The impact of recipient HLA-Cw and donor killer immunoglobulin-like receptor genotyping on the outcome of patients receiving HLA-matched sibling donor haematopoietic stem cell transplantation for myeloid malignancies

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Summary

BACKGROUND: The alloreactivity of natural killer cell and certain subsets of T lymphocyte are regulated by the interaction between killer immunoglobulin-like receptors (KIRs) of donor cells and human leukocyte antigen (HLA)-class I molecules on target cells. The interaction has been shown to influence the outcome of allogeneic haematopoietic stem cell transplantation (HSCT). Homozygous C1 or C2 and heterozygous C1/C2 were divided by HLA-Cw typing and they influenced the outcome of HSCT.

OBJECTIVE: The purpose of the study was to analyse the impact of interaction between recipient HLA-Cw and donor KIR on outcome.

METHODS: The genotypes of recipient HLA-Cw ligands and donor KIRs were correlated with the clinical outcomes of 52 patients who received HLA-matched, sibling donor HSCT for myeloid malignancies.

RESULTS: The incidence of chronic graft versus disease (GVHD) was significantly lower in C1 or C2 homozygotes than in C1/C2 heterozygotes (p = 0.000). Higher overall survival (OS) and disease-free survival (DFS) rates were observed in C1 or C2 homozygotes than in C1/C2 heterozygotes (OS, 81% ± 8% vs 54% ± 10%, p = 0.034; DFS, 81% ± 8% vs 54% ± 10%, p = 0.024). A lower incidence of chronic GVHD and higher OS and DFS were observed in the HLA-KIR mismatched group (chronic GVHD, p = 0.007; OS, 84% ± 7% vs 47% ± 13%, p = 0.003; DFS, 84% ± 7% vs 47% ± 13%, p = 0.002).

CONCLUSION: The interaction between recipient HLA ligand and donor KIR had a significant impact on the outcome of patients receiving matched sibling HSCT. C1/C2 heterozygotes or HLA-KIR matched patients may benefit from additional intensified therapy with better outcome.

Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is a possible treatment for many patients with haematological malignancies. The alloreactivity of NK cells and certain subsets of T lymphocytes is regulated by the interaction between killer immunoglobulin-like receptors (KIRs) of donor cells and human leukocyte antigen (HLA)-class I molecules on the target recipient cells. HLA-Cw is the main ligand for most inhibitory KIRs and can be classified into two subgroups, C1 and C2, which bind to KIR2DL2/3 and KIR2DL1, respectively [1]. Other human inhibitory KIRs with known ligands include KIR3DL1, which binds to the HLA-Bw4 epitope [2] and KIR3DL2, which binds to HLA-A3 or HLA-A11 [3]. Previous studies showed that HLA-KIR interactions have a significant impact on the outcomes of haploidentical [4–10], unrelated donor [11–13] and matched related donor (MRD) [14–17] HSCT, including relapse, graft versus host disease (GVHD) and transplant-related mortality (TRM). Other studies revealed that alloreactivity in the HSCT had a confounding effect for which there are many explanations and hypotheses whilst the underlying mechanism remains to be elucidated.

The aim of the study was to assess the impact of interaction between recipient HLA-Cw and donor KIR on patient outcome. Recipient HLA ligands and donor KIRs were genotyped for 52 allogeneic HSCT patients.

Patients and methods

Patients and clinical data

From January 2006 to December 2007, 52 patients with myeloid malignancies underwent HLA-matched, sibling donor HSCT at the Institute of Haematology and Blood Diseases Hospital, CAMS and PUMC. The median duration of follow-up was 500.5 (range, 45–965) days. The median age of the patients was 38 (range, 14–55) years and that of donors was 36 (range, 9–52) years. Of the recipients, 18 were females and 34 were males; of the donors, 22 were females and 30 were males. There were 20 acute myeloid leukaemia (AML) cases, 31 chronic myeloid leukaemia (CML) cases, and one myelodysplastic syndrome (MDS) case. Patients were assigned to either a standard or a high pre-transplant risk group. The high-risk group included patients with AML other than first complete remission (CR1), CML other than first chronic phase (CML not CP1), and refractory anaemia with excess blasts (RAEB). Standard-risk patients were those with AML CR1 and CML CP1. There were 10 cases in the high-risk group and 42 cases in the standard-risk group.

This study was approved by the Research Ethics Committee of the Institution.

