Clinical Outcomes of Unrelated Donor Umbilical Cord Blood Transplantation for 30 Adults with Hematological Malignancies

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Abstract. *Background: Umbilical cord blood transplantation (CBT) has increasingly been used as a therapeutic option for adult patients for whom allogeneic stem- cell transplantation is not indicated, due to the availability of cord blood. However, myeloablative conditioning regimens are associated with significant mortality, and high relapse rates in reduced-intensity regimens may result in a poor rate of disease-free survival for those with advanced stages of hematological malignancies. Therefore, it remains unknown whether CBT is a truly effective option for such adults with high-risk disease, as well as for those with standard-risk disease. Patients and Methods: Thirty adult patients with a median age of 45 years (range: 16-67) with standard or high-risk disease underwent CBT from unrelated donors at Okayama University Hospital between October 2002 and May 2007. Twenty-one patients had diseases classified as high-risk for transplantation. The median number of nucleated cells in infused cord blood was 2.65×10^7/kg (range: 1.73-4.87). Results: Twenty-three patients achieved neutrophil engraftment at a median time of 22 days (range: 13-42) after CBT. The cumulative incidence of grade II to IV acute graft-versus-host disease (GVHD) was 53.6% . Out of the 30 patients, 11 were alive and disease-free at a median time of 446 days (range: 124-1153) after CBT. The cumulative 1-year overall survival in patients with standard-risk or high-risk disease was 63.5% and 15.4% , respectively (p=0.01). Conclusion: Although from a retrospective study, these results suggest that unrelated donor CBT could be safe and effective for adult patients with standard-risk disease who cannot find a suitable HLA-matched volunteer marrow or peripheral blood donor.*

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Umbilical cord blood transplantation (CBT) has increasingly been used as a therapeutic option for hematological malignancies (1, 2). Although CBT was initially introduced for pediatric patients, its indication is now rapidly expanding to adults. Several investigators have reported the transplant outcomes of CBT in adult patients, confirming successful restoration of hematopoiesis and further demonstrating favorable outcomes, comparable with those of bone marrow transplantation (BMT) from unrelated donors (3-6). Several recent studies have indicated that cord blood from unrelated donors could be as safe and effective a source of stem cells as bone marrow or mobilized peripheral blood from related donors for adult patients when used as a primary unrelated stem-cell source.

In Japan, CBT is considered for patients with hematological malignancies who lack human leukocyte antigen (HLA)-matched related or unrelated donors, require prompt transplantation because of high-risk disease in the absence of HLA-compatible related donors, or require salvage therapy for graft failure after primary hematopoietic stem- cell transplantation (HSCT) (7-9). Due to the availability of cord blood, CBT has emerged as an effective form of therapy for treating patients for whom allogeneic stem- cell transplantation is not indicated (5, 10, 11). However, the number of institutions capable of performing CBT is limited and there are differences in clinical results for this procedure between centers. The role of unrelated cord blood as an alternative stem cell source is still not well defined in adult patients.

Conventional myeloablative conditioning regimens are associated with significant morbidity and mortality, particularly

in older patients or those with extensive prior therapy or other clinical features associated with transplant-related mortality (TRM) (10-14). On the other hand, high relapse rates may result in a poor rate of disease-free survival (DFS) in reduced-intensity regimens for patients with advanced stages of hematological malignancies. It remains unknown whether CBT is a truly effective option for such patients with advanced or high-risk hematological malignancies, as well as for those with standard-risk hematological malignancies.

Here, the clinical outcomes in 30 consecutive adult patients with standard or high-risk hematological malignancies who received CBT from unrelated donors, is presented.

Patients and Methods

Patiets. Adult patients (age ≥16) with hematological malignancies were eligible for CBT if no HLA-compatible related donor or unrelated bone marrow donor could be identified, if prompt transplantation was considered necessary because of high-risk disease in the absence of HLA-compatible related donors, if salvage therapy was required for graft failure after primary HSCT, or if the patient consented to undergo CBT from an unrelated donor. Between October 2001 and May 2007, a total of 30 consecutive patients underwent CBT from unrelated donors at Okayama University Hospital. A retrospective review of their characteristics and transplant outcomes was conducted.

HLA typing and selection of cord blood units. The HLA-A and HLA-B antigens were typed using standard serological techniques. HLA-DRB1 alleles were typed using low-resolution DNA techniques. Cord blood units were found through the Japan Cord Blood Bank Network. Cord blood units matched at four or more of six HLA loci were selected.

