Table 1 continued

Gene	Polymorphism	Function, ref.	Cohort (cases)	Type of GVHD	Genome	Ref.
TNF	(TNFd)n	Yes [73]	MRD (49)	Acute	R	[7]
TNF	(TNFd)n	Yes [73]	MRD (80)	Acute	R	[73]
TNF	(TNFd)n	Yes [73]	MRD and URD (62)	Acute	D	[92]
TNF	rs1799964	Yes [117]	URD (922)	Acute	M	[28]
TNF	rs1800610	U	MRD (160)	Acute, chronic	R, D	[61]
TNF	rs1800630	No [118]	URD (462)	Acute	R, D	[119]
TNF	rs1799724	U	URD (462)	Acute	R, D	[119]
TNFRII	rs1061622	Yes [120]	MRD (104)	Acute	R	[120]
TNFRII	rs1061622	Yes [120]	MRD (104)	Chronic	D	[120]
TNFRII	rs1061622	Yes [120]	URD (462)	Chronic	D	[119]
TSER	(28 bp)n	Yes [121]	MRD and URD (304)	Acute	D	[99]
UGT2B17	129 kbp deletion	Yes [122]	MRD (1,345)	Acute	M	[41]
VDR	intron 8 CNP	Yes [123]	MRD (88)	Acute	R	[93]
VEGFA	rs699947	Yes [124, 125]	MRD (98)	Acute	R	[126]
VEGFA	rs833061	Yes [124, 125]	MRD (98)	Acute	R	[126]
U	rs6937034	U	URD (1,598)	Acute	M	[127]
KRAS	rs1137282	U	URD (1,598)	Acute	M	[127]
U	rs9657655	U	URD (1,598)	Acute	M	[127]
U	rs5998746	U	URD (1,598)	Acute	R	[127]
U	rs11873016	U	URD (1,598)	Acute	R	[127]

CNP copy number polymorphism, *TR* tandem repeat, *U* unknown, *MRD* matched-related donor, *URD* unrelated donor, *D* donor, *R* recipient, *M* mismatch between recipient and donor

CCL4, CCL5 and CCL3L1. A large cohort study demonstrated that the donor *CCL5* genotype significantly influenced the risk of severe acute GVHD and disease-free survival [27].

Harkensee et al. [28] reevaluated 41 previously documented SNPs in two independent, large cohorts, and showed an association of the *TNF* and *CTLA4* SNPs with acute GVHD and an association of the *IL-2* SNP with chronic GVHD.

The *PTPN22* gene encodes lymphoid-specific phosphatase (Lyp) and is an important negative regulator of T-cell activation involved in the dephosphorylation and inactivation of TCR-associated kinases. A SNP of the *PTPN22* promoter gene, rs2488457 (G/C), is associated with the susceptibility to autoimmune diseases. In unrelated bone marrow transplantation, the recipient C/C genotype is associated with a significantly lower incidence of grade II–IV acute GVHD and a higher incidence of relapse, which predict worse survival outcomes for patients with high-risk disease [15].

Functional polymorphisms

IL-17 is the hallmark cytokine of Th17 cells and plays important roles in the host defense, the pathophysiology of autoimmune diseases and organ allograft rejection. Although several studies using mouse models showed a significant impact of IL-17 on the development of acute GVHD [29–35], the results were not consistent. Espinoza et al. were the first to report an association of the rs2275913 SNP (G/A) in the promoter of the IL-17 gene with the development of acute GVHD [17, 36]. Notably, the rs2275913 SNP is located within a binding motif for nuclear factor activated T cells (NFAT), which is a critical regulator of the *IL-17* promoter [37]. The same group demonstrated that the A allele of the *IL-17* gene makes patients susceptible to acute GVHD because it correlates with more efficient IL-17 secretion through its higher affinity for NFAT than the G allele [17]. These findings suggest not only the functional relevance of the *IL-17* promoter SNPs with the development of acute GVHD, but also the involvement of IL-17 in the development of acute GVHD, leading to a hypothesis that IL-17-producing cells can modify the function of host dendritic cells (DCs) through unknown mechanisms. The direct interaction between IL-17 and host DCs may be supported by the fact that DCs express IL-17 receptors [38]. A better understanding of the molecular mechanism by which this promoter SNP controls the production of IL-17 may therefore offer some novel therapeutic insights into the mechanisms underlying the development of other IL-17-related diseases, including rheumatoid arthritis, periodontal disease,

multiple sclerosis, allergic rhinitis, psoriasis, inflammatory bowel disease and organ allograft rejection [39].

mHAs

McCarroll et al. [40] identified 1316 CNPs using genotyping arrays with higher SNPs density and copy number probes accompanied by newer algorithms. Among them, donor-negative and recipient-positive mismatch of the *UGT2B17* CNP showed an association with acute GVHD [41]. This is consistent with a previous report [42] showing that the protein encoded by the *UGT2B17* gene is a mHA that is selectively expressed in the liver, intestine and antigen-presenting cells, and that it plays a causative role in acute GVHD.

Cellular proteins encoded by the Y-chromosome can also operate as mHAs when male recipients receive SCT grafts from female donors [43, 44].

Conclusion

The determination of the non-HLA genotypes associated with GVHD prior to transplantation will provide patients an opportunity to receive optimal strategies in terms of the selection of the donor, type of graft, conditioning treatment and GVHD prophylaxis. However, several issues remain unresolved that need to be addressed before mainstream non-HLA genotyping can be implemented in clinical practice. First, the abundance of non-HLA gene polymorphisms identified should be validated by individual, multiracial cohorts irrespective of whether CGS and GWAS approaches were used, because the study populations may critically impact on results, as has also been seen in HLA association studies [4, 45, 46]. Second, whether a polymorphic gene has a functional role and mHA nature should be determined to obtain a better understanding of the molecular mechanisms by which the gene polymorphism can influence the GVHD, offering novel therapeutic insights into GVHD, as well as other autoimmune diseases in which the polymorphic gene is involved. There is also a possibility that the gene polymorphism of interest may coordinate with other genes, and/or have close linkage with another gene with functional and/or immunogenic properties. Finally, systemic discovery of new genetic biomarkers using GWAS will add weight in the decade ahead, but informed consent and privacy protection remain issues that need specific attention, because GWAS create a large amount of individual-specific digital information that is easy to share across international borders [47].

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bjh research paper

Impact of a single human leucocyte antigen (HLA) allele mismatch on the outcome of unrelated bone marrow transplantation over two time periods. A retrospective analysis of 3003 patients from the HLA Working Group of the Japan Society for Blood and Marrow Transplantation

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Summary

A previous Japanese study revealed that a human leucocyte antigen (HLA)-A or -B allele mismatch was associated with higher overall mortality, whereas an HLA-C or -DRB1 allele mismatch did not affect mortality after serologically matched unrelated bone marrow transplantation (BMT). This study reanalysed 3003 adult patients who underwent unrelated BMT from a serologically HLA-A, -B, or -DR matched unrelated donor between 1993 and 2009 using the latest database, that included 1966 HLA-matched unrelated BMT and 187, 31, 524, and 295 unrelated BMT with a single HLA-A, -B, -C, or -DRB1 allele mismatch, respectively. As opposed to our previous findings, HLA-C and -DRB1 mismatches had a significant negative impact [hazard ratio (HR) 1·35, $P < 0·001$, and HR 1·45, $P < 0·001$] on survival in the period 2000–2009. The negative impact of each single HLA allele mismatch was not significantly different among the HLA-A, -B, -C, and -DRB1 mismatches ($P = 0·79$). An interaction test revealed that the effects of single HLA-C and -DRB1 allele mismatches significantly differed over the two time periods ($P = 0·032$ and $P = 0·0072$, respectively). In conclusion, the impact of a single HLA allele mismatch changed over time. In the recent cohort, the negative impact of HLA-DRB1 and -C mismatches became apparent.