HLA and KIR typing

All patients and donors were HLA typed by nucleic acid-based molecular methods. HLA class I (HLA-A*, -B* and -Cw*) and II (DRB1*) typing were performed by polymerase chain reaction- sequence-specific priming (PCR-SSP) (Pel Freez) according to the manufacturer's instructions. These methods provided intermediate-resolution allele assignment, as well as high-resolution allele assignment in some cases. KIR genotyping was also performed by the PCR–SSP (Pel Freez) method according to the manufacturer's instructions. The typing determined the presence or absence of KIR genes and provided information about particular KIR alleles or variants. In 48 cases, donor DNA samples were available; thus, KIR genotyping was performed retrospectively to determine the inhibitory KIR (KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, and KIR3DL2) and activating KIR (KIR2DS1, KIR2DS2) genotypes. Patients were grouped based on the expression of HLA ligand: (1) HLA-A3 or -A11, (2) HLA-Bw4, and (3) HLA-Cw groups (homozygous C1 or C2 and heterozygous C1/C2). The patients were further sub-grouped based on the combination of HLA and KIR genotypes: patients with three HLA ligands (C1, C2, Bw4) for donor inhibitory KIRs were assigned to the matched group and the remaining to the mismatched group [18].

Transplant protocols

The majority of patients received a busulfan – (3.2 mg/kg/day for three days, intravenously) and cyclophosphamide – (60 mg/kg/day for two days) based preparatory/conditioning regimen. For acute GVHD prophylaxis, methotrexate plus cyclosporine (25 cases) or tacrolimus (27 cases) based regimens were used. The median dose of CD34+cells in the graft was 2×10^6/kg of patient body weight. No manipulation of the graft, such as ex vivo T-cell depletion, was performed in any of the cases.

Definitions

The endpoints included overall survival (OS), calculated from the date of stem cell infusion until the date of death from any cause, or the last follow-up; disease-free survival (DFS), calculated from the date of stem cell infusion until the date of relapse or death from any cause, or if the patient was alive in CR at the last follow-up; transplant-related mortality (TRM), defined as all causes of death without evidence of initial disease.

Acute GVHD was diagnosed and graded according to previously reported criteria [19]. All patients surviving more than seven days after transplant were considered at risk for developing acute GVHD. Chronic GVHD defined as GVHD occurring in patients after day 100 post-transplantation, classified as previously described [20]. Only patients still alive at day 100 and for whom chronic GVHD information had been collected were included in the chronic GVHD analysis.

Cytomegalovirus (CMV) infection was diagnosed when CMV screening became positive by quantitative plasma PCR with a detection threshold of 10^3/ml.

Statistical considerations

For categorical variables, the chi-square statistic or Fisher's exact test was used to establish differences in their distributions; a 2-sided p value of 0.05 was considered significant. The incidences of post-transplant variables (platelet engraftment >20,000/µl, GVHD, TRM, relapse, CMV infection) were estimated as cumulative incidence. Kaplan-Meier method was used for analysis of OS and DFS and log-rank method was used to establish their differences between subgroups. SPSS version 10.0 statistical software was used to perform the analysis.

Results

Summary of clinical outcomes

All 52 patients achieved platelet engraftment; 37 of 52 patients were alive, three patients relapsed, and 12 patients died of TRM. The overall incidence of acute GVHD was 65% (34 patients) and that of chronic GVHD was 56% (28
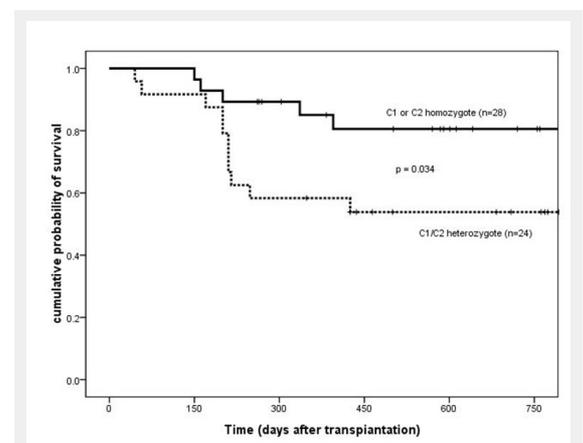

Figure 1

Overall survival of patients based on HLA-Cw ligand groups (C1 or C2 homozygote vs C1/C2 heterozygote). HLA = human leukocyte antigen.

patients). Acute GVHD of grades II–IV occurred in 13% (7 patients) of patient, and extensive chronic GVHD occurred
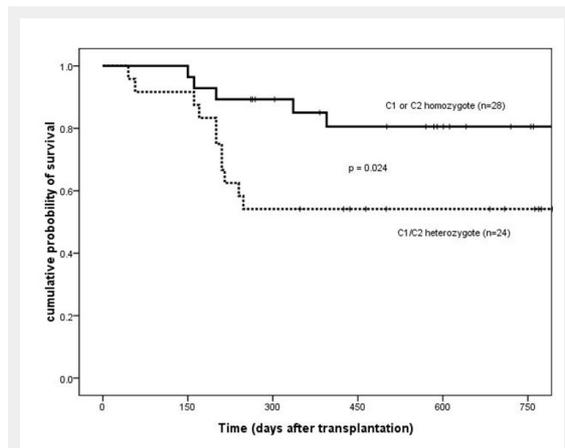