Conditioning regimens. Sixteen patients received myeloablative regimens. Eight patients received total-body irradiation at a dose of 12 Gy (TBI 12 Gy) in six fractions followed by cyclophosphamide (CY) at a dose of 60 mg/kg once daily for 2 days. Five patients with myeloid malignancies received TBI 12 Gy followed by cytosine arabinoside (Ara-C) at a dose of 3 g/m^2 every 12 h for 2 days with concurrent administration of recombinant human granulocyte colony-stimulating factor (G-CSF) and CY at a dose of 60 mg/kg once daily for 2 days, as reported previously (5). Three patients with non-Hodgkin's lymphoma were conditioned with TBI 12 Gy followed by melphalan at a dose of 70 mg/m^2 once daily for 2 days.

Fourteen patients received a fludarabine (FLU) -based reduced-intensity regimen that was indicated for patients who were ineligible for myeloablative conditioning because of age (≥55 years old) and/or comorbidities. Ten patients received FLU at a dose of 30 mg/m^2 for 5 days and CY at a dose of 25 mg/kg for 2 days in combination with TBI 2 Gy. Two patients received FLU at a dose of 30 mg/m^2 for 5 days and Ara-C at a dose of 2 g/m^2 every 12 h for 4 days with concurrent administration of recombinant human G-CSF for 5 days. One patient received FLU at a dose of 30 mg/m^2 for 6 days and oral busulfan 8 mg/kg divided into 8 doses. One patient received FLU at a dose of 10 mg/m^2 for 2 days. In this patient, reduced-intensity CBT (RI-CBT) was performed as salvage therapy for graft failure following primary allogeneic CBT after conditioning with a regimen containing TBI 12 Gy.

Prophylaxis and diagnosis of GVHD. Seventeen patients received a standard combination of cyclosporine (CSA) and short-term methotrexate (MTX) as graft-*versus*-host disease (GVHD) prophylaxis. Ten patients conditioned with reduced-intensity regimens, received CSA and mycophenolate mofetil (MMF) at 30 mg/kg orally twice daily from day −3 to +30. One patient received tacrolimus (TCR) only. CSA or TCR was continued until day 100. If acute GVHD had not occurred by that time, the dose was tapered until complete discontinuance around day 180. Acute and chronic GVHD were diagnosed and graded according to published criteria (15, 16).

Supportive care. All the patients were isolated in a room equipped with a laminar airflow system and received trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis carinii* infection. Fluoroquinolone for prophylaxis against bacterial infection and fluconazole or micafungin for prophylaxis of fungal infection were administered. The patients were also given acyclovir as prophylaxis against herpes virus infection. Neutropenic fever was managed according to the guidelines reported previously by Hughes *et al*. (17). Cytomegalovirus (CMV) monitoring was started at the time of neutrophil recovery with a CMV antigenemia assay. If the result of monitoring became positive, the patient was placed on intravenous ganciclovir or foscarnet as reported previously (18). G-CSF (lenograstim 5 μg/kg/day or filgrastim 300 μg/m^2/day) was given intravenously for 60 minutes starting on day 1 or 5, and was continued until the absolute neutrophil count (ANC) exceeded 5×10^9/L.

Engraftment and chimerism analysis. Neutrophil engraftment was defined as ANC above 0.5×10^9/L on 3 consecutive days. Platelet engraftment was defined as counts above 20×10^9/L independent of transfusion. Chimerism analysis of peripheral blood or bone marrow was performed using quantitative PCR for microsatellite DNA markers. Whole blood and Cluster of differentiation (CD) 3-positive cell chimerism were assessed at the time of neutrophil engraftment. Primary graft failure was defined as profound, persistent pancytopenia and marrow hypoplasia without donor-derived cells on day 56 or when a second allogeneic HSCT was performed.

Statistical analysis. The results are shown as median values with specific ranges of data sets. The probabilities of neutrophil and platelet engraftment, acute and chronic GVHD, non-relapse mortality and relapse, overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan-Meier method. Uni- and multivariate analyses were used to assess the impact of potential prognostic factors in OS and EFS. Differences at $p<0.05$ were considered significant. The analysis was performed using Excel Statistics 2006 statistical software (SSRI Co., Tokyo, Japan).

Results

Characteristics of the patients and umbilical cord blood grafts. The patient characteristics are shown in Table I. Out of the 30 patients with hematological malignancies, 21 were classified as having high-risk disease. Their median age was 45 years (range: 16-67 years) and median body weight was 53 kg (range: 37-71 kg).

The characteristics of cord blood units are also shown in Table I. The median number of cryopreserved cells was 2.65×10^7/kg of patient body weight (range: 1.73-4.87×10^7/kg)

Table I. *Characteristics of CBT patients and grafts*.

