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The Effect of NIMA Matching in Adult Unrelated Mismatched Hematopoietic Stem Cell Transplantation – A Joint Study of the Acute Leukemia Working Party of the EBMT and the CIBMTR.

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Abstract

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Hematological malignancies can be cured by unrelated donor allogeneic HSCT and outcomes are optimized by high resolution HLA matching at HLA-A, -B, -C, -DRB1 and -DQB1 (10/10 match). If a 10/10 match is unavailable, 9/10 matches may be suitable. Fetal exposure to non-inherited maternal antigens (NIMA) may impart lifelong NIMA tolerance modulating the immune response, as shown in adult haploidentical transplantation. In cord blood transplantation, NIMA matching lowered rates of aGvHD and TRM; in haploidentical transplantation, sibling donors with non-shared maternal antigens showed less grade II-IV aGvHD. This retrospective analysis examined if 9/10 matched unrelated donor HSCT benefits from NIMA matching. DKMS contacted 1,735 donors and obtained 733 (42%) maternal samples. NIMA-matched and -mismatched cases with a minimum follow-up of one year were compared by univariate and multivariate analyses adjusted for co-variables for OS, DFS, relapse, TRM and a/cGvHD. The study population (N=445) comprised 31 NIMA-matched and 414 NIMA-mismatched cases. No significant differences between NIMA-matched and -mismatched groups were found for any outcomes with similar OS and TRM rates within both groups. This study provides the proof of principle that NIMA matching is possible in the unrelated donor HSCT setting; larger studies may be able to provide significant results.

Keywords

Non-Inherited Maternal Antigen (NIMA); unrelated HSCT; Donor Selection

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) offers a potential curative therapy for a variety of hematological malignancies and other diseases of the blood. Matching of human leukocyte antigen (HLA) genes is critical for optimizing transplant outcomes, including survival^[1–3]. However, only about 30% of transplant patients have an HLA-identical sibling donor, leaving 70% in need of an alternative source of stem cells from an unrelated donor, a haploidentical donor or a cord blood unit^[4, 5]. If a fully HLA-A, -B, -C, -DRB1 and -DQB1 (10/10) matched unrelated donor is unavailable, 9/10 matched donors may be an acceptable alternative and can be found at high frequency in stem cell donor registries^[5]. High- and low-risk HLA allele mismatches for severe graft-versus-host disease (GvHD) have been described^[6]. However, the prioritization and identification of permissive or acceptable HLA mismatches in the mismatched setting have proven elusive for HLA-A, -B, -C, -DRB1 and -DQB1^[7–9].

During pregnancy, the fetus and mother gain tolerance to each other's alloantigens^[10]. It has been shown that exposure to non-inherited maternal antigens (NIMAs) during *in utero* development or even only during breastfeeding can impart lifelong immunomodulating effects and long-lasting tolerance against specific NIMAs - the so called NIMA effect^[7, 10, 11]. In mismatched unrelated HSCT, if the recipient and the donor's mother share the NIMA for the mismatched HLA locus, the case is considered a NIMA match. However, the existence of this NIMA effect, especially for the outcome of adult unrelated allogeneic HSCT, is still under scientific debate^[12, 13].

