giovanni Grillo[16], Alessandro Rambaldi[17], Renato Fanin[18], Francesco Zallio[19], Nicola Di Renzo[20], Yener Koc[21], Yana Novis[22], Andrew McDonald[23], Concepcion Herrera Arroyo[24], Jaime Sanz[25], Arnon Nagler[26], Fabio Ciceri[27], Mohamad Mohty[2,3]

GRAPHICAL ABSTRACT



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ABSTRACT

Availability of haploidentical donors has broadened utilization of allogeneic hematopoietic cell transplantation (allo-HCT). Peripheral blood stem cells (PBSC) are being used with increased frequency in haploidentical allo-HCT. We evaluated extent of HLA disparity (2–3/8 versus 4/8 HLA antigen mismatches) on post-allograft outcomes when using T-cell replete PBSC from haploidentical donors for acute myeloid leukemia in first complete remission. Primary objectives entailed assessing cumulative incidence of grade 2–4 acute graft-versus-host disease (GVHD) and chronic GVHD (any grade). A total of 645 patients received a haploidentical allo-HCT from a donor with either 2–3 of 8 HLA antigen mismatches (n = 180) or with 4 of 8 HLA antigen mismatches (n = 465). Presence of 2–3 of 8 versus 4 of 8 HLA mismatches did not affect the incidence of acute GVHD (grade 2–4) and chronic GVHD (any grade). Overall survival (OS), leukemia-free survival (LFS) relapse incidence (RI), nonrelapse mortality and the composite endpoint of GVHD-free relapse-free survival were also similar among the groups. Pertaining to HLA-B leader matching effect, our analysis did not discern any difference in aforementioned post-allograft outcomes for this variable. However, in univariate analysis, absence of an antigen mismatch in HLA-DPB1 showed a trend for better OS. Notwithstanding inherent limitations associated with registry data, our results did not show an advantage of selecting a haploidentical donor with 2–3 of 8 HLA antigen mismatches over one with 4 of 8 HLA antigen mismatches when using PBSC as the cell source. Adverse cytogenetics remains a major adverse determinant of inferior OS and LFS and a higher RI. Using reduced-intensity conditioning yielded worse OS and LFS.

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INTRODUCTION

Despite the emergence of novel targeted therapies for the treatment of acute myeloid leukemia (AML), allogeneic hematopoietic cell transplantation (allo-HCT) remains the treatment modality capable of offering the highest possibility of cure for this disease.[1,2] Availability of haploidentical donors has facilitated broader applicability of allo-HCT to patients for whom a suitable HLA-matched related donor or matched-unrelated donor (MUD) was not available in the past.[3] Registry data have shown comparable outcomes when using MUD versus haploidentical donors in patients with AML undergoing their first or their second allo-HCT, whenever indicated.[4–6]

Donor–recipient HLA matching is an important predictor of outcomes following granulocyte-colony stimulating factor stimulated peripheral blood stem cells (PBSC) or unstimulated bone marrow (BM) hematopoietic cell allografting using conventional related or unrelated donors.[7–9] When using unrelated donors, an increasing number of donor HLA mismatches have been shown to adversely affect survival[8]; and several studies have shown that the clinical implications of specific HLA mismatches are somewhat dependent on the affected locus and sequence attributes in the mismatched alleles.[10,11] In the setting of haploidentical donors, a small multicenter observational study of 185 patients who received nonmyeloablative allo-HCT using BM cells and posttransplantation cyclophosphamide (PTCy) did not show a significant association between the number of HLA mismatches (3–4 versus fewer antigen mismatches) and the risk of acute graft-versus-host disease (GVHD) or event-free survival.[12] Recently, Fuchs et al[13] reported outcomes of a large study involving 1434 allo-HCT recipients with AML or myelodysplastic syndrome (MDS) using haploidentical donors with PTCy and BM or PBSC, showing that outcomes were associated with individual loci HLA mismatches rather than the total number of HLA mismatches. This study also showed that HLA-B leader matching was associated with superior overall survival (OS) as was also the case for HLA-DPB1 T-cell epitope nonpermissive mismatching.[13]

Pertaining to the therapeutic implications of the stem cell source used for allografting, a phase 3, multicenter, randomized trial of allo-HCT using PBSC or BM from unrelated donors showed a higher 2-year cumulative incidence of chronic GVHD when using PBSC (53% versus 41%; $P = 0.01$).[14] Despite these results, PBSC still remains the preferred cell source, when using related or unrelated donors, owing to its more convenient procurement. As PBSC are also being used with increased frequency in the setting of haploidentical donor allo-HCT, it is, therefore, necessary to understand the effect of the number of HLA mismatches when using this cell source in this particular setting.

The primary objectives of our study are to assess the impact of the extent of HLA disparity (2–3/8 versus 4/8 HLA antigen mismatches) on cumulative incidence of grade 2–4 acute GVHD and chronic GVHD (any grade) when analyzing HLA class I (A, B, C) and Class II (DRB1) antigens when using PBSC from haploidentical donors. We also evaluate outcomes including the HLA DQB1 antigen and the effect of the HLA-B leader matching.

METHODS

Study design and patient population

This is a retrospective observational study of patients who underwent a haploidentical allo-HCT and were reported to the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a voluntary working group of >600 transplant centers that are required to report all consecutive HCTs and follow-up once a year. Validation and the quality control program include verification of computer printouts of entered data, cross-checking with national registries, and on-site visits of selected teams. This study was approved by the ALWP of the EBMT institutional review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients included in this analysis provided written informed consent granting permission to use their information for research purposes.

Patients were eligible for inclusion in this study if they were an adult (age ≥18 y) and had received a T-cell replete haploidentical allo-HCT for the treatment of AML in first complete hematologic remission (CR1) between January 1, 2014 and December 31, 2021. There was no preset upper age limit. For the purpose of this study, a haploidentical donor was defined as a family member with 2 or more mismatches within the loci HLA-A, -B, -C, and -DRB1. Additionally, we also conducted a separate analysis including the HLA-DQB1 locus. Furthermore, we conducted an analysis on HLA-B based on the B-leader matched versus B-leader mismatched as previously described.[11] The stem cell source was limited to PBSC. Administration of antithymocyte globulin was an exclusion criterion.

Data pertaining to patient-, disease-, and treatment-related characteristics that were collected at the time of allo-HCT are shown in Table 1. A total of 645 patients received a haploidentical allo-HCT from a donor with either 2–3 of 8 HLA antigen mismatches (n = 180) or with 4 of 8 HLA antigen mismatches (n = 465) at one of the EBMT participating centers.

Statistical analysis

Patient-, disease-, and treatment-related characteristics at the time of haploidentical allo-HCT from a donor with 2–3 of 8 HLA antigen mismatches or with 4 of 8 HLA antigen mismatches were compared using the χ^2 test for categorical variables, the Mann-Whitney test for continuous parameters, and the Wilcoxon test for ordered variables. Baseline characteristics were summarized using median and interquartile range (IQR) for continuous data and frequency and percentage for categorical data.