Keywords: allogeneic haematopoietic stem cell transplantation, human leucocyte antigen, graft-versus-host disease, human leucocyte antigen mismatch, unrelated donor.

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Haematopoietic stem cell transplantation (HSCT) from an unrelated donor has been investigated for patients who lack a human leucocyte antigen (HLA)-matched sibling donor. However, the outcome of serologically HLA-matched unrelated HSCT has been shown to be inferior to that of HSCT from an HLA-matched sibling due to the development of graft failure or severe graft-versus-host disease (GVHD), which resulted partly from the presence of an HLA mismatch at the genetic level (allele mismatch). High-resolution typing is needed to detect an allele mismatch, whereas a serological HLA mismatch (antigen mismatch) requires only low-resolution typing. A retrospective study by the Japan Marrow Donor Program (JMDP) revealed that an HLA-A or -B allele mismatch was associated with higher overall mortality, whereas an HLA-C or -DRB1 allele mismatch did not affect mortality after serologically HLA-A, -B, and -DR matched unrelated bone marrow transplantation (BMT; Sasazuki *et al*, 1998). Subsequently, Morishima *et al* (2002) analysed the impact of a single allele mismatch by including only patients who were matched for all other loci. They confirmed that an HLA-A and/or -B allele mismatch, but not an HLA-C or -DRB1 allele mismatch, was associated with worse survival. However, studies from the National Marrow Donor Program (NMDP) and the Fred Hutchinson Cancer Research Center have shown conflicting results with regard to the impact of single HLA allele mismatches (Flomenberg *et al*, 2004; Petersdorf *et al*, 2004; Lee *et al*, 2007). These discrepancies could be explained by differences in the study population or study designs (Bray *et al*, 2008). For example, there are differences in the inclusion criteria for disease, phase of disease, and HLA matching (Bray *et al*, 2008).

The present study focused on the potential effect of the difference between HLA mismatches that were known and not known by the attending physicians before HSCT. In 1994, while high-resolution typing for HLA-DRB1 was started as a routine test in JMDP, only low-resolution typing was performed for HLA-A and -B until high-resolution typing for these loci became routine in 2003. More accurately, high-resolution typing for HLA-A and -B was available as an option after 1996, and these tests were gradually ordered more frequently after JMDP published the first retrospective analysis using frozen samples, which showed that HLA-A and -B allele mismatches were more important than an HLA-DRB1 allele mismatch (Sasazuki *et al*, 1998), and it has become a common practice since 2000. Therefore, in the 1990's, physicians only had information on an HLA-DRB1 allele mismatch before BMT, and this may have influenced the strategies against GVHD in patients with an HLA-DRB1 allele mismatch. In contrast, in the 2000's, physicians had information about HLA-A and -B mismatches and therefore strategies against GVHD in patients with an HLA-A or -B allele mismatch may have been more intense than those in patients with an HLA-DRB1 allele mismatch, as the latter was shown to have little effect on the incidence of severe acute GVHD (Sasazuki *et al*, 1998). With regard to HLA-C antigen, both high- and low-resolution tests for HLA-C were optional until they became routine in 2009. The intensity of immunosuppression for GVHD prophylaxis may also affect the incidence of graft failure.

We hypothesized that the availability of information about an HLA allele mismatch may affect the impact of single HLA-mismatches on survival, and reanalysed the impact of a mismatch in each single allele in the recent cohort (i.e. those who underwent BMT between 2000 and 2009). We also analysed the statistical interaction between single HLA allele mismatches and the time periods when BMT was performed.

Methods

Patients

Patients aged at least 16 years with acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), myelodysplastic syndrome (MDS), or chronic myeloid leukaemia (CML) who underwent a first BMT from a serologically HLA-A, -B and -DR matched unrelated donor between 1993 and 2009, and who had full HLA-A, -B, -C, and -DRB1 allele data, were included in this study. Clinical data for these patients were obtained from the Transplant Registry Unified Management Program (TRUMP; Atsuta *et al*, 2007). We excluded patients who lacked data on survival status, those with more than 1 allele or antigen mismatch, those who received a reduced-intensity conditioning regimen, and those who received *ex vivo* or *in vivo* T-cell depletion. Finally, 3003 patients were included in this study. The study was planned by the HLA working group of the Japan Society for Haematopoietic Cell Transplantation and was approved by the data management committees of TRUMP and by the institutional review board of Saitama Medical Centre, Jichi Medical University.

Histocompatibility

Histocompatibility data for serological and genetic typing for the HLA-A, HLA-B, HLA-C, and HLA-DR loci were obtained from the TRUMP database, which includes HLA allele data determined retrospectively by the JMDP using frozen samples (Morishima *et al*, 2002; Kawase *et al*, 2007). The extent of HLA testing was exon 2 and 3 for HLA class I and exon 2 for HLA class II, and exon 4 and exon 3 were additionally analysed for class I and class II, respectively, if required. An HLA mismatch in the GVHD was defined as when recipient antigens or alleles were not shared by the donor, and a mismatch in the host-versus-graft direction was defined as when donor antigens or alleles were not shared by the recipient. The direction of mismatch was considered in the analysis of engraftment and GVHD (Morishima *et al*, 2002; Lee *et al*, 2007).

Statistical analyses

The primary endpoint was overall survival after unrelated BMT. Secondary endpoints included the incidences of engraftment, grade III–IV acute GVHD, non-relapse mortality, and relapse. While the follow-up duration differed between patients in the two time periods [early (1993–1999) and late (2000–2009)], for the primary endpoint, we used the data obtained at last contact (Gooley *et al*, 2010). Then, we confirmed that there were no changes in the major findings, when surviving patients were censored at 5 years after BMT.

The chi-square test or Fisher's exact test was used to compare categorical variables and Student's *t*-test or an analysis of variance test was used for continuous variables. Overall survival was estimated according to the Kaplan–Meier method, and compared among groups with the log-rank test. The probabilities of non-relapse mortality, relapse, acute GVHD, and neutrophil engraftment were calculated while treating relapse, death without relapse, relapse or death without GVHD, and death without engraftment, respectively, as competing events, and compared using Gray's test (Gray, 1988).

The impacts of single HLA allele mismatches, the time period when BMT was performed, and the interaction between them were evaluated using multivariate models; Cox proportional hazards model for overall survival and Fine and Gray's proportional hazards model for the other endpoints (Fine & Gray, 1999). Potential confounding factors that were considered in these analyses included recipient/donor age, recipient/donor sex, sex mismatch, ABO major/minor mismatch, the use of total body irradiation (TBI) in the conditioning regimen, cell dose in the bone marrow graft, the use of ciclosporin (CSA) or tacrolimus (TAC) as GVHD prophylaxis, background disease, and disease risk. We divided GVHD prophylaxis regimens into only CSA-based and TAC-based regimens, because more than 95% of the patients received a combination of a calcineurin inhibitor and methotrexate. Acute leukaemia in first or second remission, CML in first or second chronic phase, CML in accelerated phase, and MDS of refractory anaemia or refractory anaemia with excess blasts were considered low-risk diseases, and other conditions were considered high-risk diseases. All of these potential confounding factors were included in the multivariate analyses and then deleted in a stepwise manner from the model to exclude factors with a *P*-value of 0·05 or higher. Finally, each single HLA allele mismatch and the time periods were added to the model to evaluate the effects of these factors adjusted for the other significant factors with or without interaction terms between the BMT time period and each single HLA allele mismatch. The model without interaction terms evaluated the impact of each single HLA allele mismatch adjusted for the BMT time period and the other significant factors. On the other hand, the model with interaction terms evaluated whether the impact of each single HLA allele mismatch was different between the two time periods, as well as the impact of each single HLA allele mismatch in each time period. Significant interaction means that the impact of the single HLA allele mismatch differs over the two time periods.

All *P*-values were two sided and *P*-values of 0·05 or less were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3) that was designed to add statistical functions frequently used in biostatistics.