Figure 2

Disease-free survival of patients based on HLA-Cw ligand groups (C1 or C2 homozygote vs C1/C2 heterozygote). HLA = human leukocyte antigen.
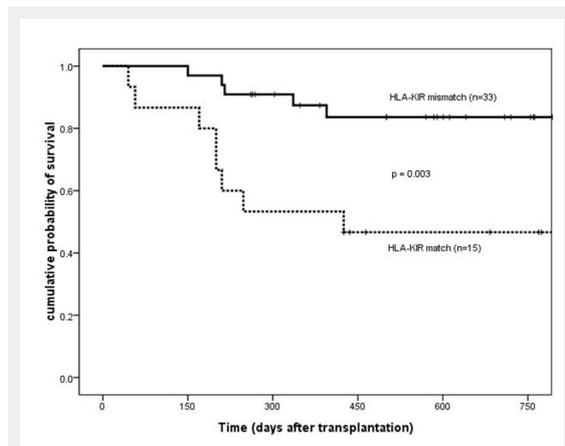

Figure 3

Overall survival of patients based on HLA-KIR match/mismatch group. HLA =human leukocyte antigen; KIR = killer immunoglobulin-like receptor.
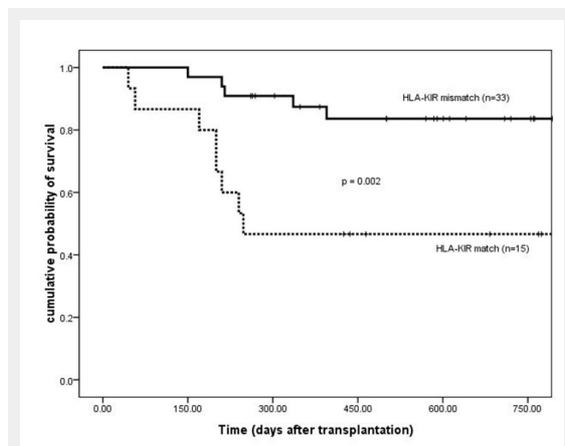

Figure 4

Disease-free survival of patients based on HLA-KIR match/ mismatch group. HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.

in 14% (7 patients). CMV infection was noted in 42% (22 patients) of patients.

Correlation between recipient HLA ligand and clinical outcome

The impact of recipient HLA ligand subtypes on clinical outcome was evaluated. 28 (54%) patients were homozygous for either C1 (25 patients) or C2 (3 patients), and 24 (46%) were C1/C2 heterozygotes. The cumulative incidence of platelet engraftment was similar between C1/C2 heterozygotes and C1 or C2 homozygotes, and grade II–IV acute GVHD was the same (5/24 vs 2/28, p = 0.146). In comparison to homozygotes, C1/C2 heterozygotes had a significantly higher incidence of chronic GVHD (85% vs 31%, 19/22 vs 9/28, p = 0.000), including cases with extensive chronic GVHD (6/7 vs 1/7, p = 0.005).

Two years after transplantation, OS and DFS were significantly higher for C1 or C2 homozygotes than for C1/C2 heterozygotes (OS, 81% ± 8% vs 54% ± 10%, p = 0.034; DFS, 81% ± 8% vs 54% ± 10%, p = 0.024) (fig. 1 and 2). No difference in the baseline characteristics was found between these two groups (table 1). Three relapsed cases were C1/C2 heterozygous. The cumulative incidence of relapse two years after transplantation was significantly higher for C1/C2 heterozygous cases (15%) than for homozygous cases (0%; p = 0.048). No significant difference was found as to TRM between the heterozygous (8 patients, 35%) and the homozygous cases (4 patients, 18%; p = 0.149).

Correlation between HLA-KIR matching and clinical outcome

Platelet engraftment and the incidence of acute GVHD were similar between HLA-KIR matched and mismatched patients. For HLA-KIR-mismatched patients, there was a significantly lower incidence of chronic GVHD (43% vs 85%, 14/33 vs 11/13, respectively; p = 0.007). OS and DFS two years after transplantation were higher in HLA-KIR mismatched patients than in matched cases (OS, 84% ± 7% vs 47% ± 13%, p = 0.003; DFS, 84% ± 7% vs 47% ± 13%, p = 0.002) (fig. 3 and 4). The baseline patient characteristics were similar (table 2). The incidence of relapse and TRM at two years after transplantation were lower in HLA-KIR mismatched patients than in HLA-KIR matched cases (relapse, 0% vs 17%, p = 0.023; TRM, 15% vs 43%, p = 0.018).