The primary end points were cumulative incidences of grade 2–4 acute GVHD and chronic GVHD (any grade). Secondary end points included OS, leukemia-free survival (LFS), cumulative relapse incidence (RI), nonrelapse mortality (NRM), and the composite end point of GVHD-free, relapse-free survival (GRFS).

Definitions

OS was defined as time from intervention (allo-HCT) to death, regardless of the cause. LFS was defined as survival without evidence of relapse or progression. RI was defined as leukemia recurrence at any site. NRM was defined as death without evidence of relapse or progression. The intensity of the preparative regimen was defined based on the established criteria.[15] Pertaining to nonmyeloablative conditioning regimens, these were included under the broader reduced-intensity conditioning

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Table 1

Patient-, Disease-, and Treatment-related Characteristics

Variables	2–3/8 Mismatches (n = 180)	4/8 Mismatches (n = 465)	*P*-value
Patient median age (IQR), y	59.1 (46.8–65.6)	58.2 (46.6–65.0)	0.79
Donor median age (IQR), y	37.9 (27.8–44.5)	36.8 (28.5–46.0)	0.79
Patient gender			0.61
Female	74 (41.1%)	181 (38.9%)	
Male	106 (58.9%)	284 (61.1%)	
Donor gender			0.31
Female	72 (40.0%)	166 (35.7%)	
Male	108 (60.0%)	299 (64.3%)	
Diagnosis			0.32
De novo AML	152 (84.4%)	377 (81.1%)	
Secondary AML	28 (15.6%)	88 (18.9%)	
Cytogenetic risk group at presentation			0.53
Favorable	7 (4.3%)	21 (5.0%)	
Intermediate	113 (69.3%)	272 (64.8%)	
Adverse	43 (26.4%)	127 (30.2%)	
Unknown/not available/failed	17	45	
Year of allogeneic transplant			0.14
Median (min–max)	2019 (2014–2021)	2020 (2014–2021)	
Female donor→male recipient			0.72
No	144 (80.0%)	366 (78.7%)	
Yes	36 (20.0%)	99 (21.3%)	
Regimen intensity			0.12
MAC	87 (48.3%)	193 (41.5%)	
RIC	93 (51.7%)	272 (58.5%)	
KPS			0.055
90	31 (17.9%)	111 (25.2%)	
90	142 (82.1%)	330 (74.8%)	
Missing	7	24	
HCT-CI			0.68
0	78 (43.8%)	222 (48.4%)	
1 or 2	57 (32.0%)	114 (24.8%)	
3	43 (24.2%)	123 (26.8%)	
Missing/unknown	2	6	
HLA-A mismatch loci			-
None	73 (40.6%)	0	
One	107 (59.4%)	465 (100%)	
HLA-B mismatched loci			-
None	26 (14.4%)	0	
One	154 (85.6%)	465 (100%)	
HLA-C mismatched loci			-
None	47 (26.1%)	0	
One	133 (73.9%)	465 (100%)	
HLA-DRB1 mismatched loci			-
None	59 (32.8%)	0	
One	121 (67.2%)	465 (100%)	
HLA-DQB1 mismatched loci	57 (33.3%)	27 (5.9%)	-
None	114 (66.7%)	427 (94.1%)	
One	9	11	
HLA-DPB1 mismatched loci			-
None	26 (28.6%)	15 (5.9%)	
One	65 (71.4%)	238 (94.1%)	
Missing/unavailable/unknown	89	212	
HLA B-leader			-
Matched	126 (70%)	293 (63%)	
Mismatched	54 (30%)	172 (37%)	
Prophylactic immune suppressive therapies in addition to posttransplant cyclophosphamide			0.49
CSA + MMF	101 (56.1%)	289 (62.2%)	
TAC + MMF	54 (30.0%)	120 (25.8%)	
SIRO + MMF	8 (4.4%)	14 (3.0%)	
Others	17 (9.4%)	42 (9.0%)	
Patient CMV serologic status			0.61
Negative	47 (26.3%)	130 (28.3%)	
Positive	132 (73.7%)	330 (71.7%)	

(Continued)

Table 1 (Continued)

Variables	2–3/8 Mismatches (n = 180)	4/8 Mismatches (n = 465)	*P*-value
Missing	1	5	
Donor CMV serologic status			0.26
Negative	69 (38.9%)	202 (43.9%)	
Positive	108 (61.1%)	258 (56.1%)	
Missing	3	5	
Donor/patient CMV serologic status			0.62
–/–	28 (15.8%)	91 (19.9%)	
+/–	18 (10.2%)	39 (8.5%)	
–/+	41 (23.2%)	109 (23.8%)	
+/+	90 (50.8%)	219 (47.8%)	
Missing/unknown	3	7	
Median time (IQR) from diagnosis to allo-HCT, mo	5.0 (4.1-6.5)	5.2 (4.1-6.6)	0.41

allo-HCT = allogeneic hematopoietic cell transplantation; AML = acute myeloid leukemia; CSA = cyclosporin; CMV = cytomegalovirus; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HLA = human leucocyte antigen; IQR = interquartile range; KPS = Karnofsky performance score; MAC = myeloablative conditioning; MMF = mycophenolate mofetil; RIC = reduced-intensity conditioning; SIRO = sirolimus; TAC = tacrolimus.

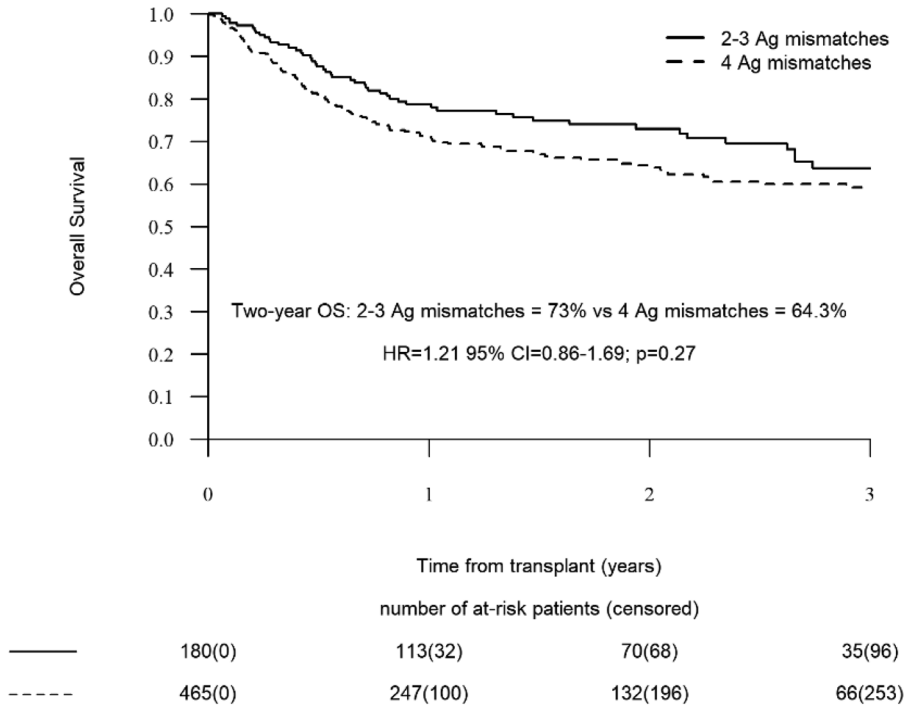

Figure 1. Overall survival.

