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Original Article

Donor KIR3DL1/receptor HLA-Bw4-80I Combination Reduces Acute Leukemia Relapse after Umbilical Cord Blood Transplantation without in Vitro T-cell Depletion

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Abstract. ***Background:*** **Donor natural killer (NK) cell alloreactivity in umbilical cord bone marrow transplantation (UCBT) can lead to leukemic relapse. However, NK cell function is calibrated by interaction with human leukocyte antigens (HLAs). This study aimed to investigate graft-resistant leukemia after transplantation and compared specific genotypes of killer immunoglobulin-like receptors (KIRs) in donors and human leukocyte antigen ligands in patients.**
Methods: **We retrospectively analyzed 232 patients with acute leukemia from a single center. Patients had undergone UCBT with myeloablative conditioning and without anti-thymocyte globulin. We identified the KIR genotypes of cord blood donors using polymerase chain reaction with sequence-specific primers. All of the donors contained KIR3DL1.**
Results: **The patients were divided into three groups according to the HLA-B locus. The donor KIR3DL1 and recipient HLA-Bw4-80I combination was predictive of being highly educated and was associated with a lower relapse (*P*=0.006) and better overall survival (probability of relapse=0.13, *P* < 0.001) than the uneducated group. We found no significant increase in the incidence of acute or chronic graft-versus-host disease.**
Conclusions: **Our data suggest that the donor KIR3DL1/receptor and HLA-Bw4-80I combination in UCBT results in stronger graft-versus-leukemia effects and improved outcomes in patients with acute leukemia.**

Keywords: Acute myeloid leukemia; Natural killer cells; Killer immunoglobulin-like receptors; Umbilical cord blood transplantation; Acute lymphocytic leukemia.

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Introduction. Umbilical cord blood transplantation (UCBT) is widely used for treating hematological malignancies.[1] Natural killer (NK) cells are an essential component of umbilical cord blood stem cells and are the fastest recovering cells in the early stage after UCBT. Therefore, NK cells are an essential component of the graft-versus-leukemia (GVL) response and are critical for positive outcomes after UCBT.[2,3] NK cells have a

highly specific and complex target-cell recognition receptor system. NK cells are regulated by many inhibitory and activating receptors and trigger cytotoxicity and secretion of chemokines and cytokines.[4,5] Killer immunoglobulin-like receptors (KIRs) are essential for the development and function of human NK cells,[6] which is achieved through a process called education. Education is governed by the interaction between NK cell receptors and major histocompatibility complex proteins.[7]

Hematopoietic stem cell transplantation provides an opportunity for NK cells to re-develop. Different combinations of KIRs and their ligands result in different NK education levels, through which NK cells enhance cytotoxicity against Human leukocyte antigen (HLA) class I molecular tumors compared with unlicensed cells.[8] The most typical KIR HLA ligand pair is KIR3DL1 and HLA-B. HLA-B is classified into non-binding (Bw6) and binding (Bw4) types. Bw4 is further classified into Bw4-80I and Bw4-80T according to whether the amino acid at position 80 is isoleucine or threonine. The KIR3DL1 and HLA-Bw4-80I pair has the most potent educational ability,[9-11] which means that allogeneic proliferating NK cells combined with donor KIR3DL1 and recipient HLA-Bw4-80I more effectively reduce the recurrence of leukemia. Therefore, this study aimed to determine whether specific combinations of KIR receptors and HLA ligands in patients undergoing UCBT have a better clinical outcome.

Materials and Methods.

Patients and transplant protocols. All participants in the study provided written informed consent. Participants included patients with lympho-and myeloproliferative malignancies who received UCBT at the Center of Hematology, Anhui Provincial Hospital between Jul 31, 2012, and Dec 31, 2017. Donor sources were unrelated from a cord blood bank and matched at alleles of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci. All patients underwent allogeneic transplantation after having undergone either myeloablative or reduced-intensity regimens.

The primary outcomes included the following: 1) probability of relapse (PR), which was defined as any morphologically proven recurrence of leukemia occurring after the allograft; 2) overall survival (OS), which was defined as the time from transplantation to death; and 3) disease-free survival (DFS), which was the time from transplantation to relapse.

