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Recovery of natural killer cells and prognosis after cord blood transplantation

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ABSTRACT

The relationship between immune reconstitution and the prognosis after cord blood transplantation is unclear. We investigated the influence of natural killer (NK) cell recovery on transplant outcomes. The maximum number of CD56+CD3− cells or CD57+CD16+ cells was determined to assess NK recovery. Although the high CD56+CD3− group and high CD57+CD16+ group showed significantly better overall survival (OS) than the low group on univariate analysis, the high CD57+CD16+ group was associated with better OS on multivariate analysis. These results suggest that CD57+CD16+ cell recovery is more closely related to the outcome after CBT than CD56+CD3− cell recovery.

1. Introduction

A relationship between immune reconstitution after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and the prognosis has been reported [1–4]. In particular, the recovery of alloreactive natural killer (NK) cells was suggested to be related to the graft-versus-leukemia (GVL) effect in previous reports [5–7]. Cord blood is an alternative stem cell source for allogeneic transplantation and cord blood transplantation (CBT) is increasingly being performed in adult patients. NK cells in cord blood are immature and acquisition of alloreactivity by such cells in the setting of CBT is unclear. Accordingly, we focused on the recovery of NK cells after CBT and investigated the influence of NK recovery on relapse, non-relapse mortality (NRM), and the prognosis.

2. Materials and methods

Patients who underwent CBT for hematologic malignancies from September 2003 to September 2012 at Kanagawa Cancer Center (Yokohama, Japan) were retrospectively investigated. Patients who received second transplantation for graft failure or died before engraftment were excluded. Analysis of lymphocyte subsets by flow cytometry was carried out on days 70, 100, 180, and 365 after CBT. We determined the maximum number of CD56+CD3− cells (max CD56) or CD57+CD16+ cells (max CD57) within 1 year after CBT as an indicator of NK recovery, and the maximum value was categorized as low (<median) or high (≥median). We also evaluated CD3+ cells, CD4+CD8− cells, CD4−CD8+ cells, CD4+CD25− cells, and CD20+CD2− cells in the same way. Standard risk disease was defined as acute myeloid leukemia (AML)/acute lymphoblastic leukemia (ALL) in the first remission, myelodysplastic syndrome (MDS) without leukemic transformation, and chronic myeloid leukemia (CML) in the chronic phase, while all other conditions were defined as high risk disease. Grading of acute graft-versus-host disease (GVHD) was done according to established criteria [8]. Killer immunoglobulin-like receptor (KIR)-ligand incompatibility (HLA-C group, HLA-Bw4 group, and/or HLA-A3/A11) was defined as existing when there was one or more mismatch in the graft-versus-host (GVH) direction.

Statistical analysis was performed with R software (version 2.11.1; R Development Core Team). Differences between groups were analyzed by the Wilcoxon rank sum test or Fisher's exact test, as appropriate. Overall survival (OS) was calculated from the date of transplantation to the date of death from any cause or the date of last follow-up. Non-relapse mortality (NRM) was defined as death without disease relapse or resistance. Death without relapse was a competing risk for relapse, relapse was a competing risk for NRM, and relapse and death without GVHD were considered to be competing risks for GVHD. Time-to-event curves were drawn according to the Kaplan–Meier method and the statistical significance of differences between curves was assessed by the log rank test. Prognostic factors included age, sex, donor mismatch, disease risk, number of nuclear cells in cord blood, number of CD34+ cells in cord blood, conditioning regimen, corticosteroid therapy, and NK recovery. Either the Cox proportional hazard model or the Fine–Gray proportional hazard model was used for multivariate analysis.

3. Results

Thirty-three patients who received CBT for hematologic malignancy were included in this study. The median follow-up time for the survivors was 19.4 months (range: 3.5–109.7 months). Patient characteristics are shown in Table 1. The median age of the subjects was 56 years (range: 20–67 years). There were 16 men and

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Table 1
Patient characteristics.

Characteristics	Number
Age (years), median (range)	56 (20–67)
Sex	
Male	16
Female	17
Disease	
Acute myelogenous leukemia	16
Acute lymphoblastic leukemia	13
Myelodysplastic syndrome	3
Chronic myeloid leukemia	1
Disease risk at transplantation	
Standard risk	22
High risk	11
NCC CD34 ($\times 10^7/\mu l$), median (range)	2.85 (1.10–4.83)
CD34(+) cells ($\times 10^5/\mu l$), median (range)	0.58 (0.12–2.01)
Conditioning regimen	
Myeloablative	19
Reduced-intensity	14
GVHD prophylaxis	
Cyclosporine + sMTX	1
Tacrorimus + sMTX	32
HLA disparity	
Match	2
Mismatch	31
Sex mismatch	
Other	25
Female to male	8
CS administration 100 days after transplantation	
No	20
Yes	13
KIR-ligand incompatibility	
No	27
Yes	6

NCC, nuclear cells count; GVHD, graft-versus-host disease; sMTX, short term methotrexate; CS, corticosteroid; KIR, killer immunoglobulin-like receptor.

