HLA discrepancy between graft and host rather than that graft and first donor impact the second transplant outcome

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Supplemental Table 1. Effect of HLA allele mismatch on acute GVHD, chronic GVHD and engraftment by A, B and DR allele mismatch

	HLA mismatch for graft versus host		HLA mismatch for graft versus first donor	
	A allele Match (N=346)	A allele mismattch (N=300)	A allele match (N=284)	A allele mismattch (N=362)
Grades III to IV acute GVHD				
SHR[1] (95%CI)	1 (ref)	0.87 (0.52-1.46, p=0.591)	1 (ref)	0.86 (0.54-1.37, p=0.535)
Chronic GVHD				
SHR[1] (95%CI)	1 (ref)	0.86 (0.57-1.31, p=0.487)	1 (ref)	0.73 (0.51-1.05, p=0.094)
Neutrphil Engraftment				
SHR[1] (95%CI)	1 (ref)	1.03 (0.85-1.25, p=0.733)	1 (ref)	1.07 (0.90-1.27, p=0.448)
	B allele match (N=261)	B allele mismattch (N=385)	B allele match (N=191)	B locus mismattch (N=455)
Grades III to IV acute GVHD				
SHR[1] (95%CI)	1 (ref)	**2.87 (1.42-5.79, p=0.003)**	1 (ref)	1.58 (0.91-2.75, p=0.107)
Chronic GVHD				
SHR[1] (95%CI)	1 (ref)	0.83 (0.51-1.35, p=0.443)	1 (ref)	0.71 (0.47-1.05, p=0.089)
Neutrphil Engraftment				
SHR[1] (95%CI)	1 (ref)	0.93 (0.76-1.13, p=0.475)	1 (ref)	1.12 (0.93-1.35, p=0.243)
	DR allele match (N=205)	DR allele mismattch (N=441)	DR allele match (N=168)	DR allele mismattch (N=478)
Grades III to IV acute GVHD				
SHR[1] (95%CI)	1 (ref)	0.83 (0.51-1.36, p=0.451)	1 (ref)	0.98 (0.59-1.62, p=0.927)
Chronic GVHD				
SHR[1] (95%CI)	1 (ref)	1.08 (0.74-1.56, p=0.705)	1 (ref)	1.28 (0.86-1.92, p=0.225)
Neutrphil Engraftment				
SHR[1] (95%CI)	1 (ref)	**0.80 (0.67-0.95, p=0.011)**	1 (ref)	1.09 (0.88-1.34, p=0.440)

*boldface denotes statistical significance

1 Adjusted for recipient age at transplant (continuous), recipient sex, sex mismatch (match, male to female, female to male, unknown), diagnosis (AML, ALL, CML, MDS, ML or others), disease risk at transplant (standard or high), stem cell source (bone marrow, peripheral blood, cord blood), conditioning regimen (myeloablative or reduced intensity), GVHD prophylaxis (CsA based, Tac based, others), in vivo T-cell depletion (Yes, No), year of transplant (1994-2010, 2011-2016), Interval between first and second SCT (<12 months, ≥12-23 months, ≥24 months, missing) and Interval between first SCT and relapse (<2 months, ≥2-12 months, ≥12 months, missing).

Abbreviations: GVHD, graft versus host disease; SCT, stem cell transplantation

Supplemental Table 2. Effect of HLA allele mismatch on transplant-related mortality, relapse and overall survival by A, B and DR allele mismatch