Secondary outcomes included engraftment, hematopoietic chimerism, and acute or chronic graft-versus-host disease (GVHD). Recovery of neutrophils was defined by a neutrophil count of a least 0.5×10^9/L for three consecutive days. Graft failure was defined as no sign of neutrophil recovery, as well as transient engraftment of donor cells within 60 days after transplantation. The platelet recovery was defined by a count of a least 20,000/μl for three consecutive days within 120 days after transplantation. Full donor chimerism was defined as the presence of > 95% of the donor cells. Acute GVHD (aGVHD) was defined as the development of grade II to IV GVHD during the first 100 days post-transplantation. Severe aGVHD involved the development of grade III to IV GVHD. Chronic GVHD (cGVHD) occurred over 100 days post-transplantation.

HLA typing. Genomic DNA was extracted from patients' whole blood and cord blood with the QIAamp DNA blood mini kit (Qiagen, Hilden, Germany). HLA classes I and II alleles were hybridized with the LAB Type SSO kit (One Lambda, Hannover, GERMANY). HLA sequences were read with a LAB Scan 200 (Luminex, Texas, USA) and computer-assisted HLA Fusion software. According to the HLA-B locus of donors, patients were divided into the following three groups: HLA-Bw6, HLA-Bw4-80T, and HLA-Bw4-80I.

KIR genotyping. According to the manufacturer's instructions, KIR genotyping was performed using polymerase chain reaction with the KIR typing kit (BAG Healthcare, Lich, Germany). The KIR genotype of cord blood donors was detected by the sequence-specific primer method. The KIR genotype of cord blood donors all contained KIR3DL1.

Statistical analysis. The Kaplan–Meier method was used to calculate probabilities of relapse-free, OS, and DFS, including the 95% confidence interval (CI). The nonparametric test was used for comparing outcomes by three different HLA-B groups. Finally, Cox regression models were constructed to assess HLA groups' effect on the outcome variables while controlling for demographic and other covariates that showed an association with the primary outcomes. The cumulative incidence was used to estimate non-recurring mortality (NRM), neutrophil and platelet recovery, and aGVHD and cGVHD. Calculations were performed using SPSS version 17.0.

Results. The ages of the 232 AL and MDS patients ranged from 2 to 45 with a median of 13 years, contains 110 women and 122 men. All the patients were diagnosed with acute myeloid leukemia (AML, n=112), acute lymphocyte leukemia (ALL, n=104), and myelodysplastic syndrome (MDS, n=16). All patients were Chinese. One hundred sixteen patients were at first remission, 52 patients at Second /third remission, 64 patients were not in remission when transplantation. All the patients received UCBT. 23 pairs were 6/6 allele matched at HLA-A, -B, -C, -DRB1, and -DQB1; the rest were 1 (n=98) or >=2 HLA allele (n=101) mismatched. Most of them (n=180) received reduced-intensity conditioning (RIC), which contains fludarabine (Flu),

busulfan (BU), and cyclophosphamide (CY); some of them (n=47) received conditioning total body irradiation (TBI), cytarabine (Ara-c) and CY, 5 of them received conditioning Ara-c, BU and CY. There were no significant differences in other clinical variables. We classified patients according to the presence of genes encoding recipient HLA-B ligands for donor inhibitory KIRs. None of the patients received rabbit anti-thymocyte globulin. GVHD prophylaxis regimens for UCBT included cyclosporine A and mycophenolate mofetil. We classified patients according to the presence of genes encoding recipient HLA-B ligands. The characteristics of each HLA-B group are shown in **Table 1**.

Table 2 shows the comparison of the transplantation results of the three groups. Only nine of the total patients had primary graft failure. The median recovery time of neutrophils in the Bw6, Bw4-80T, and Bw4-80I groups was 16 (14-20) days,17 (14-21) days, and 17 (14-19) days, respectively. The engraftment rate in the Bw6, Bw4-80T, and Bw4-80I groups was 96.5%, 95.5%, and 96.2%, respectively (P=0.202). The median recovery time of platelet recovery in Bw6, Bw4-80T, and Bw4-80I groups was 36 (29-47) days, 38 (29-60) days, and 38 (31-45) days. The days of neutrophils and platelet recovery showed no significant difference among the three groups. The cumulative incidence of recovery of neutrophils by day 42 in the three groups was 96.5% (95% CI, 89.4% to 98.8%), 95.6% (95% CI, 86.6% to 98.5%), and 94.8%, respectively (95% CI, 86.7% to 98%; P=0.81).