17 women, and 8 patients had the combination of female donor with male recipient. The diagnosis was AML in 16 patients, ALL in 13, MDS in 3, and CML in 1. The disease risk at transplantation was standard in 22 patients and high in 11 patients. Myeloablative conditioning was used in 19 patients, while 14 patients received reduced intensity conditioning. None of the patients received anti-thymocyte globulin or T cell depletion for GVHD prophylaxis. Instead, cyclosporine or tacrolimus with short-term methotrexate was used for GVHD prophylaxis. Corticosteroid therapy was administered to 13 patients for various reasons within 100 days after transplantation. We could evaluate lymphocyte subsets in 28, 30, 24 and 21 patients in days 70, 100, 180 and 365 after CBT, respectively.

The median value of max CD56 cells and CD57 cells was 435/μl (range: 33–1405/μl) and 294/μl (range: 3–1172/μl), respectively. The high max CD56 group ($n = 23$) showed significantly better 2-year OS compared with the low max CD56 group ($n = 10$) (77.4% vs. 50.0%, $P = 0.020$) and also had significantly better NRM (0.0% vs. 30.0%, $P = 0.007$). However, there was no significant difference of relapse (22.9% vs. 20.0%, $P = 0.988$) (Fig. 1 and Table 2). On the other hand, the high max CD57 group ($n = 22$) showed significantly better 2-year OS compared with the low max CD57 group ($n = 11$) (89.6% vs. 22.7%, $P < 0.001$), as well as significantly better NRM (0.0% vs. 27.3%, $P = 0.012$) and relapse (9.1% vs. 45.5%, $P = 0.016$) (Fig. 2 and Table 2). The incidence of grade II–IV acute GVHD did not differ between high and low max CD56 ($P = 0.933$) or high and low max CD57 ($P = 0.243$). KIR-ligand incompatibility ($n = 6$) was not related to OS, NRM, relapse, acute GVHD or max CD56 and CD57 cells.

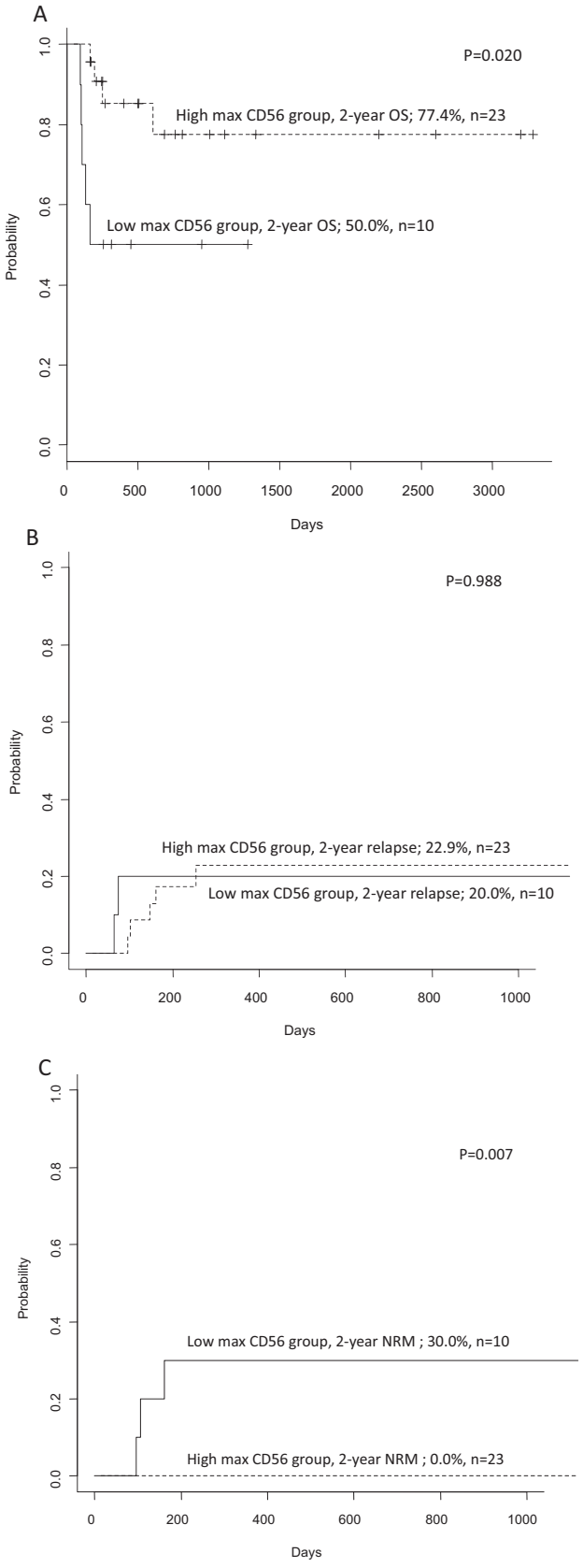

Fig. 1. Outcomes stratified according to max CD56. (A) Overall survival. (B) Cumulative incidence of relapse. (C) Non-relapse mortality.