Number of subjects	30
Gender (male/female)	15/15
Age, median years (range)	45 (16-67)
Body weight, mean kg (range)	53 (37-71)
Performance status	
0-1	17
2-4	13
Underlying diseases	
Acute myelogenous leukemia	6
Myelodysplastic syndrome	7
Acute lymphoblastic leukemia	4
Chronic myelogenous leukemia	1
Non-Hodgkin's lymphoma	12
Risk of underlying diseases	
High	21
Standard	9
Previous history of stem-cell transplantation[a]	
Yes	11
No	19
Serological HLA mismatches	
0	5
1	10
2	15
Recipient CMV serological status	
Positive	28
Negative	2
Conditioning regimen	
Myeloablative	
TBI 12Gy+CY	8
TBI 12Gy+AraC/G-CSF+CY	5
TBI 12Gy+L-PAM	3
Reduced-intensity	
TBI 2Gy+FLU+CY	10
FLU+AraC/G-CSF	2
FLU+BU	1
FLU alone	1
GVHD prophylaxis	
Cyclosporine + short-term MTX	17
Cyclosporine + MMF	10
Cyclosporine + methyl prednisone	1
Tacrolimus + short-term MTX	1
Tacrolimus alone	1
Transplanted nuclear cells ($\times 10^7$/kg)	
median (range)	2.65 (1.73-4.87)
Transplanted CD34 positive cells ($\times 10^5$/kg)	
median (range)	0.94 (0.21-7.00)

HLA: human leukocyte antigen, CMV: cytomegalovirus, TBI: total body irradiation, CY: cyclophosphamide, AraC: cytosine arabinoside, G-CSF: granulocyte colony-stimulating factor, L-PAM: melphalan, FLU: fludarabine, BU: busulfan, GVHD: graft-versus-host disease, MTX: methotrexate, MMF: mycophenolate mofetil. Acute leukemia in first or second complete remission, chronic myelogenous leukemia in chronic phase, non-Hodgkin lymphoma in remission and myelodysplastic syndrome in first remission were defined as standard -risk disease. All other conditions were defined as high -risk disease. [a]autologous and allogeneic hematopoietic stem- cell transplantation.

and the number of mismatched HLA loci was one in ten patients and two in 15 patients. T-cell depletion was not performed.

Hematological reconstitution and chimerism analysis. Out of the 30 patients, 23 achieved neutrophil engraftment at a median time of 22 days (range: 13-42 days) after CBT. Nineteen out of the 23 patients with neutrophil engraftment achieved platelet engraftment at a median time of 44 days (range: 18-83 days) after CBT. Primary graft failure was diagnosed in two patients (6.7%). One patient with acute myelogenous leukemia (AML) transformed from myelodysplastic syndrome (MDS) was conditioned with a myeloablative regimen. This patient underwent a second CBT from another donor after conditioning with a FLU-based reduced-intensity regimen. The other patient with MDS (Refractory anemia with excess of blasts -2) was conditioned with a myeloablative regimen. This patient showed autologous recovery at day14 and survival in complete response (CR) for 494 days. Chimerism analysis was performed using peripheral blood or bone marrow cells in all patients on day 21 or 28. All except one patient with durable hematological reconstitution achieved complete donor chimerism.

Acute and chronic GVHD. Eighteen out of the 22 patients who could be evaluated developed acute GVHD (grade I in six patients, grade II in nine patients, grade III in two patients and grade IV in one patient) and the cumulative incidence of grade II to IV acute GVHD was 53.6 % (95% confidence interval (95% CI): 33-74%) (Figure 1-A). Eight out of the 15 patients who could be evaluated developed chronic GVHD from day 71 to day 128, including four patients who had the extensive type and four who had the limited type. The cumulative incidence of chronic GVHD was 60.8 % at 1 year (95% CI: 33-88%) (Figure 1-B). Acute and chronic GVHD was well controlled by CSA and/or systemic glucocorticoid.

Non-relapse mortality and relapse. Out of the 30 patients, 19 died. Nine out of these 19 patients died of disease progression after CBT. All except one of these patients had diseases classified as high-risk for transplantation. The causes of non-relapse mortality (NRM) were bacterial infections including bacteremia in four patients, pneumonia in two patients, fungal infection of disseminated candidemia in one patient, acute GVHD in one patient, thrombotic microangiopathy in one patient and intestinal hemorrhage in one patient.

The incidences of NRM were 25.6% (95% CI: 9.1-42%) at day 100 and 41.4% (95% CI: 20-62%) at 1 year among the CBT recipients (Figure 2-A). The cumulative incidences of 100-day and 1-year NRM in the patients with standard-risk disease were 11.1% (95% CI: 0.0-32%) and 23.8% (95% CI: 0.0-53%), and in those with high-risk disease were 32.4% (95% CI: 11-54%) and 49.9% (95% CI: 23-77%), respectively (p=0.17).