Donor KIR genotyping analysis

The types of specific KIR genes were examined in the donors. All donors expressed 2DL1, 2DL2/L3, and 3DL2, and 51 donors (98%) expressed 3DL1. The expression rate of activating KIR differed (18–98%). The impact of the expression of donor activating KIR genes on the clinical outcomes was further evaluated, but there was no significant difference as to platelet engraftment, incidence of acute and chronic GVHD, OS, DFS, and TRM.

CMV infection

The impact of recipient HLA ligand, HLA-KIR matching, and donor activating KIR on the incidence of active CMV infection was evaluated. The presence of KIR2DS2 was significantly correlated with CMV infection: a higher in-

cidence of CMV infection was observed in patients with donor KIR2DS2 (70% vs 34%, 7/10 vs 13/38, respectively; p= 0.041). There was no other significant correlations with CMV infection.

Multivariate analysis for OS and DFS

Multivariate analysis showed that C1/C2 heterozygosity and HLA-KIR match were independent risk factors for OS and DFS (table 3 and 4).

Discussion

The alloreactivity mediated by the interaction between donor KIR and recipient HLA ligand showed some influence on the outcome of HSCT. Controversy still exists in terms of this observation and the underlying mechanism. Some data suggest that alloreactive cells exert a marked GVL effect and improve the outcome [4–6, 15], whilst others suggest that alloreactivity is associated with higher TRM and has a deleterious effect [7, 11].There are hypothetical explanations, including conditioning regimen, T-cell depletion, disease type and disease status. It should be noted that KIR receptors are also expressed by some sub-

sets of T cells and they might contribute to alloreactivity in HSCT [7].

The results of the present study indicated worse outcomes in C1/C2 heterozygotes than in C1 or C2 homozygotes, which is in agreement with the report of Sobecks et al. [16, 21]. C1/C2 heterozygosity was correlated to a higher incidence of chronic GVHD (cGVHD), particularly extensive cGVHD, and was associated with lower OS and DFS and higher disease relapse. This difference in outcome may be due to the weaker alloreactivity among C1/C2 heterozygotes than in C1 or C2 homozygotes. As C1/C2 heterozygotes have more opportunity to engage inhibitory KIRs than C1 or C2 homozygotes, they have greater inhibitory effects on KIR-positive NK and T cell populations involved in the alloreactivity. Theoretically, greater inhibition leads to weaker alloreactivity. Therefore, C1/C2 heterozygotes activate alloreactive cells to a lesser extent.

Meanwhile, the present study showed that HLA-KIR mismatched patients had a better outcome, which is in line with some earlier reports [15, 16, 22]. HLA-KIR mismatch was associated with reduced incidences of cGVHD and TRM, a lower relapse rate and prolonged OS and DFS. This impact is in concordance with the influence of C1 or C2 homozygosity. Stronger alloreactivity exists in HLA-

Table 1: Patient characteristics based on HLA-Cw group.

	C1 or C2 homozygote (n = 28)	C1/C2 heterozygote (n = 24)	*p* value
Age at transplant (years)	37.5 (14–51)	38 (15–55)	0.85
Gender (female/male)	12/16	6/18	0.18
Standard risk / high risk	22/6	20/4	0.74
CD34+ cell dose (×106/kg)	2.954 (1.14–6.90)	2.10 (0.9–6.48)	0.18
Total nucleated cell dose (×108/kg)	5.0 (1.47–8.80)	5.11 (1.16–7.72)	0.63
ABO match/mismatch	18/10	10/14	0.10
HLA =human leukocyte antigen.			

Table 2: Patient characteristics based on HLA-KIR match/mismatch group.

	HLA-KIR match (n = 15)	HLA-KIR mismatch (n = 33)	*p* value
Age at transplant (years)	38 (27–54)a	38 (14–55)	0.89
Gender (female/male)	4/11	13/20	0.39
Standard risk / high risk	12/3	26/7	1.0
CD34+ cell dose (×106/kg)	2.48 (1.25–4.62)	2.35 (0.90–6.90)	0.62
Total nucleated cell dose (×108/kg)	5.0 (1.16–6.30)	5.0 (1.47–8.80)	0.31
ABO match / mismatch	7/8	18/15	0.61
HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.			

Table 3: Independent risk factors for DFS in patients.