Results

Patients

The patients characteristics are summarized in Table I. The total number of patients was 3003, and 751 and 2252 BMTs were performed in the early and late time periods, respectively. Of these, 1966 patients received a graft from an HLA-A, -B, -C, and -DRB1 allele matched donor, whereas 187, 31, 524, and 295 patients, respectively, underwent single HLA-A, -B, -C, and DRB1 allele-mismatched BMT. Only the HLA-C mismatch group included HLA mismatch at a serological (antigen) level. Bone marrow was exclusively used as the stem cell source.

Overall survival

To adjust the impact of HLA mismatch for possible confounding factors, we identified the following independently significant factors for overall survival: recipient age, disease, disease risk, and GVHD prophylaxis. After we adjusted for these factors, all single allele mismatches were significantly

Table I. Patient characteristics.

		1 allele mismatch				
	Match $n = 1966$	A $n = 187$	B $n = 31$	C $n = 524$	DRB1 $n = 295$	*P* value
Transplantation time period						
1993–1999	480	74	8	126	63	<0·001
2000–2009	1486	113	23	398	232	
Antigen mismatch						
No	1966 [480/1486]	187 [74/113]	31 [8/23]	38 [7/31]	295 [63/232]	<0·001*
Yes	0	0	0	486 [119/367]	0	
Mismatch in GVH direction						
No	1966 [480/1486]	22 [6/16]	1 [0/1]	38 [9/29]	11 [3/8]	0·0068*
Yes	0	165 [68/97]	30 [8/22]	486 [117/369]	284 [60/224]	
Mismatch in HVG direction						
No	1966 [480/1486]	13 [3/10]	0	43 [10/33]	18 [4/14]	0·29*
Yes	0	174 [71/103]	31 [8/23]	481 [116/365]	277 [59/218]	
Age, years						
Median (range)	37 (16–70) [30/39]	34 (16–56) [30/37]	34 (17–59) [28·5/35]	36 (16–67) [30/38]	37 (16–64) [26/39]	0·21
Age (donor), years						
Median (range)	34 (20–55) [34/34]	35 (20–55) [33/36]	35 (23–49) [29/37]	34 (20–54) [33/34]	34 (20–53) [34/34]	0·90
Sex						
Female	747 [183/564]	76 [31/45]	16 [4/12]	233 [57/176]	117 [30/87]	0·055
Male	1219 [297/922]	111 [43/68]	15 [4/11]	291 [69/222]	178 [33/145]	
Sex (donor)						
Female	651 [159/492]	62 [25/37]	14 [4/10]	218 [45/173]	119 [21/98]	0·016
Male	1307 [317/990]	124 [49/75]	17 [4/13]	303 [81/222]	175 [42/133]	
N.A.	8 [4/4]	1 [0/1]	0	3 [0/3]	1 [0/1]	
Sex mismatch						
Match	1241 [287/954]	101 [36/65]	21 [6/15]	310 [70/240]	159 [28/131]	0·077
Female to Male	311 [83/228]	36 [16/20]	4 [1/3]	99 [22/77]	69 [13/56]	
Male to Female	406 [106/300]	49 [22/27]	6 [1/5]	112 [34/78]	66 [22/44]	
N.A.	8 [4/4]	1 [0/1]	0	3 [0/3]	1 [0/1]	
ABO blood type						
Match	1119 [248/871]	91 [38/53]	13 [6/7]	190 [45/145]	135 [25/110]	<0·001
Minor mismatch	375 [92/283]	44 [14/30]	7 [1/6]	149 [34/115]	69 [17/52]	
Major mismatch	300 [93/207]	23 [8/15]	10 [1/9]	120 [32/88]	56 [13/43]	
Bidirectional mismatch	156 [37/119]	27 [13/14]	1 [0/1]	60 [12/48]	31 [7/24]	
N.A.	16 [10/6]	2 [1/1]	0	5 [3/2]	4 [1/3]	
Disease						
AML	876 [161/715]	64 [15/49]	13 [1/12]	216 [38/178]	136 [22/114]	0·029
ALL	563 [139/424]	58 [21/37]	9 [2/7]	136 [32/104]	81 [20/61]	
CML	321 [142/179]	44 [33/11]	7 [3/4]	94 [41/53]	53 [17/36]	
MDS	206 [38/168]	21 [5/16]	2 [2/0]	78 [15/63]	25 [4/21]	
Disease risk						
Low	1302 [327/975]	120 [51/69]	19 [6/13]	336 [79/257]	180 [36/144]	0·58
High	593 [136/457]	63 [22/41]	10 [1/9]	166 [41/125]	105 [25/80]	
N.A.	71 [17/54]	4 [1/3]	2 [1/1]	22 [6/16]	10 [2/8]	
Cell dose (cells/kg)						
Median	2·80 [3·07/2·70]	2·99 [2·97/2·99]	2·71 [3·10/2·58]	2·79 [3·15/2·60]	2·78 [3·10/2·61]	0·40
GVHD prophylaxis						

Table I. (*Continued*)

		1 allele mismatch				
	Match $n = 1966$	A $n = 187$	B $n = 31$	C $n = 524$	DRB1 $n = 295$	*P* value
CSA-based	918 [377/541]	93 [62/31]	14 [7/7]	243 [100/143]	115 [47/68]	0·17
TAC-based	1017 [93/924]	89 [10/79]	16 [1/15]	267 [24/243]	175 [15/160]	
N.A.	31 [10/21]	5 [2/3]	1 [0/1]	14 [2/12]	5 [1/4]	
Conditioning regimen						
TBI regimen	1634 [467/1167]	168 [74/94]	29 [8/21]	430 [121/309]	249 [63/186]	0·21
Non-TBI regimen	257 [10/247]	14 [0/14]	1 [0/1]	68 [5/63]	37 [0/37]	
N.A.	75 [3/72]	5 [0/5]	1 [0/1]	26 [0/26]	9 [0/9]	

Numbers in the square brackets show the data separated according to the time periods.
HVG, host-versus-graft; GVH (D), graft-versus-host (disease); AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; N.A., not available; CSA, ciclosporin; TAC, tacrolimus, TBI, total body irradiation.
*Comparison excluding the HLA-matched group.

associated with inferior survival except that the effect of HLA-A allele mismatch was nearly significant [HR 1·22, 95% confidence interval (CI) 1·00–1·51, $P = 0·055$, HR 1·60, 95% CI 1·03–2·49, $P = 0·038$, HR 1·23, 95% CI 1·07–1·41, $P = 0·00037$, and HR 1·26, 95% CI 1·07–1·49, $P = 0·0068$ for HLA-A, -B, -C, and -DRB1 mismatch, respectively]. However, when the effects of single HLA allele mismatches were evaluated separately in the early and late BMT time periods by adding interaction terms between HLA allele mismatches and time periods, only an HLA-B allele mismatch was associated with significantly inferior survival (HR 2·47, 95% CI 1·16–5·24, $P = 0·019$) in the early time period, whereas HLA-A, -C and -DRB1 mismatches did not exhibit a significant effect (HR 1·16, 95% CI 0·84–1·59, $P = 0·37$, HR 0·96, 95% CI 0·73–1·26, $P = 0·77$, and HR 0·83, 95% CI 0·58–1·19, $P = 0·32$, Table II). On the other hand, HLA-C and -DRB1 mismatches were associated with significantly inferior survival in the late time period (HR 1·35, 95% CI 1·15–1·59, $P < 0·001$, and HR 1·45, 95% CI 1·20–1·75, $P < 0·001$). The effects of HLA-A and -B allele mismatches were not statistically significant in the late time period, but the HR values (HR 1·24, 95% CI 0·95–1·62, $P = 0·12$, and HR 1·36, 95% CI 0·78–2·35, $P = 0·28$) were almost equivalent to those of HLA-C and -DRB1 mismatches. In fact, the negative impact of each single HLA allele mismatch was not significantly different among the HLA-A, -B, -C, and -DRB1 mismatches ($P = 0·79$ by the Wald test). Fig 1 shows the survival curves adjusted for other significant factors. In the early time period, the survival curves of the HLA-C and -DRB1 mismatch groups were at least equivalent to that of the HLA matched group, whereas that of the HLA-B mismatch group was separate from those of the other groups (Fig 1A). On the other hand, in the late time period, the survival curves of all of the single HLA allele mismatch groups were close to each other (Fig 1B).