(RIC) category. Performance status was graded using the Karnofsky performance score (KPS) and the hematopoietic cell transplantation-specific comorbidity index.[16]

Statistical methods

All surviving patients were censored at the time of last documented contact. Probabilities of OS and LFS were calculated using the Kaplan-Meier method. All transplant-related deaths were competing events when studying relapse-related deaths. Cumulative incidence was used to estimate the end points of RI, NRM, acute GVHD, and chronic GVHD to accommodate for competing risks.[17] When assessing cumulative incidence of acute GVHD and chronic GVHD, we considered relapse and death as competing events. Univariable analyses were performed using the log-rank test for OS and LFS; and Gray's test for cumulative incidence functions.[17]

All conclusions were based on the results of multivariable analyses performed using the Cox proportional-hazards regression model, including variables with unbalanced distribution between the 2 groups and those known to potentially influence posttransplant outcomes. Continuous variables were included without categorization in the Cox proportional-hazards regression model. Patients with missing information were excluded from the analyses.

Results were expressed as the hazard ratio with a 95% confidence interval. The type I error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All *P*-values were 2-sided. Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL) and R 3.4.0 (R Core Team [2017]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.).

RESULTS

The total number of EBMT centers that contributed data to this analysis was 136. The median number of reported haploidentical

allo-HCTs per center was 3 (range, 1–62). The median (IQR) follow-up period from the time of haploidentical allo-HCT for all 645 patients was 22.7 (20.9–24.5) months. The median (IQR) follow-up period was comparable for haploidentical allo-HCT recipients of 2–3 of 8 HLA antigen mismatches (26.1 [22.7–29.0] mo) versus 4 of 8 HLA antigen mismatches (21.2 [17.9–23.8] mo), $P = 0.20$.

The groups were comparable for patient ($P = 0.79$) and donor ($P = 0.79$) median age; and the majority of patients in each group had a KPS ≥ 90 (82.1% and 74.8% in 2–3/8 HLA antigen mismatches and 4/8 HLA antigen mismatches, respectively; $P = 0.055$). In both groups, RIC allo-HCT was the most commonly prescribed regimen with 51.7% versus 58.5% of 2–3 of 8 HLA antigen mismatches versus 4 of 8 HLA antigen mismatches, respectively ($P = 0.12$). These and other results are summarized in Table 1.

Graft failure

Only 4 (2.3%) of 174 evaluable patients in the 2–3 of 8 HLA antigen mismatches group and 20 (4.3%) of 462 evaluable

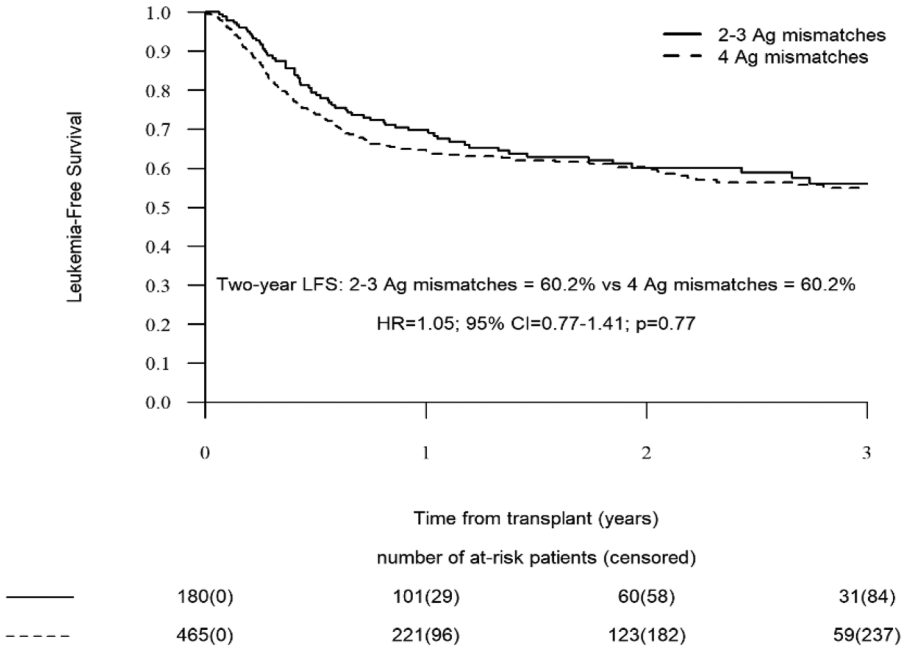

Figure 2. Leukemia-free survival.

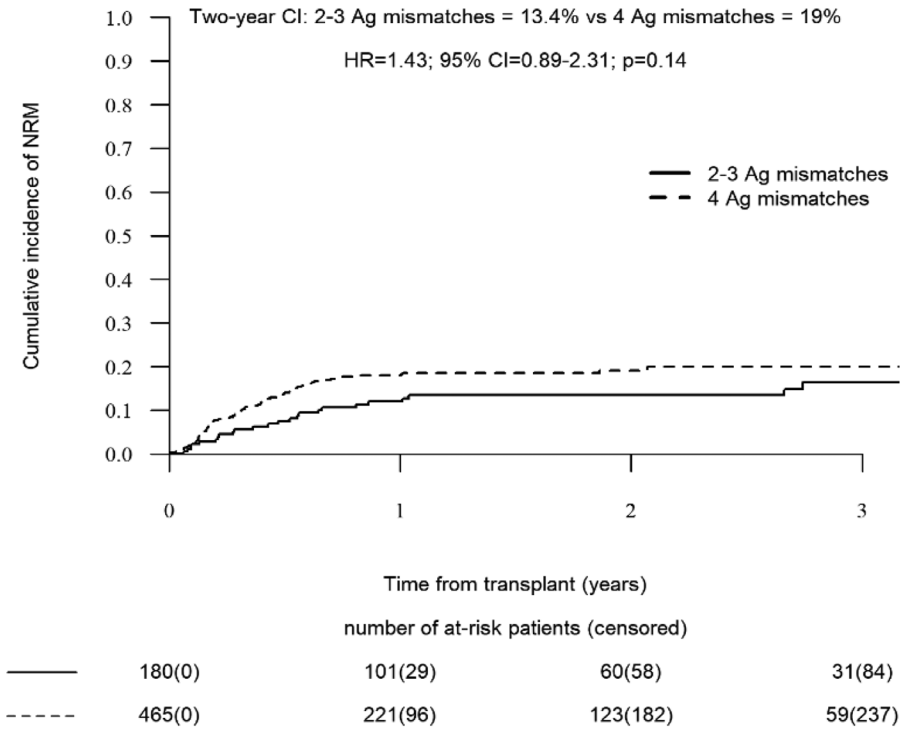

Figure 3. Cumulative incidence of nonrelapse mortality.

patients in the 4 of 8 HLA antigen mismatches group developed graft failure (P = 0.35).