	HLA mismatch for graft versus host		HLA mismatch for graft versus first donor	
	A allele Match (N=346)	A allele mismatch (N=300)	A allele match (N=284)	A allele mismatch (N=362)
Transplant-related mortality				
SHR[1] (95%CI)	1 (ref)	0.81 (0.60-1.10, p=0.183)	1 (ref)	0.95 (0.71-1.26, p=0.706)
Relapse				
SHR[1] (95%CI)	1 (ref)	1.18 (0.91-1.52, p=0.204)	1 (ref)	1.05 (0.83-1.32, p=0.711)
Overall survival				
HR[1] (95%CI)	1 (ref)	1.02 (0.84-1.24, p=0.854)	1 (ref)	0.96 (0.79-1.15, p=0.642)
	B allele match (N=261)	B allele mismatch (N=385)	B allele match (N=191)	B allele mismatch (N=455)
Transplant-related mortality				
SHR[1] (95%CI)	1 (ref)	1.09 (0.77-1.55, p=0.613)	1 (ref)	0.74 (0.53-1.03, p=0.070)
Relapse				
SHR[1] (95%CI)	1 (ref)	0.91 (0.67-1.24, p=0.553)	1 (ref)	1.31 (0.97-1.76, p=0.079)
Overall survival				
HR[1] (95%CI)	1 (ref)	1.17 (0.92-1.48, p=0.212)	1 (ref)	1.07 (0.85-1.34, p=0.547)
	DR allele match (N=205)	DR allele mismatch (N=441)	DR allele match (N=168)	DR allele mismatch (N=478)
Transplant-related mortality				
SHR[1] (95%CI)	1 (ref)	**1.44 (1.03-2.00, p=0.033)**	1 (ref)	0.93 (0.66-1.31, p=0.674)
Relapse				
SHR[1] (95%CI)	1 (ref)	**0.75 (0.58-0.95, p=0.018)**	1 (ref)	1.04 (0.79-1.38, p=0.765)
Overall survival				
HR[1] (95%CI)	1 (ref)	0.99 (0.81-1.21, p=0.914)	1 (ref)	0.90 (0.72-1.12, p=0.339)

*boldface denotes statistical significance

1 Adjusted for recipient age at transplant (continuous), recipient sex, sex mismatch (match, male to female, female to male, unknown), diagnosis (AML, ALL, CML, MDS, ML or others), disease risk at transplant (standard or high), stem cell source (bone marrow, peripheral blood, cord blood), conditioning regimen (myeloablative or reduced intensity), GVHD prophylaxis (CsA based, Tac based, others), in vivo T-cell depletion (Yes, No), year of transplant (1994-2010, 2011-2016), Interval between first and second SCT (<12 months, ≥12-23 months, ≥24 months, missing) and Interval between first SCT and relapse (<2 months, ≥2-12 months, ≥12 months, missing).

Abbreviations: GVHD, graft versus host disease; SCT, stem cell transplantation

Supplemental Table 3. Main Causes of transplant-related mortality by HLA allele mismatch for graft versus host

	HLA mismatch for graft versus host					
	Match (N=85)		1 locus mismattch (N=160)		≥2 locus mismatch (N=401)	
Cause of death	No.	(%)	No.	(%)	No.	(%)
Engraftment failure	0	0.0	1	2.0	4	2.9
Infection	7	43.8	11	21.6	34	24.6
Interstitial Pneumonia	0	0.0	1	2.0	16	11.6
ARDS	0	0.0	1	2.0	2	1.5
TMA	0	0.0	2	3.9	10	7.3
Acute GVHD	0	0.0	6	11.8	15	10.9
Chronic GVHD	1	6.3	3	5.9	3	2.2
VOD	1	6.3	1	2.0	5	3.6
Organ failure	5	31.3	9	17.7	22	15.9
Secondary Malignancy	0	0.0	2	3.9	1	0.7
Bleeding	0	0.0	3	5.9	5	3.6
Others	1	6.3	2	3.9	6	4.4
Missing	1	6.3	7	13.7	15	10.9
Total	16	100.0	51	100.0	138	100.0

Abbreviations: ARDS, acute respiratory distress syndrome; TMA, thrombotic microangiopathy; GVHD, graft versus host disease; VOD, veno-occlusive disease;

Supplemental Table 4. Effect of HLA allele mismatch on acute GVHD, chronic GVHD and engraftment by stem cell source