Parameter	OR	95% CI	*p* value
C1/C2 heterozygotes and homozygotes	3.829	1.228–11.941	0.021
HLA-KIR match / mismatch	0.219	0.071–0.672	0.008
Low / high risk	2.071	0.504–8.514	0.313
Type of disease (AML/CML)	0.875	0.515–1.485	0.620
CMV infection	1.774	0.652–4.831	0.262
HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.			

Table 4: Independent risk factors for OS in patients.

Parameter	OR	95% CI	*p* value
C1/C2 heterozygotes and homozygotes	3.791	1.207–11.911	0.022
HLA-KIR match / mismatch	0.229	0.075–0.703	0.010
Low / high risk	2.168	0.521–9.019	0.287
Type of disease (AML/CML)	0.874	0.515–1.482	0.617
CMV infection	1.867	0.686–5.081	0.222
HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.			

KIR mismatched cases. These studies support the hypothesis that alloreactivity may decrease cGVHD and relapse and thus lead to a better prognosis. The incidences of aGVHD between HLA-KIR matched and mismatched patients were the same, the reasons are unknown and may be connected with the different pathogenesis of aGVHD and cGVHD or the relatively small cohort of patients.

We analysed donor KIR genotype. It is important to note that nearly 100% of the donors possessed inhibitory KIRs corresponding to the HLA ligands. It is known that alloreactivity is induced by the absence of an HLA ligand that corresponds to the specific inhibitory KIR. In other words, the absence of an HLA ligand indicates alloreactivity [15, 22, 23], and less HLA ligand leads to stronger alloreactivity. This is consistent with the present findings that C1 or C2 homozygosity leads to a lesser inhibitory effect, which translates to stronger alloreactivity and better outcome. Limited information is available on specific ligands and functions of activating KIRs [18, 24–28]. We hypothesize that activating KIRs may be associated with clinical outcomes.

Some studies have shown that the incidence of active CMV infection correlated with activating KIR [29–31], but the results remain contradictory. Hadaya et al. [32] showed that the presence of activating KIR genes in the recipients was associated with a lower rate of CMV infection after kidney transplantation. We have no information on the recipient's KIR. The present study demonstrates that activating KIR2DS2 increased the incidence of CMV infection. The relationship between CMV infection and activating KIRs remains unclear and warrants further investigation.

There are some limitations in the present study. Firstly, we performed HLA-DQ typing of seven patients and donors, they were matched. We have no information as to HLA-DP and other HLA-DQ typing. The influence of HLA-DQ and HLA-DP on the results is unknown. Secondly, a relatively small cohort of patients from a single centre was included, and the study size was limited. Many centres and larger scale studies are required to confirm our findings.

Conclusion

Analysis of the role of HLA ligand and HLA-KIR interactions has important clinical implications for allogeneic HSCT. The finding that C1/C2 heterozygosity and HLA-KIR match are poor prognostic factors suggests that additional intensified therapy, such as stronger conditioning regimens or stronger GVHD prophylactic regimens, may be appropriate for such patients. Future approaches examining the outcome in relation to specific KIR phenotype may also be useful in optimising the selection of haematopoietic stem cell donors for haematopoietic stem cell transplantation.