Prior solid organ transplantation studies revealed tolerance to NIMAs suggesting that the patient's immune system does not recognize these antigens as foreign. Although maternal kidney allografts did not show a better survival compared to paternal ones^[12], another study on kidney grafts showed a superior 5- and 10-year post-transplantation survival when donated by haploidentical siblings with a matched paternal haplotype and differing maternal haplotype compared to haploidentical siblings sharing the maternal haplotype and not the paternal one^[14]. This result was consistent with a study showing that kidney transplants with a mismatched HLA-A antigen identical to the patient's NIMA had superior long-term graft survival^[15]. In umbilical cord blood transplantation (UCBT), transplant-related mortality (TRM) at 5 years post transplantation was reduced after NIMA-matched compared to NIMA-mismatched transplantation, 18% versus 32%, respectively^[16]. Overall survival (OS) was also increased after NIMA-matched UCBT^[16]. An analysis by van Rood et al. found that NIMA matches in UCBT between a recipient and an unrelated donor in HLA-A, -B or -DRB1 resulted in reduced TRM, overall mortality and treatment failure and was attributed to a faster neutrophil recovery^[7]. In contrast, another report showed no association between NIMA-matched UCBTs and TRM or overall mortality^[17]. For HSCT, comparing durable engraftment with organ allograft survival, it could be expected that there should be less GvHD and consequently superior transplantation success if the mismatched donor is NIMA-matched to the patient. In studies of non-T-cell-depleted HSCT with HLA-haploidentical donors risk for acute GvHD (aGvHD) grade II-IV was reduced when the sibling donor shared the paternal haplotype but not the maternal one, as found before in kidney transplantation^[18, 19]. However, van Rood et al. showed that haploidentical sibling transplantation with no shared maternal antigens had similar graft failure rates and survival, while TRM was reduced for sibling donors compared to parental donors^[18].

Because of the general unavailability of maternal HLA typing, no studies to date have analyzed the NIMA effect in the unrelated adult donor HSCT setting. This joint European Society for Blood and Marrow Transplantation (EBMT)-Center for International Blood and Marrow Transplant Research (CIBMTR) retrospective study was specifically designed to study the effect of NIMAs on the outcome of adult unrelated mismatched HSCT. A verification of the benefit in outcome by NIMA matching could have a considerable impact on donor search and selection by routinely requesting a maternal sample during confirmatory typing and using NIMA matching as a criterion for mismatched donor selection.

MATERIALS AND METHODS

Study Population

Patients eligible for this study received a T-cell-replete mismatched unrelated bone marrow or peripheral blood stem cell transplant for acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) between 1999 and 2013. Further eligibility criteria were the following: (1) all donors were listed with the German donor center DKMS; (2) recipient-donor pairs' outcome data were recorded with a minimum one year follow-up at the EBMT or the CIBMTR; (3) recipient-donor pairs had exactly one HLA mismatch at HLA-A, -B, -C, -DRB1 or -DQB1; (4) DNA sample from donor's mother could be obtained for high-

resolution HLA typing of the mismatched locus. Recipient-donor pairs fulfilling the inclusion criteria were selected from EBMT and CIBMTR databases. Cases where the patient received a second HSCT were censored at the time of second transplantation. Information about the donor mother's HLA typing results were not available at the start of the study. The institutional review board of the Technische Universität Dresden (IRB00001473) approved the study design that included contacting the donor's mother. For maternal DNA sample retrieval, DKMS prepared a sendout package to the donors containing study information material, an informed consent form and a buccal swab kit for sample collection to be sent on to the donors' mothers.

HLA typing and match assignment

DNA samples of donors and donors' mothers were HLA-typed at high resolution for the 5 loci HLA-A, -B, -C, -DRB1 and -DQB1 at DKMS Life Science Lab, Dresden, Germany, using sequencing-based methods. European recipients were HLA-typed by the respective Transplant Center's partner laboratory. U.S. recipients and their respective DKMS donors were HLA-typed at high resolution through the CIBMTR retrospective typing program using stored samples from the CIBMTR Research Repository as previously described^[20]. Recipient-donor pairs had exactly one mismatch resulting in 9/10 matching. HLA information of all available recipient-donor-mother triplets was analyzed at the specific mismatched locus to identify NIMA-matched and -mismatched cases. A NIMA match was found when recipient and donor's mother shared the same allele for the specific allele and locus where the donor did not match the recipient. These cases were assigned to the NIMA-matched group, all other cases without NIMA match were assigned to the NIMA-mismatched group.