Within 100 days after transplantation, the incidence of grades II to IV aGVHD in the Bw6, Bw4-80T, and Bw4-80I groups was 38.4% (95% CI, 25.1% to 48.5%), 35.3% (95% CI, 24.1% to 46.7%), and 42.3% (95% CI, 31.2% to 53.0%), respectively (P=0.68). The cumulative incidence of severe aGVHD (grades III and IV) in the three groups was 15.1% (95% CI, 8.5% to 23.6%),

Table 1. Patients' characteristics for the three groups, according to HLA-B subtype.

Characteristic, n (%)	Bw4*80I	Bw4*80T	Bw6	P value
Patients	86	68	78	
Median Recipient age, y, (range)	13（1-44）	12（1-43）	13（1-45）	0.820
Median weight, Kg, (range)	41 (37.3-45.9)	41.5 (36.5-46.4)	42.7（38.2-47.2）	0.909
Recipient gender				0.634
Female	38	35	37	
Male	50	36	36	
Diagnose				0.657
AML	37	35	40	
ALL	44	28	32	
MDS	5	5	6	
HLA Compatibility				0.658
6/6	7	9	7	
5/6	42	27	29	
4/6 or 3/6	37	32	32	
Disease stage				0.754
First remission	41	34	41	
Second /third remission	23	13	16	
Not remission	17	23	24	
Disease risk status				0.652
Poor	16	5	8	
Intermediate	70	63	70	
TNC (10^7/Kg)	4.44 (3.86-15.01)	4.5 (3.9-15.1)	4.34 (3.87-14.81)	0.877
CD34 (10^5/Kg)	2.52 (2.1-12.8)	2.49 (1.99-12.98)	2.34（2.0-12.69）	0.788
Conditioning regimen				0.675
Flu+BU+CY	63	52	65	
Ara-c+BU+CY	4	1	0	
TBI+Ara-c+CY	19	15	13	

CR1: complete remission at the first time; CR2/3: complete remission at the second or third time; NR: refractory/relapsed disease; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome；FLU: fludarabine；TBI: total body irradiation; CY: cyclophosphamide；BU: busulfan；Ara-c: cytarabine.

Table 2. Transplantation results of the three groups, according to HLA-B subtype.

Results n (%)	Bw4*80I	Bw4*80T	Bw6	*P value*
Recovery time of neutrophils days, (range)	16 (14-20)	17 (14-21)	17 (14-19)	0.951
Recovery time of neutrophils days, (range)	36 (29-47)	38 (29-60)	38 (31-45)	0.871
Acute GVHD	33 (38.4%)	24 (35.3%)	33 (42.3%)	0.093
Chronic GVHD	7 (8.1%)	6 (8.8%)	13 (16.7%)	0.759
Relapse	5 (6.4%)	9 (13.2%)	21 (24.4%)	0.023
Have disease	5 (6.4%)	10 (14.7%)	25 (29.0%)	0.0004
Death	18 (23.1%)	18 (26.5%)	27 (31.4%)	0.4785

22.1% (95% CI, 13.0% to 32.6%), and 24.7% (95% CI, 15.7% to 34.8%), respectively (P=0.38). Among the patients who survived for longer than 100 days, the cumulative incidence of cGVHD at 2 years showed a tendency to be higher in the Bw4-80I group. The cumulative incidence of cGVHD at 2 years after transplantation in the Bw6, Bw4-80T, and Bw4-80I groups was 10.6% (95% CI, 4.4% to 19.9%), 10.6 % (95% CI, 4.1% to 20.5%), and 20.6% (95% CI, 10.5% to 33.0%), respectively (P=0.18).