The incidences of disease relapse or progression for the 30 patients receiving CBT for hematological malignancies

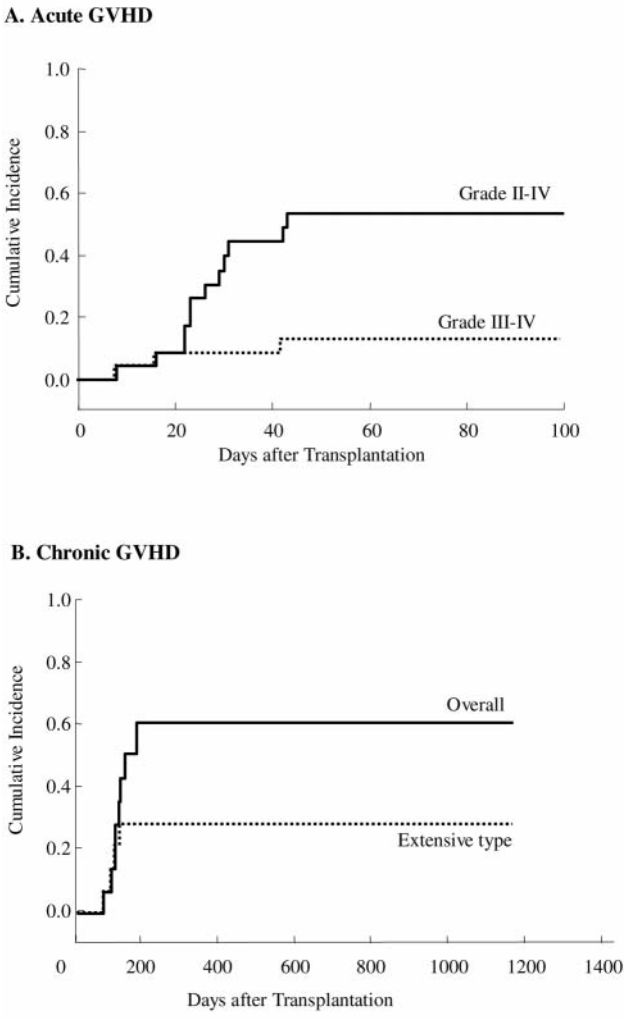

Figure 1. *Cumulative incidence of graft-versus-host disease (GVHD) after cord blood transplantation. (A) Cumulative incidence of acute GVHD. The rate of grade II–IV acute GVHD on day 100 was 53.6% (95% CI, 33-74%). The rate of grade III–IV acute GVHD on day 100 was 13.3% (95% CI, 0.0-27%). (B) Cumulative incidence of chronic GVHD in patients surviving more than 100 days. The rate of overall chronic GVHD was 60.9% (95% CI, 33-88%) at 1 year after cord blood transplantation. The rate of extensive-type chronic GVHD was 28.6% (95% CI, 4.9-52%) at 1 year after cord blood transplantation.*

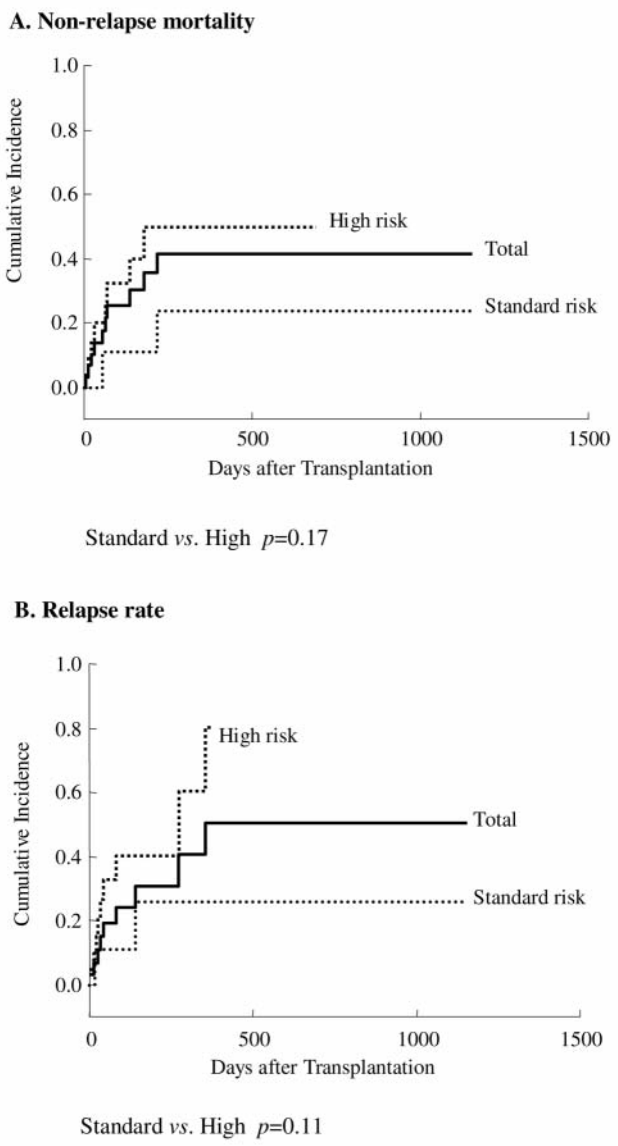

Figure 2. *Cumulative incidence of non-relapse mortality and relapse after cord blood transplantation. (A) Cumulative incidences of 100-day and 1-year NRM were 25.6% (95% CI, 9.1-42%) and 41.4% (95% CI, 20-62%) in CBT recipients, respectively. (B) Cumulative incidences of 100-day and 1-year relapse rate among recipients were 24.3% (95% CI, 7.1-42%) and 50.4% (95% CI, 23-78%) after CBT, respectively.*