Outcomes

The study considered overall survival (OS) as primary end point, and disease-free survival (DFS), relapse, transplant-related mortality (TRM), aGvHD and cGvHD as secondary end points. Outcomes were defined as follows: TRM: death without evidence of disease recurrence, DFS: time to death or relapse, OS: time to death from any cause. Incidence of III-IV aGvHD was evaluated in patients surviving 100 days with evidence of engraftment, incidence of cGvHD in recipients surviving 1 year after transplantation with engraftment.

Statistical Analysis

For discrete variables, the number of cases and their respective percentages were calculated. χ^2 tests or Fisher's exact tests compared discrete variables between NIMA-matched and -mismatched groups. For continuous variables, median and ranges were calculated, and the variables were compared between the NIMA-matched and -mismatched groups using the non-parametric Kruskal-Wallis test. Probabilities for OS, DFS or treatment failure were calculated using the Kaplan-Meier estimator with variances estimated by Greenwood's formula. Values for other outcomes were calculated according to cumulative incidences using a Taylor series linear approximation to estimate the variances. Multivariable analysis was performed using Cox proportional hazards models adjusting for significant co-variables for OS, DFS, relapse, TRM and aGvHD or cGvHD comparing NIMA-matched to -mismatched groups. All clinical variables were tested for affirmation of the proportional

hazards assumption. Factors violating the proportional hazards assumption were adjusted through stratification. Then stepwise forward-backward procedures were performed to select adjusted clinical variables with a significance threshold of $p < 0.05$ for retaining in the multivariable models. Interaction between the main testing variable (i.e., NIMA-matched versus -mismatched) and the adjusted co-variables were tested, and no significant interaction was detected. A significance threshold of $p < 0.01$ was used for the main comparison of NIMA-matched versus -mismatched to adjust for multiple testing. All p-values are 2-sided. Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study population

Characteristics of patients and donors are listed in Tables 1a and 1b, respectively. A total of 1735 donors were contacted with 733 maternal samples collected. 50 NIMA matches were found reflecting the rate of 7% expected from previous studies^[7]. To meet inclusion criteria, 126 cases were removed for incomplete follow-up and outcome reporting. To minimize heterogeneity, the population was further restricted to HCT for acute leukemia due to the very low frequency of NIMA matches in Non-Hodgkin lymphoma, chronic myelogenous leukemia and myelodysplastic syndrome groups (102 cases excluded: 12 CML, 34 MDS, 32 NHL and 24 other leukemia with in total < 5 NIMA matches). Further, only 9/10 mismatches were considered as other cases were rare (60 cases excluded). The final analysis population consisted of 445 9/10 matched cases with a single mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 transplanted for AML (N=301, 68%) or ALL (N=144, 32%), with the majority receiving myeloablative conditioning regimens (N=304, 68%) between 1999 and 2013. Thereof, 157 cases were recorded in the CIBMTR database and 288 at the EBMT. Within the final population, 31 NIMA-matched (7%) and 414 NIMA-mismatched (93%) cases were studied further. The NIMA-matched and -mismatched groups were well-balanced for disease, patient and donor characteristics (Table 1). The average age of patients was 45 and 43 years with 48% and 56% male participants for NIMA-matched and mismatched-groups, respectively (Table 1a). The only significant difference between NIMA-matched and -mismatched groups was found in the mismatched HLA loci with more HLA-C mismatches (65% vs. 34%) and less HLA-A mismatches (13% vs. 30%) in the NIMA-matched group (Table 1b).