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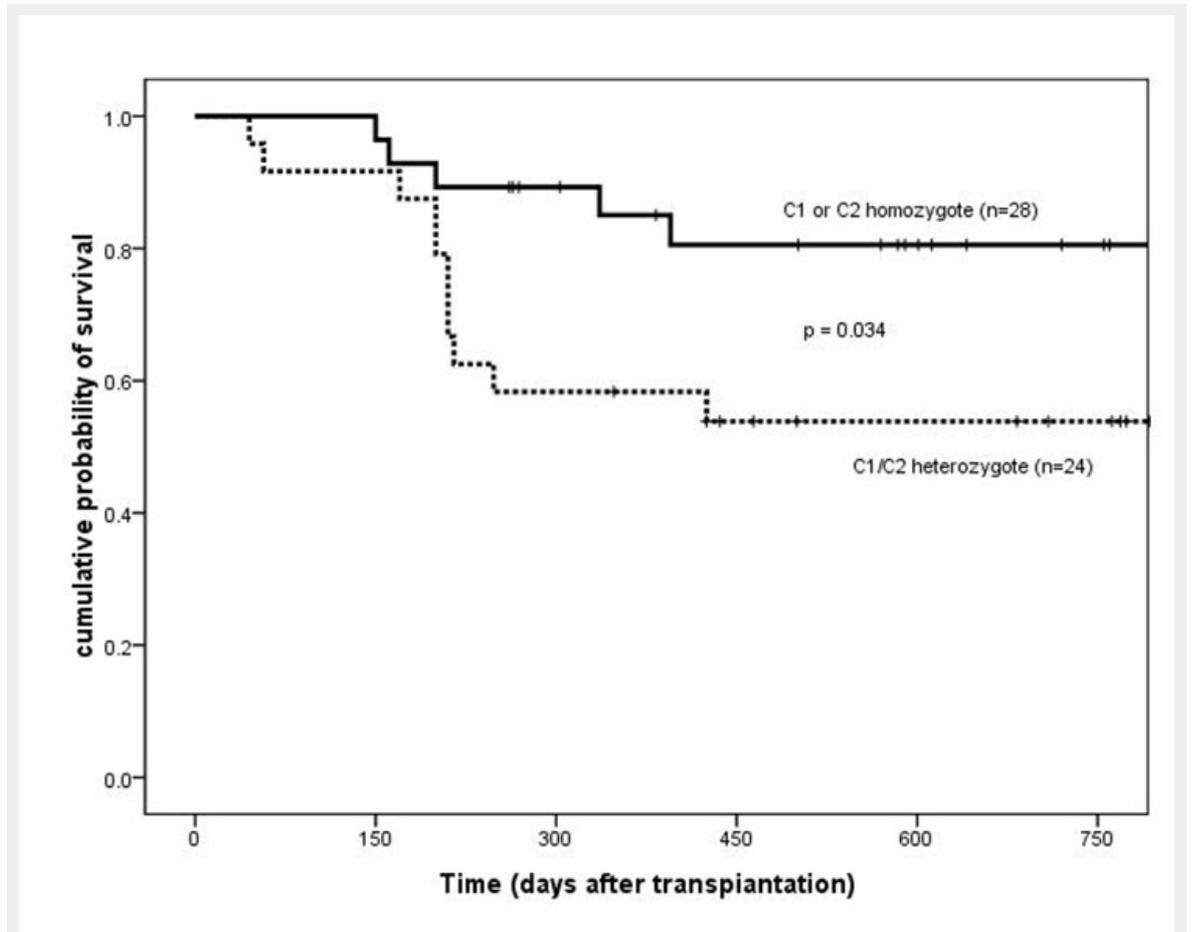
Figures (large format)

Figure 1

Overall survival of patients based on HLA-Cw ligand groups (C1 or C2 homozygote vs C1/C2 heterozygote). HLA = human leukocyte antigen.
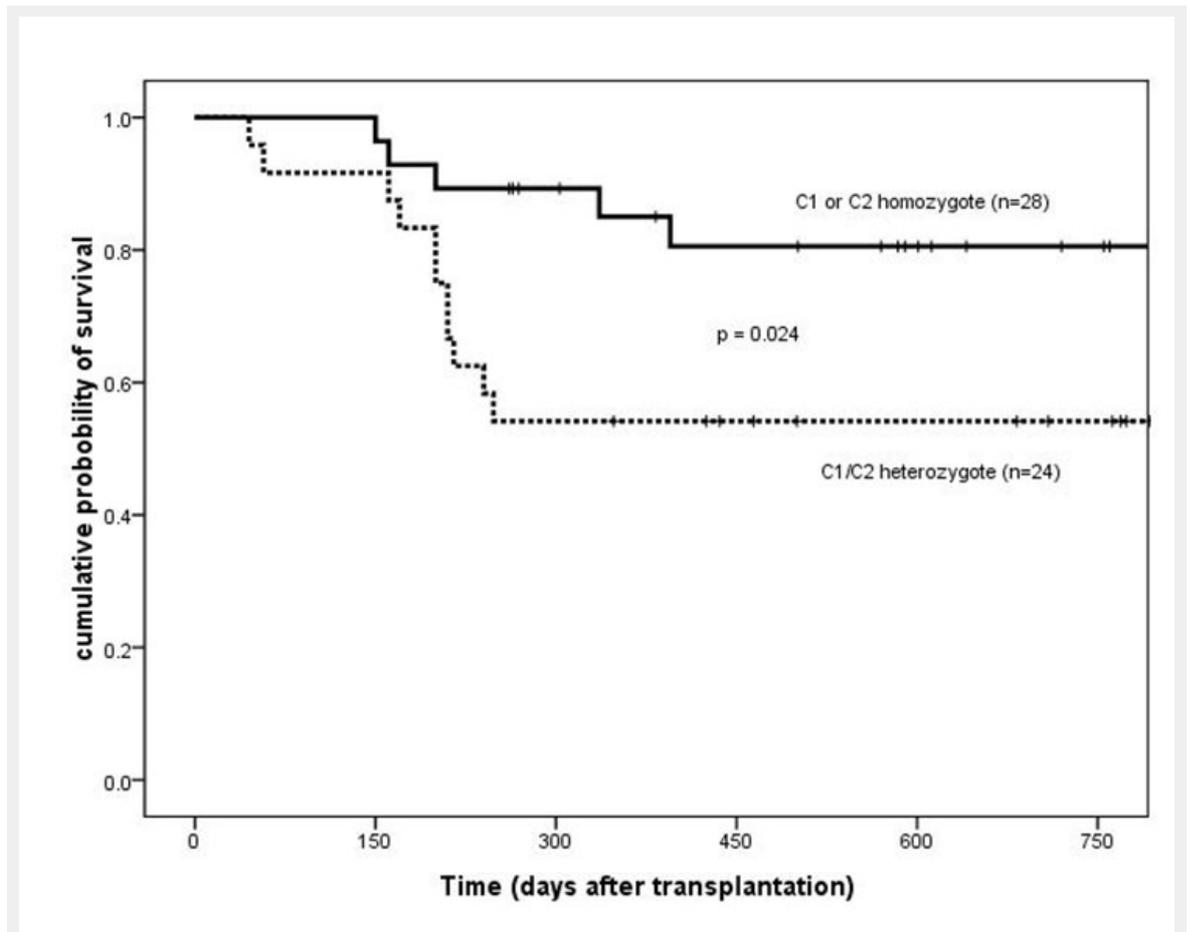
Figure 2

