Feasibility of cord blood transplantation in chemosensitive adult T-cell leukemia/lymphoma: A retrospective analysis of the Nagasaki Transplantation Network

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Abstract

It has been reported that cord blood transplantation (CBT) for patients with aggressive adult T-cell leukemia/lymphoma (ATL) results in poorer outcomes than transplantation using other stem cell sources. To identify a subset of ATL in which CBT is feasible, we retrospectively analyzed 27 patients treated with CBT at three institutions in Nagasaki Prefecture, Japan. The estimated overall survival (OS) rate at three years was 27.4%. Of 16 patients that received CBT during remission (complete, CR, or partial, PR), the OS rate at three years was 50%, while during refractory periods (non-CR or non-PR), the OS rate was 9.1%. Reduced intensity conditioning (RIC) was given to 18 patients, and myeloablative conditioning (MAC) was used in nine, with 3-year OS of 50.0% and 0%, respectively. Of the 19 deaths, nine were due to progressive disease, eight (five MAC and three RIC) to infection, and two to multiple organ failure. These results suggest that CBT provides similar results with those in other transplantation procedures for selected ATL patients, such as those in CR or PR. Further studies are needed to evaluate the use of CBT in aggressive ATL.

Keywords: cord blood transplantation, adult T-cell leukemia/lymphoma, chemosensitivity,

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been applied as a curative option to patients with aggressive ATL [1, 2]. Several reports have demonstrated that allo-HSCT from related and unrelated peripheral blood (PB) or bone marrow (BM) is effective for ATL with a 3-year overall survival (OS) between 30 to 40%, despite high transplant-related mortality (TRM) rate [3-8]. It was also shown that allo-HSCT could provide long-term survival for some patients with aggressive ATL probably associated with graft-versus-lymphoma (GVL) effects [9].

A recent nationwide retrospective study of allo-HSCT in 386 patients with ATL based on the registry data of the Japan Society for Hematopoietic Cell Transplantation, the Japan Marrow Donor Program (JMDP) and the Japan Cord Blood Bank Network demonstrated that the 3-year OS of cord blood transplantation (CBT) is inferior to that of HLA-matched related and unrelated transplantation (17% vs 41% and 39%, respectively), and CBT was one of the four recipient factors associated with lower survival rate [8]. The same group also reported the effect of graft-versus-host disease (GVHD) and the intensity of conditioning regimen (reduced intensity conditioning, RIC, myeloablative conditioning, MAC) in allo-HSCT for ATL. They showed that grade I/II acute GVHD was associated with improved survival after allo-HSCT (including CBT) for ATL. The beneficial effect of mild acute GVHD was selected by multivariate analysis, suggesting that it would work in the setting of CBT as well [9]. Interestingly, the intensity of conditioning before transplantation did not have a significant impact on the overall survival for ATL patients that received allo-HSCT using BM or PB as stem cell sources [10], although HSCT with RIC was significantly associated with ATL-related mortality.

Based on these reports, we thought that there might be a subset of ATL patients for which CBT could provide survival benefit, probably through graft-versus-ATL (GvATL) effect. To evaluate this possibility,

we analyzed retrospectively our experiences of CBT for 27 ATL patients in the Nagasaki Transplantation Network. We could demonstrate that there were several long-term survivors after CBT, and that CBT might be an option for selected ATL patients such as those within clinical remission.

Patients and method

Study design and data collection

Between October 2004 and July 2010, 27 patients with aggressive ATL underwent CBT using both myeloablative and reduced-intensity conditioning at three institutions in Nagasaki prefecture. Data were collected and updated in September 2011. Three patients were included in a previous report of a nationwide retrospective study of the allo-HSCT for ATL by Hishizawa et al. [8], and the data of two of these patients were updated. Before the transplantation procedure, all patients received conventional chemotherapy including anthracyclines. The median duration from diagnosis to transplantation was 114 days (range: 56–481 days).

Transplantation

Of the 9 patients who received MAC, 3 received cyclophosphamide (CY; 60 mg/kg i.v. daily for 2 days) and busulfan (BU; 4 mg/kg p.o. or 3.2 mg/kg i.v. daily for 4 days), and 6 received CY and total body irradiation (TBI; total 12 Gy, 6 fractions) with or without cytarabine (2 g/m^2 i.v. for 4 days). All 18 patients except one in RIC group received fludarabine (FLU) and melphalan (MEL) with or without TBI regimen. 13 received FLU (25 mg/m^2 i.v. daily for 5 days), MEL (80 mg/m^2 i.v. for one day), and TBI (4 Gy), 4 received FLU and MEL, and 1 received FLU, BU (3.2 mg/kg i.v. daily for 2 days) and TBI (2 Gy). Prophylaxis against GVHD was as follows: tacrolimus (Tac), n=12; Tac and methotrexate (MTX), n=7;

cyclosporine A (CyA) and MTX, n=7; and CyA only, n=1 (Table 1).

Statistical analysis and definition

OS was measured from day 0 of transplantation until death from any cause or the last known follow-up. TRM was defined as all causes of non-relapse death after transplantation. Response was judged using Japan Clinical Oncology Group criteria for ATL as described [11, 12]. Survival curves were estimated using the Kaplan-Meier method.

Results

Patient characteristics

Clinical characteristics of the patients are summarized in Tables 1 and 2. All patients had aggressive ATL (17 acute and 10 lymphoma). Median age was 52 (range: 41–63) years. Sixteen patients showed a clinical response to prior chemotherapy (5 complete remission, 10 first partial remission (PR), and 1 second PR). These patients were categorized as being “chemosensitive”, while others were as “refractory” to chemotherapy. Number of chemosensitive patients was 4 and 12, and that of refractory patients was 5 and 6 in the MAC group and RIC group, respectively.