Univariate and multivariate outcomes

Unadjusted probabilities of the study end points OS, DFS, relapse, TRM, aGvHD and cGvHD are given in Table 2 for the NIMA-matched and -mismatched groups. No significant differences were observed for any of the analyzed outcomes. Multivariate models of OS, DFS, relapse, TRM and GvHD adjusted for co-variables are shown in Table 3. The cumulative incidences of OS, DFS, relapse and TRM for NIMA-matched and -mismatched groups through 5 years post HSCT are shown in Figure 1. The cumulative incidence of aGvHD through 100 days and cGvHD through 2 years post HSCT are shown in Figure 2. No significant associations of NIMA matching were observed in these multivariate analyses for any outcome. TRM rates were similar between the groups at 1 year with 24% (95% CI: 11–41%) and 23% (95% CI: 19–28%) in NIMA-matched and -mismatched groups,

respectively (Table 2). At 3 and 5 years after transplant, TRM was not significantly different between NIMA-matched and -mismatched groups (Table 2 and Figure 1d). In multivariate analysis, a hazard ratio (HR) of 0.79 was observed for TRM compared to the NIMA-mismatched group (Table 3). A HR of 0.61 was found for aGvHD III-IV compared to the NIMA-mismatched group and showed same directionality in the univariate analysis. After 1 and 2 years, cGvHD was elevated in the NIMA-matched compared to NIMA-mismatched group with an HR of 1.75 (Table 3), but did not reach the threshold for statistical significance study with $p=0.058$.

Antigen frequency and NIMA matching

HLA typing results were analyzed for the mismatched loci (see Table 4). The resulting NIMA mismatch frequencies within loci HLA-A, -B, -C, -DRB1 and -DQB1 were 13%, 6%, 65%, 0% and 16%, respectively. The most frequent NIMA match ($N=6$; 19%) was found at HLA-C*07:01g, followed by HLA-C*03:04g and HLA-DQB1*03:01g ($N=3$, 10% each)^[21]. Interestingly, these are not the most common HLA alleles in the European Caucasian population being contrarily located on HLA-A locus and represented by HLA-A*02:01 and HLA-A*01:01 with a frequency of 28.5% and 15.7%, respectively^[21]. HLA-C*07:01 accounts for the most frequent allele within HLA-C locus with a frequency of 15.2% in the European Caucasian population, however HLA-C*03:04 accounts only for a frequency of 8.4%^[21]. HLA-A*02:01 was found in only two cases (6%), and HLA-A*01:01 in one case of NIMA match (3%). Patient's mismatched alleles are more often rare as these are difficult to match. However, it is more likely to find the patient's mismatched allele on the non-inherited maternal haplotype if this mismatched allele is frequent in the donor's and his mother's ethnic background.

DISCUSSION

The primary objective of this study was to assess the influence of NIMA matching on transplantation outcomes in adult unrelated donor HSCT. Previous studies on the NIMA effect indicate that NIMA exposure results in a lifelong immunomodulating influence leading to antigen tolerance against maternal antigens later in life^[18]. A beneficial influence of a NIMA effect on transplantation outcome parameters like graft failure, TRM, OS and GvHD was seen in organ transplantations, UCBTs and haploidentical HSCTs (Table 5). This provides theoretical evidence that HLA-mismatched transplants from unrelated donors that are NIMA-matched to the recipient could also result in superior transplant outcomes. Our study was designed to address this gap in knowledge whether these same principles apply to adult unrelated donors.

As previous studies revealed NIMA effects in unrelated UCBT as well as in related HSCT for adult patients, we anticipated finding similar results for unrelated adult HSCT (Table 5). However, in this study no significant associations between NIMA matching status and OS, DFS, TRM, relapse, aGvHD or cGvHD were found. aGvHD III-IV rates compared to NIMA mismatches were lower, but not significantly different in this study. Prior studies of NIMA matching have reported lower rates of aGvHD and cGvHD when a haploidentical sibling donor was used^[18, 19].

From a biological perspective, as the tolerance towards NIMA has been demonstrated in haploidentical transplantations, we would have expected the tolerance to persist into the adult life of a donor. However, contrarily to haploidentical transplantation, we here evaluate cases with a single HLA mismatch and one NIMA match instead of NIMA matching of one haplotype. In cord blood studies, NIMA matching has been shown to be beneficial, however, considering that these studies analyzed cases matched 5/6 or 4/6 with HLA-A and -B in low resolution and only HLA-DRB1 in high resolution, the NIMA effect might well be outweighed by higher degree of matching as for example shown by Eapen et al. reporting a benefit of HLA-A, -B, -C, -DRB1 matching in cord blood transplantation^[22].