BMT (N=167)	HLA mismatch for graft versus host		P for heterogeneity among stem cell sources[2]	HLA mismatch for graft versus first donor		P for heterogeneity among stem cell sources[2]
	Match (N=66)	≥1 allele mismatch (N=101)		Match (N=37)	≥1 allele mismatch (N=130)	
Grades III to IV acute GVHD						
SHR[1] (95%CI)	1 (ref)	1.36 (0.49-3.78, p=0.558)	0.333	1 (ref)	0.63 (0.16-2.44, p=0.505)	0.581
Chronic GVHD						
SHR[1] (95%CI)	1 (ref)	1.41 (0.75-2.64, p=0.283)	0.301	1 (ref)	1.03 (0.52-2.06, p=0.930)	0.477
Neutrphil Engraftment						
SHR[1] (95%CI)	1 (ref)	0.84 (0.61-1.14, p=0.257)	0.356	1 (ref)	1.20 (0.84-1.71, p=0.316)	0.341
PBSCT (N=181)	Match (N=13)	≥1 allele mismatch (N=168)		Match (N=18)	≥1 allele mismatch (N=163)	
Grades III to IV acute GVHD						
SHR[1] (95%CI)	1 (ref)	8.76 (0.98-78.0, p=0.052)		1 (ref)	3.06 (0.40-23.4, p=0.280)	
Chronic GVHD						
SHR[1] (95%CI)	1 (ref)	2.15 (0.27-17.0, p=0.469)		1 (ref)	0.52 (0.14-1.99, p=0.342)	
Neutrphil Engraftment						
SHR[1] (95%CI)	1 (ref)	**0.55 (0.32-0.95, p=0.032)**		1 (ref)	1.03 (0.62-1.70, p=0.909)	
CBT (N=298)	Match (N=6)	≥1 allele mismattch (N=292)		Match (N=17)	≥1 allele mismatch (N=281)	
Grades III to IV acute GVHD						
SHR[1] (95%CI)	1 (ref)	NA		1 (ref)	0.36 (0.11-1.23, p=0.104)	
Chronic GVHD						
SHR[1] (95%CI)	1 (ref)	0.25 (0.05-1.18, p=0.080)		1 (ref)	1.51 (0.37-6.11, p=0.568)	
Neutrphil Engraftment						
SHR[1] (95%CI)	1 (ref)	0.70 (0.31-1.61, p=0.403)		1 (ref)	0.97 (0.55-1.69, p=0.903)	

*boldface denotes statistical significance

1 Adjusted for recipient age at transplant (continuous), recipient sex, sex mismatch (match, male to female, female to male, unknown), diagnosis (AML, ALL, CML, MDS, ML or others), disease risk at transplant (standard or high), conditioning regimen (myeloablative or reduced intensity), GVHD prophylaxis (CsA based, Tac based, others), in vivo T-cell depletion (Yes, No), year of transplant (1994-2010, 2011-2016), Interval between first and second SCT (<12 months, ≥12-23 months, ≥24 months, missing) and Interval between first SCT and relapse (<2 months, ≥2-12 months, ≥12 months, missing).

2 In analysis for heterogeneity among stem cell sources, products of scores for HLA mismatch (match, mismatch) and stem cell source (bone marrow, peripheral blood, cord blood) were included as intearction terms.

Abbreviations: BMT, bone marrow transplant; PBSCT, peripheral blood stemcell transplant; CBT cord blood transplant; GVHD, graft versus host disease; SCT, stem cell transplantation

Supplemental Table 5. Effect of HLA allele mismatch on overall survival, transplant-related mortality and relapse by stem cell source