Comparison of 2–3 of 8 versus 4 of 8 HLA mismatches

In univariate analysis, presence of 2–3 of 8 versus 4 of 8 HLA antigen mismatches did not result in significant difference in 2-year OS (73.0% [65.0%-79.4%] versus 64.3% [59.1%-69.1%]; P = 0.11), LFS (60.2% [51.8%-67.5%] versus 60.2% [55.0%-65.0%]; P = 0.42), RI (26.4% [19.5%-33.8%] versus 20.8% [16.8%-25.1%]; P = 0.46), and NRM (13.4% [8.7%-19.2%] versus 19.0% [15.3%-23.0%]; P = 0.10). This was also the case for day +180 acute GVHD (grade 2–4) (30.7% [23.9%-37.7%] versus 30.6% [26.4%-34.9%], P = 0.94) and day +180 acute GVHD (grade 3–4) (9.3% [5.5%-14.2%] versus 11.1% [8.4%-14.3%];

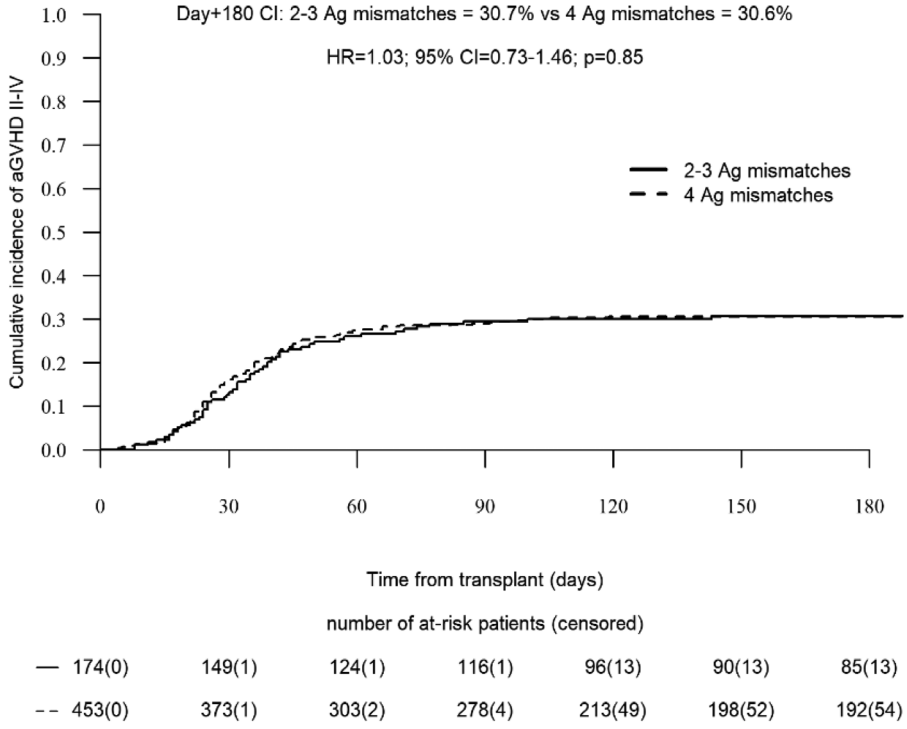

Figure 4. Cumulative incidence of acute GVHD (grade 2–4). GVHD = graft-versus-host disease.

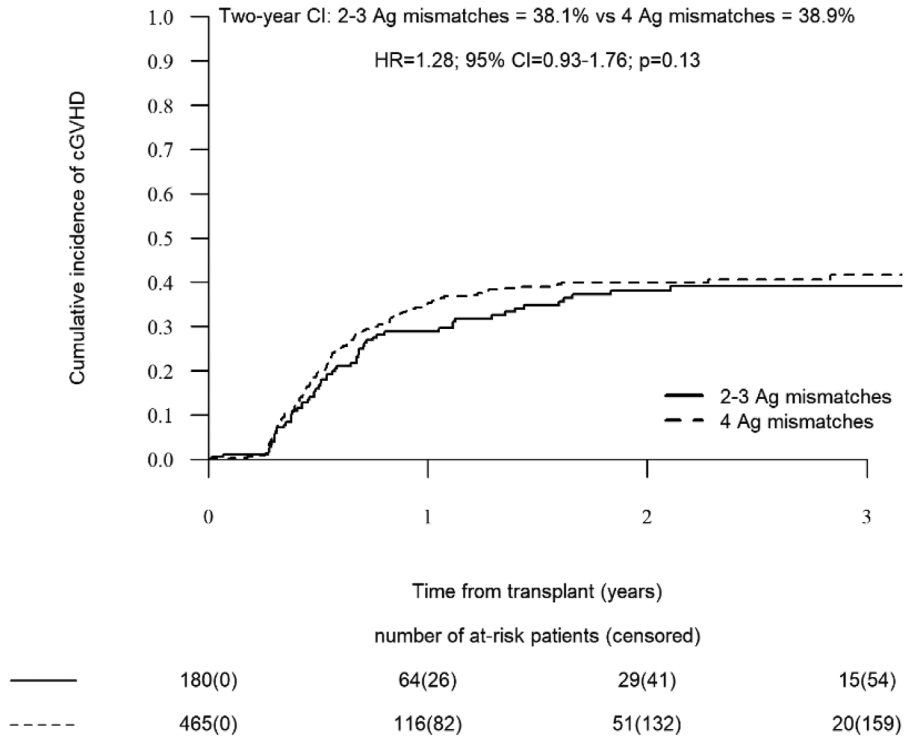

Figure 5. Cumulative incidence of chronic GVHD (any grade). GVHD = graft-versus-host disease.