Our inability to detect statistically significant differences in HSCT outcome between NIMA-matched and -mismatched groups may also be explained by the small sample size. A post-hoc sample size analysis suggested a required sample size of 1,804 donor-recipient pairs - including 90 NIMA matches (~5%). The major limitations of this study were the difficulty to retrieve maternal samples retrospectively, identification of DKMS donors and missing outcome data in the two databases and potentially a differing effect size in adult unrelated donors compared to TRM rates in UCBT that we used for sample size estimation. Nevertheless, we proceeded with the available population as it was not feasible to recruit additional cases and as the results could be relevant for prioritization of prospective or larger cohort studies.

In this study, NIMA matches were identified after transplantation and therefore NIMA matching was not used in donor selection. As a consequence of such a retrospective analysis, our number of NIMA matches was low - as it was also in several previous studies - because NIMA cases only occurred by chance^[7, 17]. Prospective evaluations could identify a higher percentage of NIMA matches by targeted selection of 9/10 matching donors with mismatched alleles of high frequency in their ethnic group. However, our study shows the difficulty and time needed to retrieve HLA information from a donor's mother and for this kind of donor selection, more donors (and their mothers) would have to be selected for verification typing. This process would add time and cost to the process that may not be available to searching patients. In addition, even if there was a relevant NIMA effect in unrelated donor transplantation, the benefit might be outweighed by the detrimental effects of disease progression during a prolonged donor search^[3, 23]. Also, recent studies evaluating the impact of multiple factors such as CMV serostatus match, age, gender match, race match, ABO match, donor's prior pregnancies revealed donor (young) age as the only significant factor beyond HLA matching that consistently impacts survival^[24].

In conclusion, earlier reports suggest that NIMA matching in HSCT may improve outcomes, especially regarding reduced TRM and aGvHD III-IV. With this study, we could not reproduce these findings in unrelated donor HSCT. Whether NIMA matching can be used to improve the outcome of adult unrelated HSCT remains unclear and might be difficult to address in future studies in the unrelated HSCT setting as shown by our proof of principle study.

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Figure 1a
Overall Survival

Figure 1b
Disease-Free Survival

Figure 1c
Relapse

Figure 1d Transplant Related Mortality

Figure 1: Probability of different outcome parameters in % within 5 years in 9/10 mismatched adult unrelated HSCT with or without NIMA matching.

(A) Overall survival (OS). 5-year probabilities: 39 or 40% after NIMA-matched or -mismatched transplantation. (B) Disease-free survival (DFS). 5-year probabilities: 40 or 34% after NIMA-matched or -mismatched transplantation. (C) Relapse. 5-year probabilities: 36 or 33% after NIMA-matched or -mismatched transplantation. (D) Transplant-related mortality (TRM). 5-year probabilities: 24 or 32% after NIMA-matched or -mismatched transplantation. Shown are NIMA-matched (continuous line) and NIMA-mismatched (dotted line) cases.

Figure 2a
Acute GvHD III-IV

Figure 2b Chronic GvHD

Figure 2: Probability of graft-versus-host disease (GvHD) in % in 9/10 mismatched adult unrelated HSCT with or without NIMA matching.
(A) Probability of acute GvHD grade III-IV within 100 days. **(B)** Probability of chronic GvHD in % within 2 years. Shown are NIMA-matched (continuous) and NIMA-mismatched (dotted line) cases.

Table 1:

Demographics of study population. (a) recipients' demographics, (b) donor and recipient demographics comparing NIMA matched and NIMA mismatched groups.