Disease-free survival of patients based on HLA-Cw ligand groups (C1 or C2 homozygote vs C1/C2 heterozygote). HLA = human leukocyte antigen.
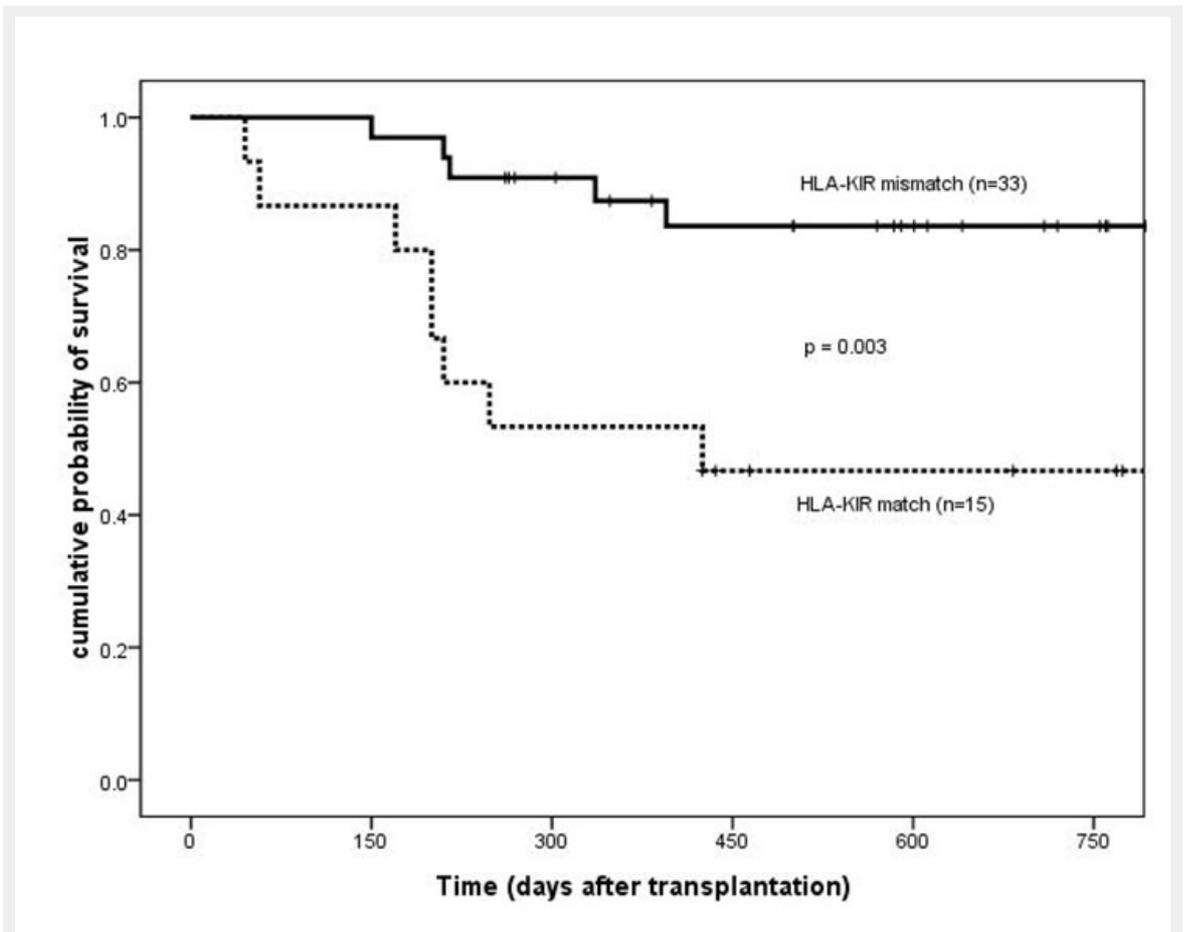
Figure 3