An interaction test between the BMT time period and each single HLA allele mismatch revealed that the effects of single HLA-C and -DRB1 allele mismatches significantly differed over the two time periods ($P = 0·032$ and $P = 0·0072$, Table II). The major reason for these significant interactions was that, while overall survival in the HLA match group significantly improved from the early to the late time periods (HR 0·75, 95% CI 0·64–0·90, $P = 0·0011$), overall survival in the HLA-C and -DRB1 mismatch groups did not improve (HR 1·00, 95% CI 0·73–1·36, $P = 0·98$ and HR 1·20, 95% CI 0·79–1·82, $P = 0·40$, Fig 2). Similarly, overall survival in the HLA-A and -B mismatch groups did not change significantly between the two time periods (HR 0·81, 95% CI 0·49–1·34, $P = 0·41$ and HR 0·55, 95% CI 0·15–2·00, $P = 0·36$).

Engraftment and acute GVHD

The achievement of engraftment was significantly improved over the two time periods (HR 1·13, $P = 0·023$) after adjusting for other significant factors. None of the single HLA allele mismatches in the host-versus-graft direction affected the incidence of engraftment in either the early or late time periods, except for HLA-B allele mismatch in the late time period (HR 0·70, $P = 0·037$, Table III). The HR for engraftment was decreased, from 1·06 to 0·95 in the HLA-A mismatch group and from 1·03 to 0·89 in the HLA-DRB1 mismatch group, but the interaction tests were not significant.

With regard to the incidence of grade III–IV acute GVHD, single HLA-C allele mismatch in the graft-versus-host direction was associated with a significantly higher incidence of severe acute GVHD in the early time period (HR 2·02, $P = 0·0029$). In the late time period, single HLA-A and DRB1 allele mismatches, in addition to the HLA-C allele mismatch, were associated with a significantly higher incidence of grade III–IV acute GVHD (HR 1·72, $P = 0·025$, HR 1·51, $P = 0·0067$, and HR 1·45, $P = 0·045$ for HLA-A, -C, and -DRB1 mismatches, respectively), but the interactions between the time period and HLA-A and DRB1 allele mismatches were not statistically significant (Table III, Fig 3).

Table II. Multivariate analysis to evaluate the impact of single HLA allele mismatches, transplantation time periods, and their interaction on overall survival.

Factor	Hazard ratio	*P* value
Main effects		
Age	1·01 (1·01–1·02)	<0·001
Disease		
AML	1	
ALL	1·16 (1·02–1·32)	0·024
CML	0·90 (0·77–1·07)	0·23
MDS	0·56 (0·47–0·68)	<0·001
Disease risk		
Low	1	
High	2·98 (2·66–3·35)	<0·001
N.A.	2·40 (1·85–3·11)	<0·001
GVHD prophylaxis		
CSA-based	1	
TAC-based	0·94 (0·84–1·06)	0·30
HLA (early years)		
Match	1	
A mismatch	1·16 (0·84–1·59)	0·37
B mismatch	2·47 (1·16–5·24)	0·019
C mismatch	0·96 (0·73–1·26)	0·77
DRB1 mismatch	0·83 (0·58–1·19)	0·32
HLA (late years)		
Match	1	
A mismatch	1·24 (0·95–1·62)	0·12
B mismatch	1·36 (0·78–2·35)	0·28
C mismatch	1·35 (1·15–1·59)	0·0003
DRB1 mismatch	1·45 (1·20–1·75)	0·0001
Transplantation time period		
Early period	1·00	
Late period	0·74 (0·63–0·86)	0·00016
Interactions		
Time period * A mismatch	1·07 (0·70–1·63)	0·75
Time period * B mismatch	0·55 (0·22–1·40)	0·21
Time period * C mismatch	1·41 (1·03–1·93)	0·032
Time period * DRB1 mismatch	1·74 (1·16–2·61)	0·0072

GVHD, graft-versus-host disease; HLA, human leucocyte antigen; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; N.A., not available; CSA, ciclosporin; TAC, tacrolimus.

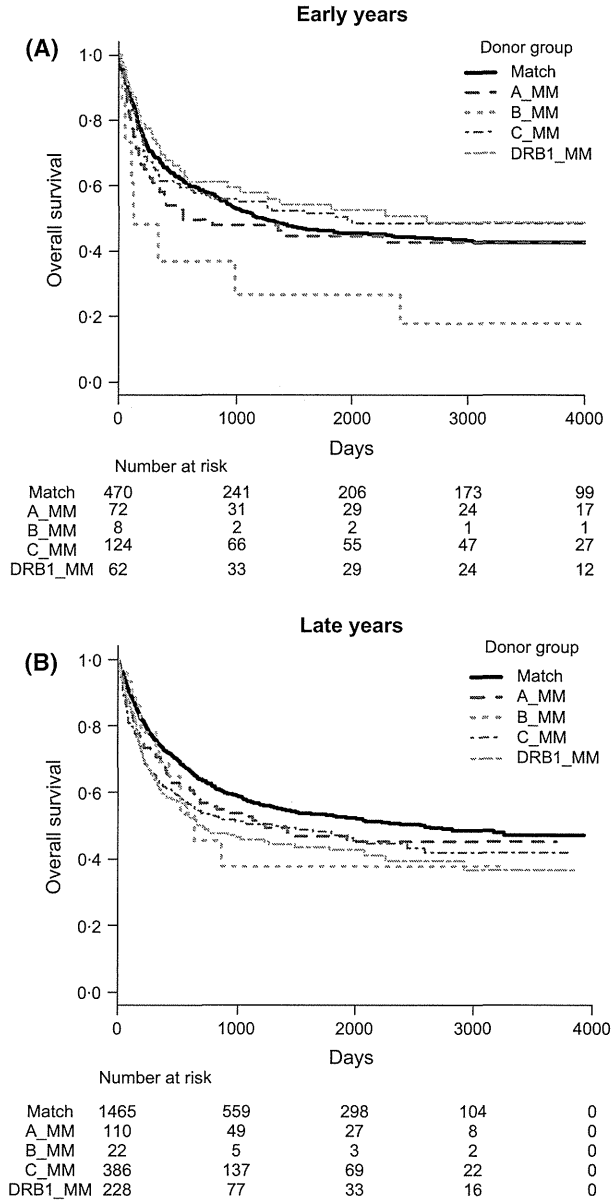

Fig 1. Overall survival grouped according to the human leucocyte antigen mismatch between the donor and recipient in the (A) early (1993–1999) and (B) late (2000–2009) time periods. The survival curves were adjusted for other significant factors by the mean of covariates method, in which average values of covariates are entered into the Cox proportional hazards model.

Non-relapse mortality and relapse

The incidence of non-relapse mortality was higher in the HLA-B allele mismatch group with borderline significance in the early time period (HR 2·48, $P = 0·069$, Table III, Fig 4). In the late time period, single HLA-A and -C allele mismatches were associated with a significantly higher incidence of non-relapse mortality (HR 1·47, $P = 0·027$ and HR 1·33, $P = 0·011$). While the HR for non-relapse mortality was highest in the HLA-B allele mismatch group (HR 1·72, $P = 0·10$), the effect was not statistically significant, probably due to the small sample size.

In the early period, a single HLA-C allele mismatch was associated with a significantly lower incidence of relapse (HR 0·46, $P = 0·0063$, Table III, Fig 5). However, an HLA-C mismatch did not have a significant relationship with the relapse rate in the late time period. There was a significant interaction between the BMT time period and an HLA-C allele mismatch ($P = 0·0094$).

Non-relapse mortality was significantly decreased from the early to late time period (HR 0·69, $P = 0·00078$), whereas the incidence of relapse was not changed (HR 0·96, $P = 0·71$).