Patients' demographics	9/10 NIMA Matched N (%)	9/10 NIMA Mismatched N (%)	p-value
Number of patients	31	414	
Recipient age, median (range), years	45 (16–69)	43 (<1–74)	0.27
0–9	0	22 (5)	0.47
10–19	1 (3)	41 (10)	
20–29	5 (16)	55 (15)	
30–39	3 (10)	60 (15)	
40–49	10 (32)	68 (17)	
50–59	7 (23)	87 (21)	
60 years	5 (16)	73 (17)	
Recipient sex - male	15 (48)	232 (56)	0.41
Conditioning regimen			0.06
Myeloablative	27 (87)	277 (67)	
RIC / NMA	3 (10)	92 (22)	
Missing / other drugs used	1 (3)	45 (11)	
Disease at transplant			0.70
AML	20 (65)	281 (68)	
ALL	11 (35)	133 (32)	
Disease status at transplant			0.41
Early	4 (13)	101 (24)	
Intermediate	19 (61)	197 (48)	
Advanced / late	6 (19)	92 (22)	
Not otherwise specified	2 (6)	24 (6)	
Karnofsky score			0.48
80	26 (84)	358 (86)	
< 80	4 (13)	31 (7)	
Unknown / missing	1 (3)	25 (6)	
GvHD prophylaxis			0.47
CD34 selections	0	1 (<1)	
Cyclophosphamide	0	1 (<1)	
TACROLIMUS + MMF ± others	1 (3)	41 (11)	
TACROLIMUS + MTX ± others	2 (6)	81 (21)	
TACROLIMUS + others	1 (3)	10 (3)	
TACROLIMUS alone	1 (3)	6 (2)	
CSA + MMF ± others	6 (19)	71 (18)	
CSA + MTX ± others	18 (58)	139 (36)	
CSA + others	0	2 (1)	
CSA alone	2 (6)	26 (7)	
Others	0	7 (2)	

Patients' demographics	9/10 NIMA Matched N (%)	9/10 NIMA Mismatched N (%)	p-value
Missing	0	29	
Recipient CMV antibodies			0.31
Negative	12 (39)	161 (39)	
Positive	15 (48)	228 (55)	
Other / missing / unknown	4 (13)	25 (6)	
Use of ATG/Campath			0.25
No	128 (31)	8 (26)	
Yes	193 (47)	19 (61)	
Missing/Unknown	93 (22)	4 (13)	
Median follow-up of survivors, months (range)	40 (5–105)	37 (<1–141)	0.89

Donors' and transplants' demographics	9/10 NIMA Matched N (%)	9/10 NIMA Mismatched N (%)	p-value
Number of donors	31	414	
Donor sex - Male	18 (58)	263 (64)	0.54
Donor age, median (range), years	31 (19–48)	31 (18–59)	0.26
18–32	15 (48)	229 (55)	0.34
33–49	16 (52)	173 (42)	
50	0	12 (3)	
Donor / recipient sex			0.81
Male / male	10 (32)	162 (39)	
Male / female	8 (26)	101 (24)	
Female / male	5 (16)	70 (17)	
Female / female	8 (26)	81 (20)	
Graft type (stem cell source)			0.54
Bone marrow	5 (16)	87 (21)	
PBSC	26 (84)	327 (79)	
HLA mismatching by locus			0.01
HLA-A	4 (13)	123 (30)	
HLA-B	2 (6)	57 (14)	
HLA-C	20 (65)	143 (34)	
HLA-DRB1	0 (0)	30 (7)	
HLA-DQB1	5 (16)	61 (15)	
Year of transplant			0.98
1999	0	1 (<1)	
2000	0	2 (<1)	
2001	0	4 (1)	
2002	0	4 (1)	
2003	1 (3)	6 (1)	
2004	0	10 (2)	
2005	3 (10)	19 (5)	
2006	3 (10)	35 (8)	

Donors' and transplants' demographics	9/10 NIMA Matched N (%)	9/10 NIMA Mismatched N (%)	p-value
2007	4 (13)	56 (14)	
2008	4 (13)	65 (16)	
2009	4 (13)	81 (20)	
2010	8 (26)	82 (20)	
2011	3 (10)	33 (8)	
2012	1 (3)	15 (4)	
2013	0	1 (<1)	

Log-rank p-value.