were 24.4% (95% CI: 7.1-42%) at day 100 and 50.4% (95% CI: 23-78%) at 1 year (Figure 2-B). The cumulative incidences of 100-day and 1-year disease relapse were 11.1% (95% CI: 0.0-32%) and 25.9% (95% CI: 10-58%) in the patients with standard-risk disease, and 40.4% (95% CI: 17-64%) and 80.1% (95% CI: 47-100%) in those with high-risk disease, respectively (p=0.11).

Survival. Out of the 30 patients, 11 were alive and disease-free between 124 and 1153 days after CBT (median: 446 days). OS was 60.0% (95% CI: 42-78%) at day 100 and 30.8% (95% CI: 13-49%) at 1 year (Figure 3-A). The cumulative 100-day and 1-year OS were 88.9% (95% CI: 68-100%) and 63.5% (95% CI: 30-97%) in the patients with standard-risk disease, and 47.6% (95% CI: 26-69%) and 15.4% (95% CI: 0.0-34%) in those with high-risk disease, respectively (p=0.01). Prognostic factors associated with OS at day 180 in univariate analysis were performance status (2-4 *vs*. 0-1,

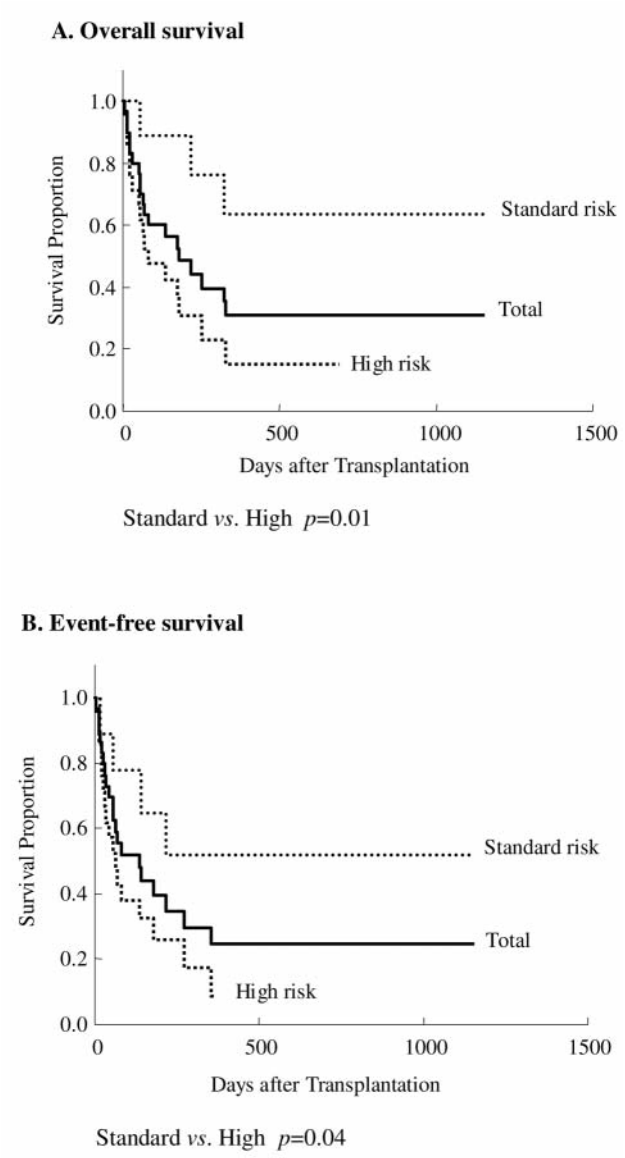

Figure 3. *Cumulative 100-day and 1-year overall survival and event-free survival after cord blood transplantation. (A) Cumulative 100-day and 1-year overall survival in total patients were 60.0% (95% CI, 42-78%) and 30.8% (95% CI, 13-49%) after CBT, respectively. Cumulative 100-day and 1-year overall survival in patients with standard-risk disease were 88.9% (95% CI, 6.8-100%) and 63.5% (95% CI, 30-97%), and in those with high-risk disease were 47.6% (95% CI, 26-69%) and 15.4% (95% CI, 0.0-34%), respectively (p=0.01). (B) Cumulative 100-day and 1-year EFS in total patients were 52.1% (95% CI, 32-68%) and 24.8% (95% CI, 6.8-41%), respectively. Cumulative 100-day and 1-year EFS in patients with standard-risk disease were 77.8% (95% CI, 51-100%) and 51.9% (95% CI, 17-86%), and in those with high-risk disease were 38.1% (95% CI, 17-59%) and 8.7% (95% CI, 0.0-24%), respectively (p=0.04).*

hazard ratio: 6.67, 95% CI: 1.24-35.71%, p=0.027) and risk of underlying disease (high *vs*. standard, hazard ratio: 16.33, 95% CI: 1.63-163.4%, p=0.017) (Table II).