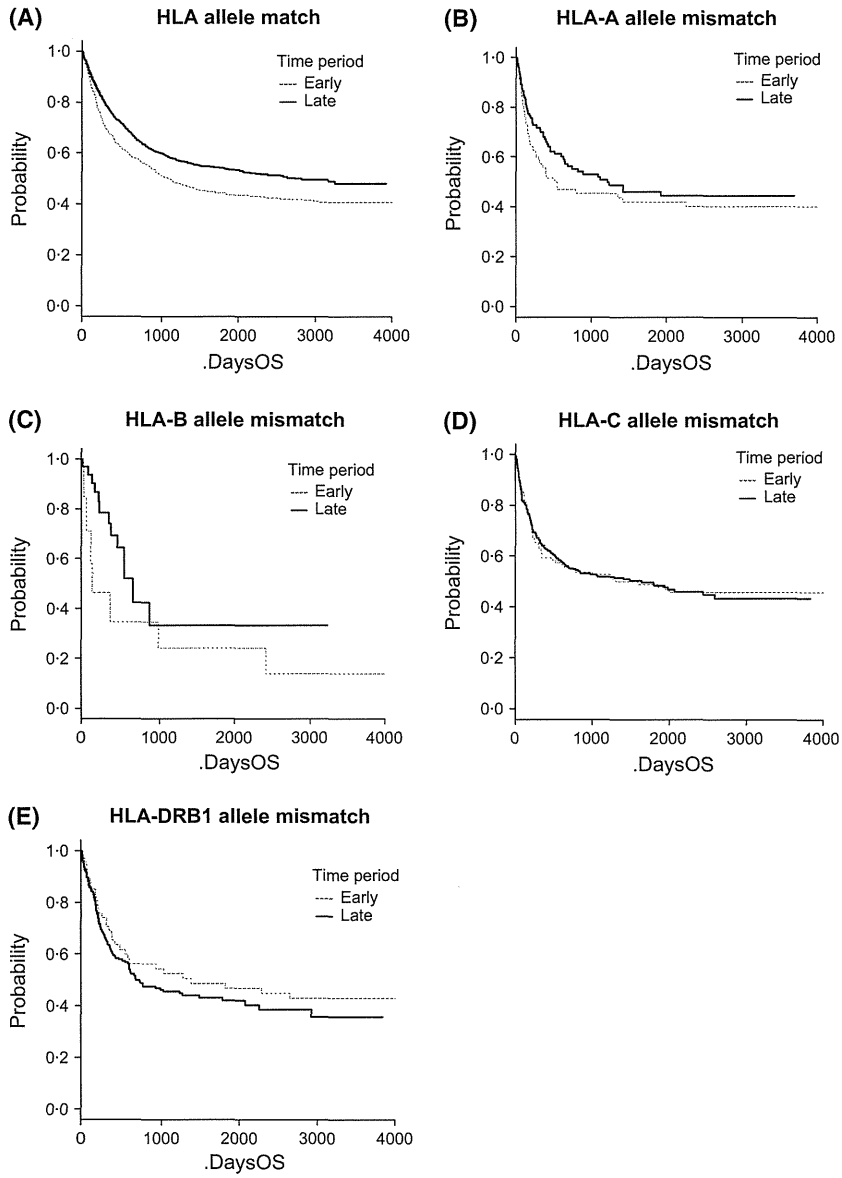

Fig 2. Overall survival grouped according to the transplantation time period in the human leucocyte antigen (HLA) match (A), HLA-A allele mismatch (B), HLA-B allele mismatch (C), HLA-C allele mismatch (D), and HLA-DRB1 allele mismatch (E) groups. The survival curves were adjusted for other significant confounding factors by the mean of covariates method, in which average values of covariates are entered into the Cox proportional hazards model. Early, transplanted between 1993 and 1999; Late, transplanted between 2000 and 2009.

Discussion

This study re-evaluated the effect of a single HLA allele mismatch on the outcome of unrelated BMT in the recent cohort. We chose 2000 as the cutoff of time period, as high-resolution typing for HLA-A and -B became a common practice in Japan after 2000. In contrast to our previous findings (Sasazuki *et al*, 1998), only the effects of single HLA-C and -DRB1 mismatches were statistically significant in the recent time period, but the negative impact of each single HLA allele mismatch was not significantly different among the HLA-A, -B, -C, and -DRB1 mismatches. Previous JMDP studies showed that HLA-A and -B allele mismatches were associated with higher overall mortality, whereas HLA-C or -DRB1 allele mismatches did not affect mortality after unrelated BMT (Sasazuki *et al*, 1998). In contrast, Petersdorf *et al* (2004) reported that a single HLA-A, -B, -C or -DRB1 allele mismatch had no significant relationship with survival in patients with leukaemia other than chronic myeloid leukaemia in chronic phase. The recent NMDP study analysed the effect of a single allele mismatch on survival in 1840 HLA-matched and 985 one-allele mismatched unrelated HSCT and showed that a single mismatch at HLA-B or -C had smaller relationship with survival than single mismatch at HLA-A or -DRB1 (Lee *et al*, 2007). These discrepancies could be explained by the difference in study population or study designs (Bray *et al*, 2008). For example, the distribution of HLA alleles is different between the US and Japanese populations. Several HLA allele mismatch combinations have been shown to have higher risk for severe acute GVHD compared to other mismatch combinations (Kawase *et al*, 2007). The proportion of high-risk mismatch combinations may affect

Table III. Multivariate analysis to evaluate the impact of single human leucocyte antigen (HLA) allele mismatches, transplantation time periods, and their interaction on the incidences of neutrophil engraftment, grade III–IV acute GVHD, non-relapse mortality, and relapse.

Factor	Hazard ratio	*P* value
Engraftment		
Main effects		
HLA (early years)		
Match	1	
A mismatch	1·06 (0·87–1·29)	0·59
B mismatch	0·65 (0·28–1·54)	0·33
C mismatch	0·93 (0·77–1·11)	0·42
DRB1 mismatch	1·03 (0·79–1·36)	0·80
HLA (late years)		
Match	1	
A mismatch	0·95 (0·77–1·18)	0·66
B mismatch	0·70 (0·50–0·98)	0·037
C mismatch	0·95 (0·73–1·08)	0·4
DRB1 mismatch	0·89 (0·77–1·03)	0·12
Transplantation time period		
Early period	1	
Late period	1·13 (1·02–1·25)	0·023
Interactions		
Time period * A mismatch	0·90 (0·68–1·21)	0·49
Time period * B mismatch	1·07 (0·43–2·67)	0·89
Time period * C mismatch	1·02 (0·82–1·27)	0·85
Time period * DRB1 mismatch	0·86 (0·63–1·17)	0·33
Grade III-IV acute GVHD		
Main effects		
HLA (early years)		
Match	1	
A mismatch	1·46 (0·79–2·69)	0·22
B mismatch	1·74 (0·22–13·55)	0·60
C mismatch	2·02 (1·27–3·20)	0·0029
DRB1 mismatch	0·80 (0·37–1·74)	0·58
HLA (late years)		
Match	1	
A mismatch	1·72 (1·07–2·77)	0·025
B mismatch	1·26 (0·42–3·79)	0·68
C mismatch	1·51 (1·12–2·02)	0·0067
DRB1 mismatch	1·45 (1·01–2·09)	0·045
Transplantation time period		
Early period	1	
Late period	1·01 (0·75–1·36)	0·96
Interactions		
Time period * A mismatch	1·18 (0·54–2·55)	0·68
Time period * B mismatch	0·73 (0·07–7·44)	0·79
Time period * C mismatch	0·75 (0·43–1·29)	0·30
Time period * DRB1 mismatch	1·81 (0·77–4·25)	0·17
Non-relapse mortality		
Main effects		
HLA (early years)		
Match	1	
A mismatch	1·41 (0·93–2·12)	0·11
B mismatch	2·48 (0·93–6·57)	0·069
C mismatch	1·20 (0·87–1·67)	0·27
DRB1 mismatch	0·86 (0·52–1·41)	0·55
HLA (late years)		
Match	1	
A mismatch	1·47 (1·05–2·07)	0·027
B mismatch	1·72 (0·90–3·29)	0·1
C mismatch	1·33 (1·07–1·66)	0·011
DRB1 mismatch	1·22 (0·93–1·60)	0·15
Transplantation time period		
Early period	1	
Late period	0·69 (0·56–0·86)	0·00078
Interactions		
Time period * A mismatch	1·05 (0·61–1·79)	0·86
Time period * B mismatch	0·69 (0·21–2·25)	0·54
Time period * C mismatch	1·11 (0·74–1·64)	0·62
Time period * DRB1 mismatch	1·42 (0·81–2·50)	0·23
Relapse		
Main effects		
HLA (early years)		
Match	1	
A mismatch	0·79 (0·45–1·39)	0·42
B mismatch	1·97 (0·57–6·76)	0·28
C mismatch	0·46 (0·27–0·81)	0·0063
DRB1 mismatch	0·90 (0·54–1·51)	0·70
HLA (late years)		
Match	1	
A mismatch	0·71 (0·44–1·14)	0·15
B mismatch	1·10 (0·49–2·49)	0·81
C mismatch	1·04 (0·81–1·33)	0·79
DRB1 mismatch	1·27 (0·95–1·68)	0·10
Transplantation time period		
Early period	1	
Late period	0·96 (0·76–1·20)	0·71
Interactions		
Time period * A mismatch	0·89 (0·43–1·87)	0·77
Time period * B mismatch	0·56 (0·13–2·46)	0·44
Time period * C mismatch	2·23 (1·22–4·08)	0·0094
Time period * DRB1 mismatch	1·40 (0·78–2·52)	0·26