The cumulative incidence of relapse two years after transplantation in the Bw4-80I group was significantly lower than that in the other two groups. In the Bw4-80I group, only 5 cases (6.4%) relapsed, while in the Bw6 group, 21 cases (24.4%) relapsed. In the univariate analysis, the HLA-B subtype was a significant risk factor for relapse (P=0.02). At 2 years after transplantation, the DFS in the Bw4-80I group (91.7%, 95% CI, 81.7% to 96.5%) was significantly higher than that in the other 2 groups (Bw6 group: 60.2%, 95% CI, 81.1% to 96.5%; Bw4-80T group: 79.3%, 95% CI, 64.2% to 88.5%, P=0.002; **Figure 1**). Multivariate analysis was performed for variables, including age, receptor weight, HLA matching, diagnosis, stage, conditioning regimen, and HLA-B subtype, to identify risk factors in the three groups (P=0.0003). TRM occurred in 12 of 86 recipients in the Bw6 group, in 15 of 68 recipients in the Bw4-80T group, and in 13 of 78 recipients in the Bw4-80I group. The main cause of death was a severe infection caused by bone marrow failure after recurrence; the first type of infection was a fungal infection. The cumulative incidence of TRM by 2 years was 14.6% (95% CI, 6.6% to 21.9%), 22.2% (95% CI, 11.6% to 31.4%), and 16.9% (95% CI, 8.1% to 24.8%) in the three groups, respectively (P=0.45). OS at 2 years was 64.6% (95% CI, 51.9% to 74.7%), 73.4% (95% CI, 61.2% to 83.4%), and 76% (95% CI, 64.9% to 84.4%) in the Bw6, Bw4-80T, and Bw4-80I groups, respectively (P=0.53), with no significant difference between the groups (**Figure 2**). In multivariate analysis, including HLA-B difference and other factors, OS at two years after transplantation in the Bw4-80I group (hazard ratio=0.13, P=0.0001) was significantly higher than that in the Bw6 group. HLA-B difference was a risk factor for OS (P=0.0003).

Discussion. The objective of this study was to investigate the effect of donor KIR and recipient ligands

Figure 1. DFS of the three groups after UCBT. DFS in the Bw4-80I group was significantly higher than that in the Bw6 group.

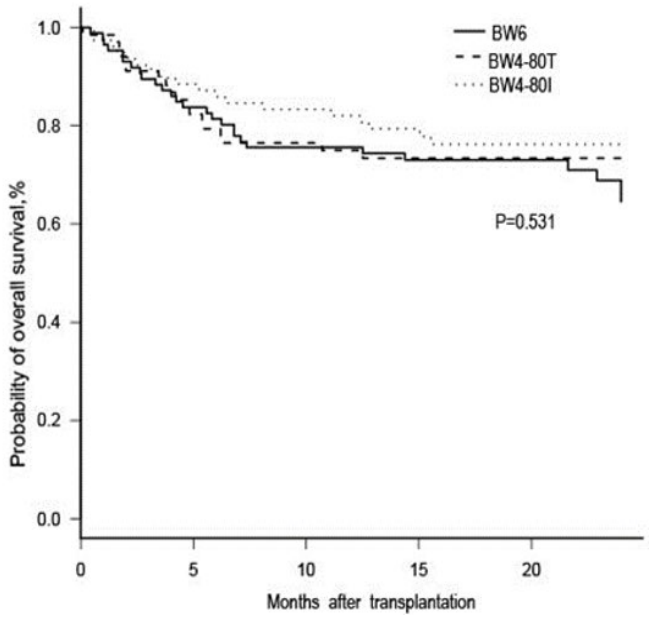
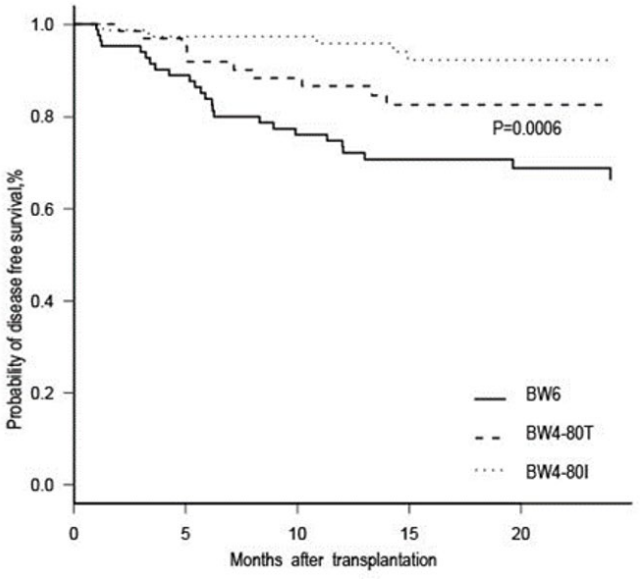