Table 2

Multivariable Analysis

	OS HR (95% CI) *P*-value	LFS HR (95% CI) *P*-value	RI HR (95% CI) *P*-value	NRM HR (95% CI) *P*-value	Acute GVHD (Grade 2–4) HR (95% CI) *P*-value	Acute GVHD (Grade 3–4) HR (95% CI) *P*-value	Chronic GVHD (Any Grade) HR (95% CI) *P*-value	Chronic GVHD (Extensive) HR (95% CI) *P*-value	GRFS (2-y) HR (95% CI) *P*-value
4 vs 2–3 HLA mismatch	1.21 (0.86-1.69)	1.05 (0.77-1.41)	0.85 (0.57-1.25)	1.43 (0.89-2.31)	1.03 (0.73-1.46)	1.21 (0.64-2.27)	1.28 (0.93-1.76)	0.91 (0.55-1.51)	1.00 (0.77-1.29)
	P = 0.27	*P* = 0.77	*P* = 0.41	*P* = 0.14	*P* = 0.85	*P* = 0.56	*P* = 0.13	*P* = 0.72	*P* = 0.99
Patient age	1.10 (0.96-1.25)	1.04 (0.92-1.17)	0.93 (0.81-1.08)	1.25 (1.01-1.53)	0.99 (0.87-1.12)	0.85 (0.69-1.04)	1.02 (0.91-1.16)	1.04 (0.85-1.26)	0.98 (0.88-1.08)
(per 10 y)	*P* = 0.18	*P* = 0.55	*P* = 0.36	*P* = 0.04[a]	*P* = 0.85	*P* = 0.12	*P* = 0.70	*P* = 0.71	*P* = 0.64
Donor age	1.02 (0.89-1.17)	0.98 (0.87-1.11)	0.98 (0.83-1.15)	0.99 (0.82-1.20)	1.23 (1.09-1.40)	1.27 (1.02-1.58)	1.02 (0.90-1.16)	1.09 (0.90-1.34)	1.07 (0.97-1.19)
(per 10 y)	*P* = 0.82	*P* = 0.81	*P* = 0.76	*P* = 0.93	*P* = 0.001[a]	*P* = 0.03[a]	*P* = 0.72	*P* = 0.37	*P* = 0.18
Adverse cytogenetics	1.72 (1.25-2.35)	1.56 (1.17-2.09)	1.88 (1.28-2.75)	1.20 (0.76-1.91)	1.33 (0.96-1.86)	1.60 (0.91-2.81)	1.04 (0.74-1.45)	1.46 (0.89-2.42)	1.66 (1.29-2.13)
	P = 0.0008[a]	*P* = 0.003[a]	*P* = 0.001[a]	*P* = 0.43	*P* = 0.09	*P* = 0.10	*P* = 0.82	*P* = 0.14	*P* < 0.0001[a]
Secondary vs de novo AML	0.78 (0.51-1.13)	0.93 (0.66-1.32)	1.24 (0.79-1.95)	0.63 (0.36-1.10)	0.88 (0.58-1.32)	0.97 (0.48-1.95)	0.93 (0.63-1.37)	1.06 (0.59-1.87)	1.04 (0.77-1.40)
	P = 0.18	*P* = 0.70	*P* = 0.35	*P* = 0.10	*P* = 0.53	*P* = 0.93	*P* = 0.71	p = 0.85	*P* = 0.80
Time from diagnosis to	1.03 (0.97-1.09)	1.02 (0.96-1.07)	0.99 (0.91-1.07)	1.04 (0.97-1.12)	0.95 (0.89-1.01)	0.99 (0.88-1.10)	0.96 (0.91-1.03)	0.98 (0.88-1.08)	1.01 (0.96-1.06)
allo-HCT, mo	*P* = 0.36	*P* = 0.53	*P* = 0.80	*P* = 0.26	*P* = 0.12	*P* = 0.80	*P* = 0.25	*P* = 0.63	*P* = 0.72
(longer vs shorter)									
Year of allo-HCT	0.99 (0.90-1.09)	0.99 (0.91-1.07)	1.04 (0.93-1.17)	0.93 (0.82-1.05)	0.91 (0.83-0.99)	1.01 (0.86-1.17)	0.89 (0.81-0.97)	0.89 (0.77-1.02)	0.97 (0.90-1.05)
(increasing)	*P* = 0.85	*P* = 0.79	*P* = 0.51	*P* = 0.26	*P* = 0.03[a]	*P* = 0.92	*P* = 0.01[a]	*P* = 0.09	*P* = 0.44
KPS ≥ 90 vs <90	0.64 (0.46-0.89)	0.61 (0.45-0.83)	0.63 (0.41-0.97)	0.61 (0.39-0.96)	0.87 (0.61-1.24)	0.54 (0.30-0.98)	1.07 (0.74-1.55)	0.95 (0.54-1.67)	0.69 (0.53-0.91)
	P = 0.009[a]	*p* = 0.002[a]	*P* = 0.04[a]	*P* = 0.03[a]	*P* = 0.43	*P* = 0.04[a]	*P* = 0.72	*P* = 0.86	*P* = 0.009[a]
HCT-CI 0 (ref)	1	1	1	1	1	1	1	1	1
HCT-CI 1 or 2	1.08 (0.74-1.56)	1.01 (0.72-1.41)	0.85 (0.54-1.35)	1.22 (0.74-2.03)	0.85 (0.58-1.25)	0.72 (0.36-1.43)	0.81 (0.56-1.17)	0.79 (0.44-1.45)	0.93 (0.70-1.25)
HCT-CI ≥ 3	*P* = 0.70	p = 0.97	*P* = 0.50	*P* = 0.44	*P* = 0.41	*P* = 0.35	*P* = 0.27	*P* = 0.45	*P* = 0.63
	1.22 (0.86-1.74)	1.06 (0.76-1.47)	0.86 (0.55-1.36)	1.38 (0.85-2.24)	0.99 (0.68-1.43)	0.77 (0.40-1.50)	1.34 (0.96-1.88)	1.13 (0.66-1.92)	1.00 (0.75-1.33)
	P = 0.27	p = 0.73	*P* = 0.52	*P* = 0.19	*P* = 0.96	*P* = 0.44	*P* = 0.09	*P* = 0.66	*P* = 0.99
Patient CMV seropositive vs	1.44 (0.99-2.10)	1.40 (1-1.97)	1.25 (0.80-1.97)	1.60 (0.95-2.68)	1.17 (0.81-1.68)	0.87 (0.47-1.60)	1.13 (0.81-1.58)	0.95 (0.56-1.60)	1.12 (0.85-1.48)
seronegative	*P* = 0.054	*P* = 0.052	*P* = 0.33	*P* = 0.08	*P* = 0.41	*P* = 0.65	*P* = 0.46	*P* = 0.84	*P* = 0.42
Donor CMV seropositive vs	1.12 (0.81-1.55)	1.14 (0.84-1.53)	1.18 (0.79-1.78)	1.11 (0.72-1.71)	0.93 (0.67-1.30)	0.93 (0.52-1.67)	0.83 (0.61-1.14)	1.16 (0.70-1.93)	0.99 (0.77-1.28)
seronegative	*P* = 0.48	*P* = 0.40	*P* = 0.42	*P* = 0.63	*P* = 0.68	*P* = 0.82	*P* = 0.25	*P* = 0.57	*P* = 0.95
RIC vs MAC regimen	2.04 (1.42-2.95)	1.62 (1.17-2.24)	1.43 (0.94-2.18)	1.92 (1.13-3.23)	1.47 (1.03-2.10)	1.70 (0.90-3.21)	1.07 (0.77-1.48)	2.06 (1.19-3.57)	1.69 (1.28-2.24)
	P = 0.0001[a]	*P* = 0.004[a]	*P* = 0.10	*P* = 0.02[a]	*P* = 0.03[a]	*P* = 0.10	*P* = 0.69	*P* = 0.01[a]	*P* = 0.0002[a]
Female donor to male	1.33 (0.92-1.91)	1.22 (0.87-1.71)	1.15 (0.73-1.82)	1.30 (0.79-2.13)	0.76 (0.51-1.14)	1.02 (0.53-1.95)	1.39 (0.99-1.94)	2.39 (1.44-3.97)	1.43 (1.08-1.88)
recipient vs others	*P* = 0.12	*P* = 0.24	*P* = 0.54	*P* = 0.30	*P* = 0.19	*P* = 0.96	*P* = 0.056	*P* = 0.0008[a]	*P* = 0.01[a]