The probability of EFS was 50.0% (95% CI: 32-68%) at day 100 and 23.8% (95% CI: 6.8-41%) at 1 year (Figure 3-B). The cumulative 100-day and 1-year EFS were 77.8% (95% CI: 51-100%) and 51.9% (95% CI: 17-86%) in the patients with standard-risk disease, and 38.1% (95% CI: 17-59%) and 8.7% (95% CI: 0.0-24%) in those with high-risk disease, respectively (p=0.04). On multivariate analysis, the conditioning regimen was a prognostic factor associated with EFS at day 180 (reduced-intensity *vs*. myeloablative, hazard ratio: 0.12, 95% CI: 0.015-0.97%, p=0.047) (Table III).

Discussion

The present findings included a trend toward a lower NRM rate and higher OS in the patients with standard-risk disease, a trend toward a higher relapse rate and lower EFS in the patients with high-risk disease and reduced-intensity conditioning (RIC) regimen as a favorable factor associated with EFS. Notably, 1-year OS in the patients with standard-risk disease was 63.5% (95% CI: 30-97%), which was almost the same as for other HSC sources reported previously (19-23). While studies in larger numbers of patients and with longer follow-up periods are needed to verify the significance of these observations, it is clear that the use of unrelated donor CBT extends the availability of transplantation to patients with standard-risk disease who cannot find a suitably HLA matched adult volunteer marrow or peripheral blood donor. In addition, the low TRM in older patients without other risk factors suggested that age alone should not be a barrier to transplantation as a therapeutic option. These observations support the suggestion that older patients with high-risk hematological diseases can now be offered umbilical CBT with nonmyeloablative conditioning as a potentially curative treatment option.

Significant delays in neutrophil and platelet engraftment rates have been reported after CBT. However, overall hematopoietic engraftment rates were almost the same for both CBT and BMT grafts (22). In the present CBT series, the cumulative incidence of neutrophil engraftment was 90.6% at day 42 after CBT. The rates of early death (death within 28 days after CBT) and primary graft failure were 17% and 8%, respectively. These encouraging CBT results reflected the availability of grafts containing sufficient cell numbers (24, 25). The median cell number was 2.65×10^7 cells/kg, and only three out of the 30 patients received cord blood containing less than 2.0×10^7 cells/kg. Immunosuppression by a combination of CSA and MTX or of CSA and MMF may also have contributed to the engraftment. However, primary graft failure is still a significant problem in unrelated CBT and is associated with a high mortality rate. Narimatsu *et al*. reported a graft failure rate following CBT with reduced-intensity conditioning of 7.3% (7), and the present CBT results showing an engraftment failure rate of

Table II. *Univariate analysis of prognostic factors associated with overall and event-free survival.*

Univariate factors	Hazard ratio	95% CI	*P*-value
Overall survival at day 180			
Age (<45 years *vs.* ≥45 years)	1.33	0.30-5.91	0.705
Gender (female *vs.* male)	1.83	0.40-8.27	0.433
Performance status (2-4 *vs.* 0-1)	6.67	1.24-35.71	0.027
Risk of underlying disease (high *vs.* standard)	16.33	1.63-163.4	0.017
Previous history of stem- cell transplantation (yes *vs.* no)[a]	0.58	0.12-2.88	0.507
HLA mismatches (2 *vs.* 0-1)	0.42	0.09-1.91	0.259
Conditioning regimen (reduced-intensity *vs.* myeloablative)	0.57	0.13-2.57	0.465
Number of infused nuclear cells ($<3.0\times10^7$ *vs.* $\geq3.0\times10^7$/kg)	0.67	0.14-3.19	0.612
Number of infused CD34 positive cells ($<1.0\times10^5$ *vs.* $\geq1.0\times10^5$/kg)	1.29	0.29-5.77	0.743
Grade II-IV acute GVHD (yes *vs.* no)	0.86	0.15-5.00	0.860
Event-free survival at day180			
Age (<45 years *vs.* ≥45 years)	1.39	0.28-6.84	0.686
Gender (female *vs.* male)	1.72	0.35-8.50	0.507
Performance status (2-4 *vs.* 0-1)	3.43	0.65-18.22	0.148
Risk of underlying diseases (high *vs.* standard)	4.67	0.48-45.55	0.185
Previous history of stem- cell transplantation (yes *vs.* no)a	0.86	0.16-4.55	0.856
HLA mismatches (2 *vs.* 0-1)	0.72	0.15-3.54	0.686
Conditioning regimen (reduced-intensity *vs.* myeloablative)	0.21	0.03-1.28	0.090
Number of infused nuclear cells ($<3.0\times10^7$ *vs.* $\geq3.0\times10^7$/kg)	0.58	0.11-2.95	0.509
Number of infused CD34 -positive cells ($<1.0\times10^5$ *vs.* $\geq1.0\times10^5$/kg)	0.91	0.18-4.50	0.907
Grade II-IV acute GVHD (yes *vs.* no)	1.5	0.20-11.54	0.697