Factors used for adjustment included donor sex, ABO major mismatch, ABO minor mismatch, cell dose, GVHD prophylaxis, and disease risk in analysis for engraftment, donor age, donor sex, female to male transplantation, cell dose, disease, and disease risk in analysis for GVHD, recipient age, donor age, donor sex, female to male transplantation, ABO major mismatch, disease, disease risk, and GVHD prophylaxis in analysis for non-relapse mortality, and donor age, disease, disease risk, and the use of TBI in analysis for relapse.

the effect of each single HLA allele mismatch. With regard to the study designs, the inclusion criteria for disease, phase of disease, and HLA matching were different among studies (Bray *et al*, 2008). Japanese studies included HLA-A, -B, and -DR antigen matched transplantation only, whereas the other studies included one-antigen mismatched transplantation. Earlier studies reported that an allele mismatch and an antigen mismatch had similar effects on mortality, although the risk of graft failure was higher with an antigen mismatch

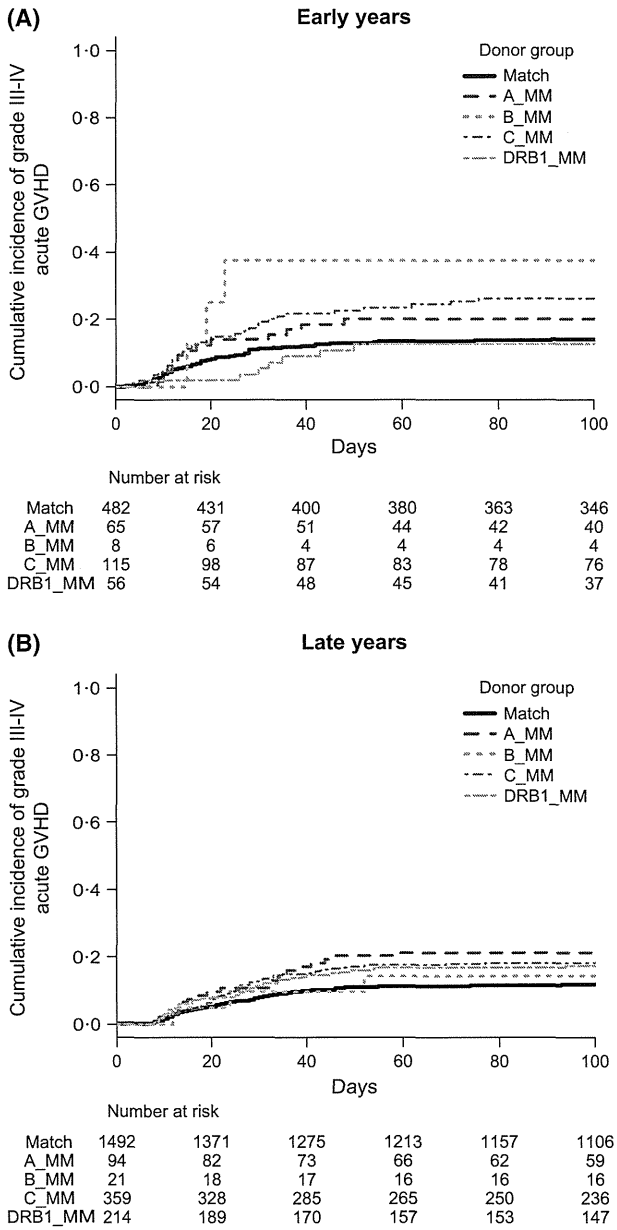

Fig 3. The cumulative incidence of grade III-IV acute graft-versus-host disease (GVHD) grouped according to the human leucocyte antigen mismatch between the donor and recipient in the (A) early (1993–1999) and (B) late (2000–2009) time periods.

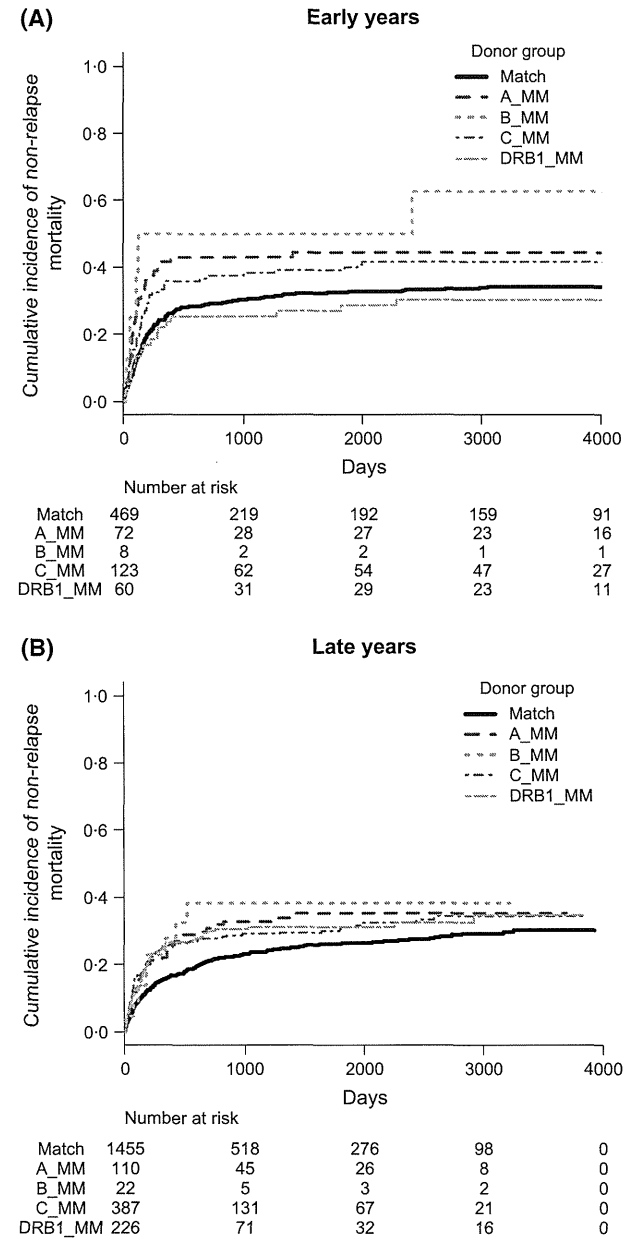

Fig 4. The cumulative incidence of non-relapse mortality grouped according to the human leucocyte antigen mismatch between the donor and recipient in the (A) early (1993–1999) and (B) late (2000–2009) time periods.