Figure 2. OS after UCBT. The Bw6 group appeared to have a worse OS than the other two groups, but this was not significant.



on DFS. HLA-B subtype was a significant on clinical outcomes after UCBT. We retrospectively analyzed data from patients with hematological malignancies who received T cell-repleted UCBTs (with neither *ex vivo* nor *in viv*o T cell depletion) at a single Chinese center. We found that the PR after UCBT was significantly lower in recipients whose HLA-B was Bw4-80I with allografts from KIRs containing 3DL1 donors than in recipients whose HLA-B was Bw6.

The role of KIRs in early reporting and their ligands in UCBT is not consistent. NK cell alloreactivity in a transplantation setting was first recognized in patients with acute myeloid leukemia in the absence of T cells with HLA-haploidentical donors and grafts.[12] However, the traditional view is that KIR mismatch of donors and recipients should be accepted in transplantation. Ruggeri and colleagues[13] first reported that KIRs not matching their ligand or ligand loss could reduce NK cell inhibition, and therefore, they were easier to activate, which resulted in enhanced GVL effects and a reduced post-transplant recurrence rate of leukemia. However, this previous study mainly focused on depleting T cells *in vitro* before transplantation.[13] Recent reports have continued to focus on the efficacy of better transplantation associated with the activating KIR gene.[14,15,16] A limitation of these studies is that they only considered KIR–ligand mismatch, without consideration for the role of NK licensing. Our study assessed the effect of NK cell licensing and education. The higher GVL effects in the donor KIR3DL1/receptor Bw4-80I group can be explained by the more active cytolytic function of alloreactivity in donor NK cells because of interaction between the Bw4-80I ligand and donor NK cells. Conversely, the donor KIR3DL1/receptor Bw6 group could not educate NK cells. Therefore, a high recurrence of leukemia was observed in this group. The KIR3DL1/receptor Bw4-80T group also educated NK cells, while its lower education conferred a mild improvement in DFS, PR, and OS. We observed that the different education results did not affect single factor analysis of OS. Conversely, in multi-factor analysis with the regression model, the effect of other confounding factors was adjusted, and it revealed the effect of each factor on the dependent variable.

The number of UCBT cases in most transplant centers has a limited investigation of the role of KIRs in UCBT. Therefore, how donor NK cells enter the recipient after cord blood transplantation and how they differentiate, educate, or play a role in the killing are unclear. Many studies have focused on the combination of KIR2DL1/2/3 and HLA-C. However, our previous findings indicated that, although the inhibitory KIR2DL1/2/3 family members' binding affinity to ligands and diversity of surface expression were observed, these differences were smaller than those in the KIR3DL1 and HLA-B ligand pair.[17,18] Therefore, we consider that focusing on the KIR3DL1-Bw pair is more meaningful.

Previous studies have shown that higher GVL effects are associated with a higher probability of GVHD, but our study did not show that aGVHD of the KIR3DL1/receptor Bw4-80I group was increased. There were no significant differences in the II-IV GVHD and III-IV GVHD in group Bw4-80I. Although group Bw4-80I showed a trend for a higher incidence of cGVHD, this difference was not significant. We also found that different KIR and donor groups did not significantly affect the neutrophil and platelet implantation rate, consistently with other studies.[19,20]

Conclusions. Our data show that the donor KIR3DL1/receptor and recipient Bw4-80I combination may affect the PR and DFS in T cell-repleted UCBT in Chinese patients. Therefore, close monitoring of the residual disease status may be recommended in patients with HLA-Bw6 receiving KIR3DL1 cord blood. Further studies are required to clarify the relationship between NK cells' education and clinical outcomes of UCBT. Examination of a larger cohort is also required to develop confident recommendations.

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