[a]This denotes statistical significance.

AML = acute myeloid leukemia; CMV = cytomegalovirus; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; HCT-CI = hematopoietic cell transplant-specific comorbidity index; HR = hazard ratio; KPS = Karnofsky performance score; LFS = leukemia-free survival; MAC = myeloablative conditioning; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; RI = cumulative incidence of relapse; RIC = reduced-intensity conditioning.

P = 0.49). No difference between the groups were observed in the 2-year chronic GVHD (any grade) (38.1% [30.3%-45.8%] versus 39.9% [34.9%-44.9%]; *P* = 0.44), 2-year chronic GVHD (extensive) (15.7% [10.4%-21.9%] versus 14.6% [11.1%-18.5%]; *P* = 0.87), and 2-year GRFS (45.7% [37.4%-53.5%] versus 46.9% [41.7%-51.9%]; *P* = 0.36).

In multivariate analysis, presence of 2–3 of 8 versus 4 of 8 HLA antigen mismatches also did not affect OS (Figure 1), LFS (Figure 2), RI, NRM (Figure 3), acute GVHD (grade 2–4) (Figure 4), acute GVHD (grade 3–4), chronic GVHD (any grade) (Figure 5), chronic GVHD (extensive), or GRFS. OS and LFS were significantly better in patients with a KPS ≥90 and worse in patients harboring adverse cytogenetics and in those receiving RIC allo-HCT regimens. RI was significantly worse in the presence of adverse cytogenetics. NRM was higher in older patients and when using RIC allo-HCT regimens. Risk of acute GVHD (grades 2–4 and 3–4) was adversely affected by the use of older donors. More recent allo-HCT had a lower risk of chronic GVHD (all grades). Chronic GVHD (extensive) was higher in recipients of RIC allo-HCT regimens and when using female donors to male recipients. GRFS was adversely affected by the presence of adverse cytogenetics, use of RIC allo-HCT regimens, KPS <90, and in the setting of a female donor to male recipient (Table 2).

Multivariate analysis including HLA-DQB1

We also conducted an analysis incorporating the class II HLA-DQB1 antigen (Table 3). Similar to our previous analysis, there was no difference in OS, LFS, RI, NRM, day +180 grade 2–4 or grade 3–4 acute GVHD, 2-year GVHD (any grade), chronic GVHD (extensive), or GRFS in patients with 2–4 of 10 HLA antigen mismatches versus 5 of 10 HLA antigen mismatches.

Multivariate analysis including each single locus HLA mismatch or HLA-B leader

As shown in Table 4, absence of an antigen mismatch in HLA-DPB1 resulted in a trend for a better 2-year OS and LFS. Matching of HLA-B leader did not appear to affect any outcome measure (Table 4).

Causes of death

There were 51 deaths in the group of 2–3 of 8 HLA antigen mismatches. AML relapse was the cause of death in 23 patients. Death from causes other than AML were as follows: infections (n = 11), GVHD (n = 8), multiorgan failure (n = 2), cardiac (n = 1), other causes not specified (n = 1), and not related to allo-HCT (n = 3). The cause of death was missing/not reported in 2 cases.

In the group of 4 of 8 HLA antigen mismatches, there were 147 deaths. AML relapse was the cause of death in 56 patients. Death from causes other than AML were as follows: infections (n = 35), GVHD (n = 20), sinusoidal obstructive syndrome (n = 4), hemorrhage (n = 3), graft failure/rejection (n = 2), multiorgan failure (n = 2), secondary malignancy (n = 1), central nervous system toxicity (n = 1), other causes not specified (n = 3), and not related to allo-HCT (n = 9). The cause of death was missing/not reported in 11 cases.

DISCUSSION

This study did not show a difference in the cumulative incidences of acute GVHD (grade 2–4) or chronic GVHD (any grade) when using haploidentical donors with 2–3 of 8 HLA antigen mismatches versus 4 of 8 HLA antigen mismatches. This was also the case when the HLA DQB1 antigen was included in the analysis (Table 3). It is plausible that mismatching of other polymorphic loci outside of HLA traits in the HLA 2–3 of 8 mismatched group might have contributed to the lack of differences in outcomes when compared with the HLA 4 of 8 mismatched group; or it could be, perhaps, the sole effect of PTCy in overcoming the impact of additional HLA disparities on posttransplant outcomes.

In contrast to the study by Fuchs et al[13] that reported a lower incidence of disease recurrence in the presence of HLA-DRB1 mismatches, our study did not show a difference in 2-year RI in the DRB1 mismatched group (Table 4). One major difference between their study and ours is the fact that our population was limited to patients with AML in CR1 whereas the former study included a more diverse population of AML, MDS, and acute lymphoblastic leukemia.[13] Furthermore, all patients in our study received PBSC as the sole stem cell source, whereas in the study by Fuchs et al,[13] 43% of patients received BM. Another multicenter study by Raiola et al[18] using unmanipulated haploidentical BM cells and PTCy in various hematologic malignancies showed that the degree of HLA mismatching was not associated with worse OS or a higher incidence of acute GVHD (grade 2–4) or chronic GVHD (any grade).