95% CI: 95% confidence interval, HLA: human leukocyte antigen, GVHD: graft-versus-host disease. [a]autologous and allogeneic hematopoietic stem- cell transplantation.

Table III. *Multivariate analysis of prognostic factors associated with overall and event-free survival.*

Multivariate factors	Hazard ratio	95% CI	*P*-value
Overall survival at day 180			
Performance status (2-4 *vs.* 0-1)	2.50	0.35-18.04	0.363
Risk of underlying diseases (high *vs.* standard)	9.33	0.71-122.6	0.089
Event-free survival at day 180			
Performance status (2-4 *vs.* 0-1)	3.36	0.35-32.62	0.296
Risk of underlying diseases (high *vs.* standard)	3.43	0.21-56.34	0.388
Conditioning regimen (reduced-intensity *vs.* myeloablative)	0.12	0.015-0.97	0.047

95% CI: 95% confidence interval.

6.7% were consistent with this report. Unlike other stem- cell sources, neutrophil recovery after CBT is delayed, and the recipients suffer severe infections such as bacteremia during neutropenia. In CBT, therefore, the transplant physician must judge whether donor cell engraftment has been achieved before deterioration of the patient's general condition.

The reported incidences of moderate to severe (grade II to IV) and severe (grade III to IV) acute GVHD after CBT in adults range from 27-73% and from 17-32%, respectively (3-6). Kishi *et al.* reported that the incidence of pre-engraftment immune reaction (PIR) was 63.3% after RI-CBT for adult patients receiving CSA alone as GVHD prophylaxis (26). The incidence of PIR in the present study was 30.0%, and most cases of PIR responded to steroid therapy. PIR after CBT may be the hyperacute immune reaction, and in the present study the early immune reaction after CBT was included in acute GVHD. Despite a high frequency of HLA-mismatched grafts, the risk of developing acute GVHD in the present study was lower than that in BMT, as described elsewhere (27, 28), which was significant for grades III and IV severe acute GVHD. In the present study, the incidence of acute GVHD was mostly due to grade II disease (40.3%) and GVHD itself was infrequently the primary cause of death (6.0%). These observations were consistent with those of other CBT reports from Japanese transplant institutes (5, 19, 29-31). The lower incidence of

severe acute GVHD in Japan compared with previous reports from western countries could be related to the higher frequency of the gene that induces higher interleukin-10 production in the Japanese population (32) or may reflect a lower degree of diversity of HLA and minor histocompatibility antigens in the Japanese population. In terms of chronic GVHD, only a small proportion of patients developed the extensive-type (cumulative incidence: 28.5% , 95% CI: 4.9-52%) and most did not require extended immunosuppression. These findings were also consistent with those of other CBT reports from Japanese transplant institutes (5, 19, 29-31), although adult series of bone marrow or peripheral blood stem- cell transplants have indicated an incidence of extensive-type chronic GVHD ranging from 30-70% (19-22).

In summary, cord blood units matched at four or more of six HLA loci are an acceptable alternative source of hematopoietic stem cells for adult patients with hematological diseases. Unrelated cord blood, which has the advantage of rapid availability, could be safe and effective for adult patients with standard-risk disease and older patients without other risk factors if no suitably HLA -matched volunteer marrow or peripheral blood donors are available.

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References

1 Benito Al, Diaz MA, Gonzalez-Vicent M *et al*: Hematopoietic stem cell transplantation using umbilical cord blood progenitors: review of current clinical results. Bone Marrow Transplant *33*: 675-690, 2004.

2 Cohen Y and Nagler A: Umbilical cord blood transplantation – how, when, and for whom? Blood Rev *18*: 167-179, 2004.

3 Sanz GF, Saavedra S, Planelles D *et al*: Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies. Blood *98*: 2332-2338, 2001.

4 Laughlin MJ, Barker J, Bambach B *et al*: Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donor. N Eng J Med *344*: 1815-1822, 2001.

5 Takahashi S, Iseki T, Ooi J *et al*: Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. Blood *104*: 3813-3820, 2004.

6 Cornetta K, Laughlin M, Carter S *et al*: Umbilical cord blood transplantation in adults: results of the Prospective Cord Blood Transplantation (COBLT). Biol Blood Marrow Transplant *11*: 149-160, 2005.