(Petersdorf *et al*, 2001, 2004). A subsequent report from NMDP confirmed that there was no significant difference in the effect on survival between a single antigen mismatch and a single allele mismatch (Lee *et al*, 2007). In the current study, only patients who underwent unrelated BMT from an HLA-A, -B, and -DR antigen matched donor were included, as such a donor can be found in more than 90% of patients in Japan. Therefore, only the HLA-C mismatch group included patients with HLA-mismatch at an antigen level. The effect of HLA-C antigen mismatch and HLA-C allele mismatch on survival was equivalent (HR 1·33 vs. 1·28) in the current cohort, although the number of patients with HLA-C allele mismatch was limited.

The second important finding is the positive interaction test that revealed the statistically significant change in the effects of HLA-C and -DRB1 mismatches from the early to the late time period. These significant interactions resulted from the fact that survival after HLA-matched BMT was significantly improved in the late time period, while there was no such improvement after HLA-C or -DRB1 mismatched

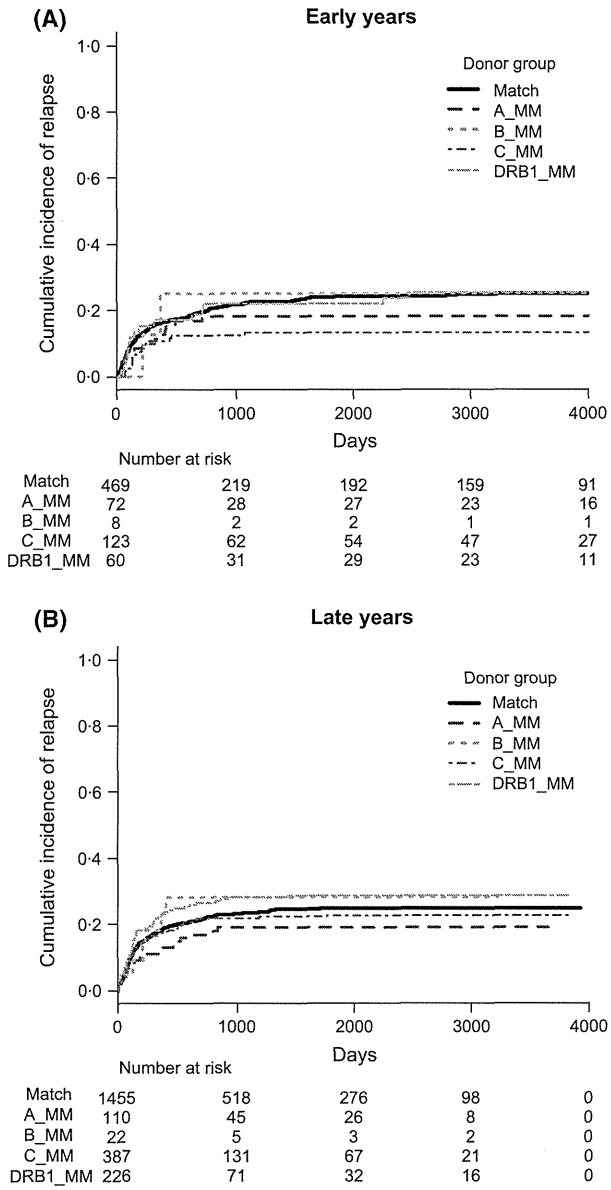

Fig 5. The cumulative incidence of relapse grouped according to the human leucocyte antigen mismatch between the donor and recipient in the (A) early (1993–1999) and (B) late (2000–2009) time periods.

BMT (Fig 2). The improvement in survival in the HLA match group is probably due to the progress in transplantation procedures, including strategies against GVHD and infectious complications. The incidence of grade III–IV acute GVHD in the HLA match group decreased from 13·9% to 11·9% over the two time periods, and furthermore, the incidence of transplant-related mortality among patients who developed grade III–IV acute GVHD decreased, from 25·4% to 15·9%. While such progress should also be reflected in the HLA-C and -DRB1 mismatch groups, other factors may have counterbalanced this benefit. With regard to HLA-DRB1 allele mismatch, significant interaction could be explained by the difference in the availability of information about HLA allele mismatch between the two time periods. In the 1990's, only the presence of an HLA-DRB1 allele mismatch was noted by physicians before BMT, whereas both HLA-A and -B mismatches were also tested before BMT in the 2000's. In addition, the landmark paper from the JMDP was published in 1998 (Sasazuki *et al*, 1998), and the presence of an HLA-A or -B mismatch was recognized as a risk factor for severe acute GVHD. These backgrounds might have induced a trend toward more intensive GVHD prophylaxis in patients with an HLA-DRB1 allele mismatch in the 1990's and in those with an HLA-A or -B mismatch in the 2000's. For example, in the early time period, TAC-based GVHD prophylaxis was most frequently used in the HLA-DRB1 mismatch group (odds ratios for the use of TAC were 0·65, 0·58, 0·97 and 1·29 for the HLA-A, -B, -C, and -DRB1 mismatch groups, respectively, compared to the HLA-matched group). On the other hand, in the late time period, TAC was used almost equally in the HLA-A, -B, and -DRB1 mismatch groups (odds ratios for the use of TAC were 1·49, 1·25, 1·00 and 1·38 for the HLA-A, -B, -C, and -DRB1 mismatch groups, respectively, compared to the HLA-matched group). The statistical interaction was significant even after an adjustment for the use of TAC, and therefore this is not the major reason for the interaction. The target blood concentrations of CSA or TAC and the dose of methotrexate in GVHD prophylaxis may also have been affected by the availability of information about HLA allele mismatch, but such data were not included in the database.

Another bias that may have been caused by the difference in the availability of information about the HLA allele mismatch is the trend to avoid HLA-mismatched BMT for patients with less advanced diseases, because the impact of HLA mismatch is generally more apparent in such diseases (Petersdorf *et al*, 2004; Lee *et al*, 2007; Kanda *et al*, 2003, 2012). In fact, the proportion of patients with low-risk disease in the HLA-DRB1 allele mismatch group was less than that in the other groups (57·1% vs. 62·7–75%) in the early time period, while equivalent proportions were seen in the late time period (62·1% vs. 56·5–65·6%). However, the HR value for HLA-DRB1 allele mismatch increased from 0·79 in the early period to 1·42 in the late period even when we only analysed patients with low-risk disease, although the interaction was not statistically significant ($P = 0·069$). The proportion of patients with a high-risk HLA allele mismatch may also affect the impact of each single HLA-allele mismatch on survival (Kawase *et al*, 2007), but the proportions were similar in the early and late time periods (6·3% and 7·3%). Therefore, this cannot explain the significant interaction between the time period and HLA-DRB1 allele mismatch.

With regard to the interaction between the time period and HLA-C allele mismatch, there was no difference in the availability of information, because HLA-C typing was not routinely performed until 2009. The significant interaction probably resulted from the increased incidence of relapse in the late time period in the HLA-C allele mismatched group.

The proportion of patients with a killer immunoglobulin-like receptor ligand mismatch in the graft-versus-host direction (KIR_L_MM_G) may affect the incidence of relapse (Dupont & Hsu, 2004; Morishima *et al*, 2007). However, the interaction test for relapse was significant even when we excluded patients with a KIR_L_MM_G mismatch ($P = 0{\cdot}022$). Therefore, we could not find a clear explanation for this interaction.