Pertaining to the HLA-B leader matching effect, our analysis did not discern any difference in 2-year OS and LFS, or in the cumulative incidences of day +180 acute GVHD (grade 2–4) or 2-year chronic GVHD (any grade). In contrast, Fuchs et al[13] showed that disease-free survival is optimized when a haploidentical donor is HLA-B leader-matched. It is unclear if the aforementioned differences between the studies may be a

Table 3

Multivariate Analysis Including DQB1 Antigen

	2–4/10 HLA Mismatches	5/10 HLA Mismatches	HR (95% CI)[a]	*P*-value
OS (2-y)	72.2% (64.5%-78.5%)	64.8% (59.4%-69.7%)	1.24 (0.88-1.73)	0.22
LFS (2-y)	60.2% (52.0%-67.4%)	60.8% (55.5%-65.7%)	1.10 (0.81-1.48)	0.54
RI (2-y)	26.1% (19.4%-33.3%)	20.0% (16.0%-24.4%)	0.88 (0.59-1.29)	0.51
NRM (2-y)	13.7% (9.0%-19.2%)	19.2% (15.4%-23.3%)	1.48 (0.93-2.36)	0.10
Acute GVHD (grade 2–4) (day +180)	31.9% (25.4%-38.6%)	29.5% (25.2%-34.0%)	0.96 (0.69-1.34)	0.82
Acute GVHD (grade 3–4) (day +180)	11.1% (7.1%-16.0%)	10.4% (7.7%-13.6%)	0.98 (0.55-1.76)	0.95
Chronic GVHD (any grade) (2-y)	40.5% (32.7%-48.0%)	40.1% (34.8%-45.2%)	1.2 (0.88-1.64)	0.25
Chronic GVHD (extensive) (2-y)	16.4% (11.2%-22.6%)	14.3% (10.8%-18.3%)	0.88 (0.53-1.45)	0.61
GRFS (2-y)	45.4% (37.4%-53.0%)	47.7% (42.4%-52.9%)	1.01 (0.78-1.3)	0.96

AML = acute myeloid leukemia; CI = confidence interval; CMV = cytomegalovirus; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HR = hazard ratio; LFS = leukemia-free survival; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; RI = cumulative incidence of relapse.

[a]Adjusted for patients age, cytogenetic risk group, secondary AML, time from diagnosis to allogeneic hematopoietic cell transplantation, year of allogeneic hematopoietic cell transplantation, Karnofsky performance score, HCT-CI score, patient and donor CMV serology status, regimen intensity, donor age, gender matching (female donor to male recipient vs other). Reference for hazard ratio was the 2–4 of 10 HLA antigen mismatches group.