Table 2:

Probabilities in % of OS, DFS, relapse, TRM and acute or chronic GvHD for NIMA-matched and NIMA-mismatched groups.

Outcome	9/10 NIMA matched	9/10 NIMA mismatched	p-value
	Prob (95% CI)	Prob (95% CI)	
Overall Survival	N = 31	N = 414	0.87 ^a
1 year	57 (39–74)	58 (53–63)	0.87
3 years	49 (31–67)	44 (39–49)	0.64
5 years	39 (18–62)	40 (34–45)	0.94
Disease-Free Survival	N = 30	N = 410	0.61 ^a
1 year	56 (37–73)	55 (50–59)	0.92
3 years	47 (29–66)	41 (36–46)	0.55
5 years	40 (21–61)	34 (29–40)	0.58
Relapse	N = 30	N = 410	
1 year	20 (8–37)	22 (18–26)	0.83
3 years	29 (14–47)	29 (25–34)	0.96
5 years	36 (18–56)	33 (28–39)	0.83
TRM	N = 30	N = 410	
1 year	24 (11–41)	23 (19–28)	0.94
3 years	24 (11–41)	30 (25–34)	0.51
5 years	24 (11–41)	32 (27–38)	0.33
aGvHD III-IV	N = 30	N = 400	
100 days	10 (2–23)	21 (17–25)	0.07
cGvHD	N = 26	N = 354	
1 year	50 (31–69)	38 (32–43)	0.23
2 years	50 (31–69)	43 (37–48)	0.47

Prob = Probability (%); CI = Confidence interval

^aLog-rank p-value

Table 3:

Multivariate analysis of hazard ratio (HR) of study endpoints in NIMA-matched HSCT cases versus NIMA-mismatched reference.

Outcome	HR	95% CI	p-value
OS	0.97	0.58–1.60	0.89
DFS	0.88	0.54–1.48	0.66
TRM	0.79	0.37–1.69	0.54
Relapse	0.93	0.47–1.86	0.84
aGvHD III-IV	0.61	0.19–1.96	0.41
cGvHD	1.75	0.98–3.13	0.058

Table 4:

Mismatched HLA loci in 9/10 NIMA matched (N=31) and NIMA mismatched cases (N = 414).

Mismatch locus	9/10 total N (%)	9/10 NIMA matched N (%)	9/10 NIMA mismatched N (%)
HLA-A	127 (28)	4 (13)	123 (30)
HLA-B	59 (13)	2 (6)	57 (14)
HLA-C	163 (37)	20 (65)	143 (34)
HLA-DRB1	30 (7)	0 (0)	30 (7)
HLA-DQB1	66 (15)	5 (16)	61 (15)
Total	445	31	414

Table 5:

Overview of NIMA effect on transplantation outcome parameters OS, TRM, graft survival, aGvHD and cGvHD in UCBT, haploidentical sibling HSCT and related kidney transplantation.

Type of transplant	UCBT	Haploidentical sibling HSCT	Related kidney transplantation
OS	↑ van Rood et al. 2009, Rocha et al. 2012 ↔ van Rood et al. 2012		↑ Burlingham et al. 1998
TRM	↓ van Rood et al. 2009, Rocha et al. 2012 ↔ van Rood et al. 2012	↓ van Rood et al. 2002	
Graft survival			↑ Burlingham et al. 1998, Smits et al. 1998 ↓ Opelz 1990
aGvHD		↓ Ichinohe et al. 2004 ↓ van Rood et al. 2002	
cGvHD		↓ van Rood et al. 2002	