The major limitation of this study is the sample size in the HLA-B mismatch groups, especially in the early time period. Although the major object of this study was to reevaluate the impact of a mismatch in each single allele in the late time period, there were only 23 patients in the HLA-B mismatch group even in the late period, and therefore we could not conclude that the effects of all single HLA mismatches were equivalent, despite that there was no significant difference in the negative impact on survival among the HLA-A, -B, -C, and -DRB1 mismatches. Another limitation of this study was the exclusion of HLA-DQ mismatch in the analyses, as the allele data for HLA-DQ was available only in 493 of the 3003 patients in this study. However, when we included HLA-DQ in the multivariate analysis for overall survival, the effect of HLA-DQ mismatch on survival was not significant (HR 0·93, 95% CI 0·63–1·38, $P = 0{\cdot}73$) and the HRs for HLA-A, -B, -C, and -DRB1 did not obviously change after the addition of HLA-DQ in the model (data not shown).

In conclusion, this retrospective study revealed that the impact of single HLA allele mismatches might have changed after HLA-A and -B mismatch information became available to physicians before BMT. In the recent cohort (BMT between 2000 and 2009), the negative impact of HLA-C and -DRB1 mismatches became apparent. We should reconsider the algorithm for unrelated donor selection in Japan.

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Author contributions

Y.K. and Y.M. designed the study. Y.K., J.K., Y.A., and S.M. analysed the data. Y.M., T.I., K.O., T.F., K.M., H.I., T.M., K.I., T.E., and K.K. gathered the data. Y.K. wrote the first draft of the paper and all other authors contributed to the final version.

Disclosure of conflicts of interest

We declare that we have no conflicts of interest.

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Changes in the Clinical Impact of High-Risk Human Leukocyte Antigen Allele Mismatch Combinations on the Outcome of Unrelated Bone Marrow Transplantation

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A B S T R A C T

Several high-risk HLA allele mismatch combinations (HR-MMs) for severe acute graft-versus-host disease (GVHD) have been identified by analyzing transplantation outcomes in Japanese unrelated hematopoietic stem cell transplant recipients. In this study, we analyzed the effects of HR-MMs in 3 transplantation time periods. We confirmed that the incidence of grade III to IV acute GVHD in the HR-MM group was significantly higher than that in the low-risk (LR) MM group (hazard ratio [HR], 2.74; $P < .0001$) in the early time period (1993 to 2001). However, the difference in the incidence of grade III to IV acute GVHD between the HR-MM and LR-MM groups was not statistically significant (HR, 1.06; $P = .85$ and HR, .40; $P = .21$, respectively) in the mid (2002 to 2007) and late (2008 to 2011) time periods. Similarly, survival in the HR-MM group was significantly inferior to that in the LR-MM group (HR, 1.46; $P = .019$) in the early time period, whereas the difference in survival between the 2 groups was not statistically significant in the mid and late time periods (HR, 1.06; $P = .75$ and HR, .82; $P = .58$, respectively). In conclusion, the adverse impact of HR-MM has become less significant over time. Unrelated transplantation with a single HR-MM could be a viable option in the absence of a matched unrelated donor or an unrelated donor with a single LR-MM.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) from an unrelated donor has been established as an effective treatment option for patients with hematological diseases who lack a human leukocyte antigen (HLA)–matched related donor. However, an HLA mismatch at the genetic level (allele mismatch) may be observed even in HSCT from a serologically HLA-matched donor (antigen match), and the presence of an allele mismatch adversely affects the incidence of severe acute graft-versus-host disease (GVHD) and survival [1-4]. We recently showed that the presence of single HLA allele mismatches at the HLA-A, -B, -C, or -DRB1 loci equivalently affect the outcome of HSCT, although a previous study from Japan reported that an HLA-A or -B allele mismatch impairs overall survival more strongly than an HLA-C or -DRB1 allele mismatch [4,5]. These findings suggest that the

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Table 1
Patient Characteristics

Characteristic	Match n = 2504			Low-Risk Mismatch n = 1057			High-Risk Mismatch n = 157		
	Early	Mid	Late	Early	Mid	Late	Early	Mid	Late
	802	814	888	412	351	294	64	71	22
Age (recipient)									
Median	32	38	43	31	38	43	33	39	41
Age (donor)									
Median	34	34	36	33	34	37	35	36	37
Sex (recipient)									
Female	292	305	378	162	165	123	27	27	9
Male	510	509	510	250	186	171	37	44	13
Sex (donor)									
Female	286	262	266	164	158	107	20	28	5
Male	512	548	622	247	190	187	43	43	17
N.A.	4	4	0	1	3	0	1	0	0
Sex mismatch									
Match	507	537	512	238	209	166	35	40	14
Male to female	148	158	244	85	72	72	17	15	6
Female to male	143	115	132	88	67	56	11	16	2
N.A.	4	4	0	1	3	0	1	0	0
ABO blood type									
Match	454	462	500	167	151	121	33	31	9
Minor mismatch	154	162	175	112	84	81	15	18	3
Major mismatch	125	114	142	82	67	61	9	18	4
Bidirectional mismatch	58	70	71	45	46	31	7	4	6
N.A.	11	6	0	6	3	0	0	0	0
Disease									
AML	269	415	495	134	168	170	15	29	12
ALL	229	229	249	116	96	76	11	23	8
CML	237	84	29	125	42	14	30	3	0
MDS	67	86	115	37	45	34	8	16	2
Disease risk									
Low	552	533	607	265	219	181	40	38	12
High	230	239	280	135	116	113	21	28	10
Others	20	42	1	12	16	0	3	5	0
Cell dose (cells/kg)									
Median	3.0	2.7	2.7	3.0	2.6	2.6	3.1	2.8	2.6
GVHD prophylaxis									
CSA-based	545	306	185	267	114	47	45	21	2
TAC-based	240	499	689	135	227	240	19	50	20
N.A.	17	9	14	10	10	7	0	0	0
Conditioning regimen									
TBI regimen	760	639	560	394	272	194	59	53	15
Non-TBI regimen	30	114	328	17	52	100	3	11	7
N.A.	12	61	0	1	27	0	2	7	0

N.A. indicates not available; AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; GVHD, graft-versus-host disease; CSA, cyclosporine; TAC, tacrolimus; TBI, total body irradiation.

clinical impact of an HLA mismatch may have changed over time periods.

Some investigators have tried to identify specific donor-recipient allele combinations that may be associated with a higher risk of severe acute GVHD [6,7]. Kawase et al. found 16 high-risk HLA allele mismatch combinations (HR-MMs) for severe acute GVHD [7]. They also showed that the number of HR-MMs was associated with severe GVHD and poor survival, whereas the presence of mismatch combinations other than HR-MMs (low-risk mismatch combinations, LR-MMs) did not affect the outcome of HSCT. However, their study included a variety of benign and malignant hematological diseases. In addition, they included donor-recipient pairs with more than 1 HLA mismatch. The impact of each specific mismatch combination was evaluated after adjusting for the number of HLA mismatches in other loci in a multivariate model, but the possible presence of HR-MMs in other loci or the interaction between HLA mismatch combinations could not be appropriately treated in their model. At that time, the study design was inevitable, because the number of each HLA mismatch combination was limited. However, several years have passed and the amount of unrelated HSCT data in the Transplant Registry Unified Management Program (TRUMP) has increased to more than 13,500 donor-recipient pairs. Therefore, in this study, we reanalyzed the impact of HR-MMs, excluding HSCT with multiple HLA mismatches in patients with relatively homogeneous background diseases. In addition, we evaluated the impact of HLA mismatch on transplantation outcomes considering the period effect, because the impact of HR-MM mismatch might have changed over time periods, as we previously reported in an analysis of single HLA allele mismatches at the HLA-A, -B, -C, and -DRB1 loci [5].

METHODS

Patients

Patients aged at least 16 years with acute myeloblastic leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia (CML) who underwent a first HSCT from a serologically HLA-A, -B, and -DR matched unrelated donors between 1993 and 2011, and who had full HLA-A, -B, -C, and -DRB1 allele data, were included in this study. Bone marrow was exclusively used as a stem cell source. Clinical data for