Table 4

Multivariate Analysis Including Each Single Locus HLA Mismatch

	OS (2-y)	LFS (2-y)	RI (2-y)	NRM (2-y)	Acute GVHD (Grade 2–4) (Day +180)	Acute GVHD (Grade 3–4) (Day +180)	Chronic GVHD (Any Grade) (2-y)	Chronic GVHD (Extensive) (2-y)	GRFS (2-y)
HLA-A	68.6% (54.4%-79.3%)	58.5% (43.9%-70.5%)	26.4% (15.2%-39.0%)	15.2% (7.3%-25.7%)	34.3% (23.4%-45.5%)	7.1% (2.6%-14.8%)	47.4% (33.7%-59.9%)	18.1% (9.1%-29.6%)	46.7% (32.6%-59.6%)
No mismatch	66.7% (62.1%-70.8%)	60.3% (55.7%-64.5%)	22.0% (18.3%-25.9%)	17.7% (14.5%-21.2%)	30.2% (26.4%-34.0%)	11.1% (8.6%-13.9%)	38.5% (34.0%-43.0%)	14.5% (11.4%-17.9%)	46.4% (41.8%-50.9%)
1 mismatch	1.06 (0.66-1.70)	1.06 (0.68-1.64)	0.93 (0.53-1.63)	1.29 (0.65-2.59)	0.90 (0.56-1.43)	1.70 (0.61-4.76)	0.79 (0.52-1.20)	0.82 (0.41-1.66)	1.13 (0.77-1.66)
HR (95% CI)	(0.82)	(0.80)	(0.80)	(p=0.47)	(0.65)	(0.31)	(0.26)	(0.58)	(0.53)
(*P*-value)									
HLA-B	62.1% (39.5%-78.3%)	49.2% (27.7%-67.6%)	30.5% (12.9%-50.2%)	20.3% (7.1%-38.4%)	20.8% (7.3%-39.0%)	8.3% (1.4%-23.7%)	27.4% (10.3%-47.8%)	4.2% (0.3%-18.3%)	44.8% (24.0%-63.6%)
No mismatch	67.0% (62.6%-71.1%)	60.5% (56.1%-64.7%)	22.2% (18.6%-25.9%)	17.3% (14.3%-20.6%)	31.1% (27.4%-34.8%)	10.7% (8.4%-13.4%)	40.1% (35.7%-44.4%)	15.4% (12.3%-18.7%)	46.5% (42.0%-50.9%)
1 mismatch	0.63 (0.35-1.16)	0.66 (0.37-1.18)	0.58 (0.28-1.21)	0.77 (0.33-1.83)	1.57 (0.64-3.87)	1.02 (0.24-4.26)	2.12 (0.92-4.86)	2.26 (0.55-9.36)	0.92 (0.54-1.56)
HR (95% CI)	(0.14)	(0.17)	(0.14)	(0.55)	(0.32)	(0.98)	(0.08)	(0.26)	(0.74)
(*P*-value)									
HLA-C	75.3% (59.8%-85.6%)	63.9% (47.9%-76.2%)	25.2% (13.4%-39.0%)	10.8% (3.9%-21.8%)	26.2% (14.4%-39.5%)	10.9% (3.9%-21.9%)	35.0% (20.7%-49.6%)	11.3% (4.1%-22.6%)	47.4% (32.3%-61.0%)
No mismatch	66.1% (61.5%-70.2%)	59.7% (55.1%-64.0%)	22.3% (18.6%-26.2%)	18.0% (14.8%-21.5%)	31.0% (27.3%-34.8%)	10.6% (8.2%-13.3%)	40.0% (35.5%-44.4%)	15.2% (12.1%-18.7%)	46.3% (41.7%-50.8%)
1 mismatch	1.33 (0.75-2.36)	1.17 (0.70-1.93)	0.94 (0.51-1.72)	1.48 (0.64-3.42)	1.22 (0.67-2.22)	0.83 (0.32-2.13)	1.27 (0.74-2.16)	1.12 (0.48-2.61)	0.93 (0.62-1.41)
HR (95% CI)	(0.33)	(0.55)	(0.84)	(0.36)	(0.52)	(0.70)	(0.39)	(0.79)	(0.74)
(*P*-value)									
HLA-DRB1	81.8% (68.8%-89.8%)	63.8% (48.9%-75.3%)	25.4% (14.2%-38.2%)	10.8% (4.3%-20.6%)	28.6% (17.4%-40.8%)	8.9% (3.2%-18.2%)	32.9% (20.3%-46.0%)	17.5% (8.5%-29.2%)	48.2% (33.8%-61.2%)
No mismatch	65.3% (60.7%-69.5%)	59.7% (55.1%-64.0%)	22.2% (18.5%-26.1%)	18.1% (14.9%-21.6%)	30.9% (27.1%-34.7%)	10.8% (8.4%-13.5%)	40.3% (35.8%-44.8%)	14.6% (11.5%-18.0%)	46.3% (41.7%-50.8%)
1 mismatch	1.69 (0.86-3.34)	1.08 (0.66-1.80)	0.84 (0.46-1.55)	1.67 (0.67-4.15)	1.09 (0.62-1.89)	1.41 (0.43-4.58)	1.6 (0.93-2.74)	0.73 (0.34-1.55)	0.96 (0.63-1.46)
HR (95% CI)	(0.13)	(0.75)	(0.58)	(0.27)	(0.77)	(0.57)	(0.09)	(0.41)	(0.85)
(*P*-value)									
HLA-DQB1	75.3% (63.0%-84.1%)	62.1% (49.0%-72.8%)	25.9% (15.6%-37.4%)	12.0% (5.8%-20.5%)	34.7% (24.4%-45.1%)	13.7% (7.2%-22.2%)	36.3% (24.6%-48.2%)	15.7% (8.2%-25.4%)	46.1% (33.5%-57.7%)
No mismatch	66.0% (61.2%-70.3%)	60.2% (55.5%-64.7%)	21.5% (17.7%-25.5%)	18.3% (14.9%-21.9%)	29.6% (25.7%-33.6%)	10.1% (7.7%-12.9%)	41.0% (36.3%-45.6%)	14.8% (11.7%-18.4%)	47.0% (42.2%-51.6%)
1 mismatch	1.33 (0.79-2.25)	1.13 (0.73-1.74)	0.86 (0.51-1.46)	1.56 (0.75-3.25)	0.84 (0.54-1.29)	0.83 (0.39-1.77)	1.31 (0.83-2.06)	0.97 (0.48-1.99)	0.97 (0.68-1.39)
HR (95% CI)	(0.28)	(0.58)	(0.58)	(0.23)	(0.43)	(0.62)	(0.24)	(0.94)	(0.87)
(*P*-value)									
HLA-DPB1	85.3% (68.1%-93.6%)	73.5% (52.7%-86.3%)	17.9% (5.9%-35.0%)	8.6% (2.2%-20.9%)	30.7% (17.0%-45.5%)	12.8% (4.6%-25.3%)	32.9% (16.0%-50.9%)	13.2% (3.8%-28.5%)	57.3% (37.2%-73.1%)
No mismatch	64.2% (57.6%-70.0%)	57.9% (51.4%-63.9%)	24.6% (19.3%-30.3%)	17.5% (13.1%-22.3%)	30.0% (24.8%-35.4%)	11.6% (8.2%-15.6%)	39.5% (33.1%-45.7%)	13.4% (9.4%-18.1%)	46.3% (39.8%-52.5%)
1 mismatch	2.39 (0.95-5.98)	1.96 (0.94-4.08)	1.90 (0.75-4.85)	2.01 (0.61-6.62)	0.96 (0.50-1.83)	0.81 (0.27-2.40)	1.93 (0.95-3.91)	1.73 (0.51-5.82)	1.54 (0.86-2.77)
HR (95% CI)	(0.06)	(0.07)	(0.18)	(0.25)	(0.89)	(0.70)	(0.07)	(0.38)	(0.15)
(*P*-value)									
HLA-B leader	67.5% (62.1%-72.3%)	59.6% (54.0%-64.8%)	23.5% (19.0%-28.4%)	16.8% (13.2%-20.9%)	29.1% (24.7%-33.6%)	11.1% (8.3%-14.5%)	39.1% (33.8%-44.3%)	15.1% (11.5%-19.2%)	45.9% (40.4%-51.3%)
Matched	65.6% (58.1%-72.0%)	60.4% (53.1%-66.9%)	21.0% (15.5%-27.1%)	18.6% (13.5%-24.3%)	33.6% (27.4%-39.9%)	9.7% (6.2%-14.0%)	40.4% (33.2%-47.5%)	14.4% (9.7%-20.0%)	46.9% (39.6%-53.8%)
Mismatched	1.10 (0.8-1.51)	1.04 (0.78-1.38)	0.84 (0.56-1.25)	1.28 (0.84-1.96)	1.21 (0.88-1.66)	0.89 (0.50-1.59)	1.06 (0.78-1.44)	0.94 (0.57-1.54)	1.00 (0.78-1.28)
HR (95% CI)	(0.56)	(0.81)	(0.39)	(0.25)	(0.25)	(0.70)	(0.70)	(0.81)	(1.00)
(*P*-value)									

Adjusted on patient and donor age, cytogenetic risk group, secondary vs de novo AML, time from diagnosis to allogeneic hematopoietic cell transplantation, year of allogeneic hematopoietic cell transplantation, HCT-CI score, Karnofsky score, regimen intensity, gender matching (female donor to male recipient).

AML = acute myeloid leukemia; CI = confidence interval; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HR = hazard ratio; LFS = leukemia-free survival; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; RI = cumulative incidence of relapse.

contributing factor to these discrepant results. One interesting aspect of our study is that in the majority of cases cyclosporine was the preferred calcineurin inhibitor to be prescribed along with mycophenolate mofetil. This contrasts with studies published in the United States, which preferentially prescribed tacrolimus as the calcineurin inhibitor of choice.[3,19]

One limitation inherent to observational registry studies is the inability to determine with absolute certainty what led transplant physicians to select a particular haploidentical donor if both options (2–3/8 versus 4/8 HLA antigen mismatches) were available. Another limitation of this study is the fact that HLA typing was performed at individual transplant centers without centralized confirmation by the ALWP of EBMT. Accordingly, HLA typing data used in this analysis represented results reported to the ALWP of the EBMT by individual transplant centers.

Notwithstanding these and other inherent limitations associated with registry data, our results did not show any advantage in selecting a haploidentical donor with 2–3 of 8 HLA antigen mismatches versus 4 of 8 HLA antigen mismatches when using PBSC as the cell source in patients with AML in CR1. Adverse cytogenetics remains a major determinant of inferior OS and LFS and a higher RI. Finally, our study also shows inferior OS and LFS when using RIC allo-HCT regimens, highlighting the beneficial role of myeloablation in patients with AML in CR1.

AUTHOR CONTRIBUTIONS

MAK-D, EA, AB (Bazarbachi), and MM designed the research study, analyzed the data, wrote the article, and approved the submission of the final version. ML designed the research study, performed the statistical analysis, analyzed the data, wrote the article, and approved the submission of the final version. DB, JV, SB, MI-R, CS, AB (Busca), EF, WR, MZ, NK, C-EB, GG, AR, RF, FZ, NDR, YK, YN, AMc, CHA, JS, AN, and FC contributed substantially to the research design, revised the article critically, and approved the submission of the final version.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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