Overall survival of patients based on HLA-KIR match/mismatch group. HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.
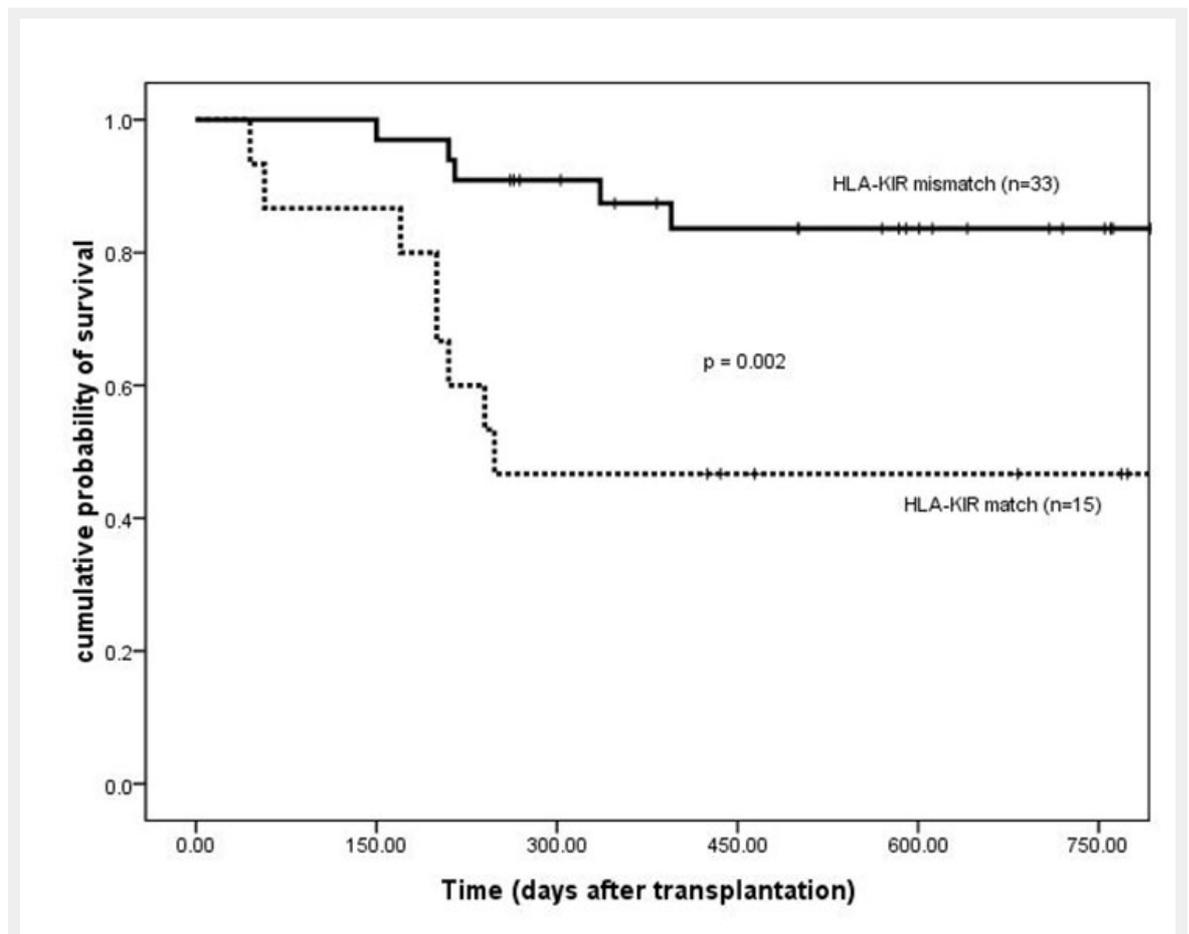
Figure 4

Disease-free survival of patients based on HLA-KIR match/mismatch group. HLA = human leukocyte antigen; KIR = killer immunoglobulin-like receptor.