7 Narimatsu H, Kami M, Miyakoshi S *et al*: Graft failure following reduced-intensity cord blood transplantation for adult patients. Br J Haematol Marrow *132*: 36-41, 2006.

8 Ohwada C, Nakaseko C, Ozawa S *et al*: Second, cord blood transplantation (CBT) with reduced-intensity conditioning for graft failure after the first CBT for AML. Bone Marrow Transplant *34*: 999-1000, 2004.

9 Shimada K, Narimatsu H, Morishita Y *et al*: Severe regimen-related toxicity of second transplantation for graft failure following reduced-intensity cord blood transplantation in an adult patient. Bone Marrow Transplant *37*: 787-788, 2006.

10 Laughlin MJ, Eapen M, Rubinstein P *et al*: Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Eng J Med *351*: 2265-2275, 2004.

11 Rocha V, Labopin M, Sanz G *et al*: Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Eng J Med *351*: 2276-2285, 2004.

12 di Grazia C, Raiola AM, Van Lint MT *et al*: Conventional hematopoietic stem cell transplants from identical or alternative donors are feasible in recipients relapsing after an autograft. Haematologica *86*: 646-651, 2001.

13 Uzunel M, Remberger M, Sairafi D *et al*: Unrelated *versus* related allogeneic stem cell transplantation after reduced intensity conditioning. Transplantation *82*: 913-919, 2006.

14 Radich JP, Gooley T, Sanders JE *et al*: Second, allogeneic transplantation after failure of first autologous transplantation. Biol Blood Marrow Transplant *6*: 272-279, 2000.

15 Przepiorka D, Weisdorf D, Martin P *et al*: Consensus conference on acute GVHD grading. Bone Morrow Transplant *15*: 825-855, 1995.

16 Shulman HM, Sullivan KM, Weiden PL *et al*: Chronic graft-*versus*-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med *69*: 204-217, 1980.

17 Hughes WT, Armstrong D, Bodey GP *et al*: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis *34*: 730-751, 2002.

18 Mori T, Okamoto S, Matsuoka S *et al*: Risk-adapted pre-emptive therapy for cytomegalovirus disease in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant *25*: 765-769, 2000.

19 Takahashi S, Ooi J, Tomonari A *et al*: Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. Blood *109*: 1322-1330, 2007.

20 Oran B, Giralt S, Saliba R *et al*: Allogeneic hematopoietic stem cell transplantation for the treatment of high-risk acute myelogenous leukemia and myelodysplastic syndrome using reduced-intensity conditioning with fludarabine and melphalan. Biol Blood Marrow Transplant *13*: 454-462, 2007.

21 Wong R, Giralt SA, Martin T *et al*: Reduced-intensity conditioning for unrelated donor hematopoietic stem cell transplantation as treatment for myeloid malignancies in patients older than 55 years. Blood *102*: 3052-3059, 2003.

22 Baron F, Storb R, Storer BE *et al*: Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. J Clin Oncol *24*: 4150-4157, 2006.

23 Barker JN, Davies SM, DeFor T *et al*: Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: result of a matched-pair analysis. Blood *97*: 2957-2961, 2001.

24 Gluckman E, Rocha V, Boyer-Chammard A *et al*: Outcome of cord-blood transplantation from related and unrelated donors: Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N Engl J Med *337*: 373-381, 1997.

25 Rubinstein P, Carrier C, Scaradavou A *et al*: Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med *339*: 1565-1577, 1998.

26 Kishi Y, Kami M, Miyakoshi S *et al*: Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. Transplant *80*: 34-40, 2005.

27 Rocha V, Cornish J, Sievers EL *et al*: Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood *97*: 2962-2971, 2001.

28 Rocha V, Wagner JE, Sobocinski KA *et al*: Graft-*versus*-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling: Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N Engl J Med *342*: 1846-1854, 2000.

29 Mori T, Aisa Y, Nakazato R *et al*: Tacrolimus and methotrexate for the prophylaxis of graft-*versus*-host disease after unrelated donor cord blood transplantation for adult patients with hematologic malignancies. Transplant Proc *39*: 1615-1619, 2007.

30 Miyakoshi S, Yuji K, Kami M *et al*: Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. Clin Cancer Res *10*: 3586-3592, 2004.

31 Miyakoshi S, Kami M, Tanimoto T *et al*: Tacrolimus as prophylaxis for acute graft-*versus*-host disease in reduced intensity cord blood transplantation for adult patients with advanced hematologic diseases. Transplant *84*: 316-322, 2007.

32 Lin M-T, Storer B, Martin PJ *et al*: Relation of an interleukin-10 promoter polymorphism to graft-*versus*-host disease and survival after hematopoietic-cell transplantation. N Engl J Med *349*: 2201-2210, 2003.

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