BMT (N=167)	HLA mismatch for graft versus host		P for heterogeneity among stem cell sources[2]	HLA mismatch for graft versus first donor		P for heterogeneity among stem cell sources[2]
	Match (N=66)	≥1 allele mismatch (N=101)		Match (N=37)	≥1 allele mismatch (N=130)	
Transplant-related mortality						
SHR[1] (95%CI)	1 (ref)	1.82 (0.94-3.53, p=0.075)	0.577	1 (ref)	0.73 (0.38-1.40, p=0.345)	0.755
Relapse						
SHR[1] (95%CI)	1 (ref)	0.77 (0.50-1.18, p=0.232)	0.690	1 (ref)	1.82 (0.98-3.40, p=0.059)	
Overall survival						
HR[1] (95%CI)	1 (ref)	1.18 (0.82-1.71, p=0.380)	0.702	1 (ref)	1.10 (0.71-1.72, p=0.658)	0.317
PBSCT (N=181)	Match (N=13)	≥1 allele mismatch (N=168)		Match (N=18)	≥1 allele mismatch (N=163)	
Transplant-related mortality						
SHR[1] (95%CI)	1 (ref)	4.54 (0.60-34.1, p=0.142)		1 (ref)	0.57 (0.24-1.36, p=0.208)	
Relapse						
SHR[1] (95%CI)	1 (ref)	**0.34 (0.15-0.78, p=0.011)**		1 (ref)	0.89 (0.41-1.94, p=0.764)	
Overall survival						
HR[1] (95%CI)	1 (ref)	0.97 (0.40-2.34, p=0.950)		1 (ref)	0.80 (0.42-1.50, p=0.484)	
CBT (N=298)	Match (N=6)	≥1 allele mismattch (N=292)		Match (N=17)	≥1 allele mismatch (N=281)	
Transplant-related mortality						
SHR[1] (95%CI)	1 (ref)	1.09 (0.33-3.62, p=0.893)		1 (ref)	1.07 (0.44-2.62, p=0.880)	
Relapse						
SHR[1] (95%CI)	1 (ref)	1.15 (0.29-4.63, p=0.845)		1 (ref)	0.95 (0.40-2.23, p=0.901)	
Overall survival						
HR[1] (95%CI)	1 (ref)	1.16 (0.42-3.19, p=0.780)		1 (ref)	0.84 (0.45-1.57, p=0.584)	

*boldface denotes statistical significance

1 Adjusted for recipient age at transplant (continuous), recipient sex, sex mismatch (match, male to female, female to male, unknown), diagnosis (AML, ALL, CML, MDS, ML or others), disease risk at transplant (standard or high), conditioning regimen (myeloablative or reduced intensity), GVHD prophylaxis (CsA based, Tac based, others), in vivo T-cell depletion (Yes, No), year of transplant (1994-2010, 2011-2016), Interval between first and second SCT (<12 months, ≥12-23 months, ≥24 months, missing) and Interval between first SCT and relapse (<2 months, ≥2-12 months, ≥12 months, missing).

2 In analysis for heterogeneity among stem cell sources, products of scores for HLA mismatch (match, mismatch) and stem cell source (bone marrow, peripheral blood, cord blood) were included as intearction terms.

Abbreviations: BMT, bone marrow transplant; PBSCT, peripheral blood stemcell transplant; CBT cord blood transplant; GVHD, graft versus host disease; SCT, stem cell transplantation

Statistical Analysis

Several potential confounders were considered in the multivariable analyses, as follows: recipient age at transplant (continuous), recipient sex, sex mismatch (match, male to female, female to male, unknown), diagnosis (AML, ALL, CML, MDS, ML, or other), disease risk at transplant (normal or high), stem cell source (bone marrow, peripheral blood, or cord blood), conditioning regimen (myeloablative or reduced intensity), GVHD prophylaxis (cyclosporine [CsA]-based, tacrolimus [Tac]-based, or other), in vivo T cell depletion (yes or no), time of transplant (1994–2010 or 2011–2016), interval between first and second HSCT (< 12 months, ≥ 12–23 months, ≥ 24 months, or missing data), and interval between first HSCT and relapse (< 2 months, ≥ 2–12 months, ≥ 12 months, or missing data). Based on the report by the Center for International Blood and Marrow Transplant Research (CIBMTR), we classified the conditioning regimens as myeloablative if total body irradiation > 8 Gy, and oral busulfan > 9 mg/kg, intravenous busulfan > 7.2 mg/kg, or melphalan > 140 mg/m2 was used in the conditioning regimen. Conditioning regimen doses lower than the threshold values were classified as "reduced intensity" [1]. For patients with insufficient data regarding the doses of the agents used in the conditioning regimen, we used the information on conditioning intensity (myeloablative or reduced intensity) reported by the treating clinicians. We defined AML and ALL in the first or second remission, CML in the first or second chronic phase or accelerated phase, MDS with refractory anemia or refractory anemia with ringed sideroblasts, lymphoma in first or second complete remission, myeloma in remission as standard-risk diseases and other conditions as high risk. Patients were further categorized as at normal risk or high risk.

EZR is a graphical user interface for the R environment (ver. 2.13.0; R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R

Commander (ver. 2.0-1), which adds statistical functions that are frequently used in biostatistics.

1. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2009;15(3):367-369.