Engraftment

All patients received a cord blood cell infusion of over 2 x 10^7/kg (median 2.75; range: 2.00–4.28 x 10^7/kg). All cord-blood grafts, except one, were HLA-mismatched; 4 with one antigen mismatch, and 22 with two antigens. Two patients did not achieve engraftment because of early relapse, and three patients were not evaluable because of early treatment-related mortality before engraftment. A total of 22 patients

achieved neutrophil regeneration, and the median number of days was 20 (range: 13–98 days).

Overall outcome

The median survival time of all cases after transplantation was 192 days (range: 6–2530 days), and the median observation time of the 8 surviving patients was 1079.5 days (range: 666–2530 days) at the time of analysis (September 2011). The estimated OS rate at 3 years in all cases was 27.4% after transplantation (Figure 1). The OS rate at 3 years in the chemosensitive group (CR and PR, 16 patients) and refractory group (primary induction failure and relapse, 11 patients) was 50.0% and 9.1%, respectively, while that in the RIC group and MAC group was 50.0% and 0%, respectively (Figures 2 and 3).

Cause of death

After transplantation, 19 patients died; 9 due to progressive disease (PD) and 10 due to TRM. Of the 10 TRM deaths, 8 were due to infection (5 bacterial, 2 adenovirus, and 1 cytomegalovirus pneumonia), and 2 were due to multi-organ failure (MOF). All 9 patients who received MAC died; 6 due to TRM (5 infections and 1 MOF) and 3 due to progressive disease (PD). Of the 4 patients with chemosensitivity in the MAC group, 2 died due to PD and 2 to infection. Of the 18 patients who received RIC, 10 patients died. There were 6 deaths (5 PD and 1 MOF) among the 13 patients who received FLU, MEL, and TBI, 3 deaths (2 infections and 1 PD) among the 4 patients who received FLU and MEL, and 1 death (infection) of a patient who received FLU, BU, and TBI. Within 6 months after transplantation, there were 6 deaths (4 infections, 1 MOF and 1 PD) in patients who received MAC and 7 deaths (3 infections, 1 MOF and 3 PD) in patients who received RIC.

Graft-versus-host disease

A total of 8 patients developed acute GVHD at a median of 28 days (range: 14–46 days); 3 with grade I, 4 with grade II, and 1 with grade IV. All four patients with grade II acute GVHD improved spontaneously. Only the grade IV patient received immunosuppressive treatment and improved. No GVHD was implicated in any deaths. Chronic GVHD was observed in 3 patients and was developed from acute GVHD; extensive type in 2 patients and limited type in 1. Among the 3 patients with chronic GVHD, 2 survived without relapse for 2.3 and 1.8 years. The other patient survived after relapse for 0.7 years and finally died due to PD.

Long-term survivors

Eleven patients survived more than one year (Table 2). After transplantation, the median follow-up period was 2.3 years, and the longest follow-up period was 6.9 years. Eight and 3 patients were in chemosensitive and refractory group, respectively. Ten patients received RIC (9 with FLU, MEL, and TBI 4 Gy, and 1 with FLU and MEL), and only 1 patient received MAC. A total of 8 patients survived for a median of 3.0 (1.8-6.9) years. Of these 8 patients 7 were in chemosensitive group and all received RIC. Three of 4 patients who survived more than 3 years were also in chemosentisitive group. One patient who relapsed after 45 months transplantation achieved another CR by local radiation therapy and was alive 5 years after transplantation.

Discussion

Previous studies reported that there was no difference in the outcome after allo-HSCT using CB compared that using HLA-matched [13] or HLA-mismatched [14] unrelated transplantation for adults

with acute leukemia. ATL was not included in these studies, however, in a nationwide retrospective study of allo-HSCT for ATL in Japan, the 3-year OS rate after CBT of 17% was significantly inferior to that of HLA-matched unrelated and mismatched related transplantation by 39% and 24%, respectively [8]. The reasons for the poor outcome of CBT for ATL were considered to be high incidence of TRM, especially with fatal infectious complications [3], that was related to the preexisting profound immunodeficiency of ATL [15, 16] .

The 3-year OS rate of CBT was 27.4 % in our study with several long-term survivors. Eight out of the 11 patients who survived more than one year showed chemosensitivity and received transplantation during CR or PR. This resulted in the difference of OS between chemosensitive (3-year OS, 50.0%) and refractory (3-year OS, 9.1%) patients (Figure 2). Considering that CBT during refractory status of ATL ended in poor outcome (5 cases of TRM, and 5 of PD), it suggested that CBT could provide reliable efficacy for limited ATL patients that were associated with chemosensitivity.

We also found that RIC showed better OS than MAC in our analysis (3-year OS of 50% and 0%, respectively, Figure 3). It has been reported that CBT after MAC is safe and effective treatment for adult patients with hematologic malignancies [17, 18], which did not include ATL. In our analysis, 6 out of 9 patients that received MAC died with TRM, although there was no highly intensified conditioning regimen in MAC. The difference of TRM in the MAC group (6 of 9 patients) and RIC group (3 of 18 patients) seemed stem from the uneven distribution of chemosensitive patients; chemosensitive patients were biased in RIC group (12 out of 18, and 4 out of 9 in RIC and MAC, respectively). This is the limitation of our study with small number of cases to evaluate the relationship of the effect of chemosensitivity and conditioning regimen. A recent nationwide retrospective study of allogeneic bone marrow and peripheral blood stem cell transplantation for ATL in Japan with special emphasis on the

effect of the preconditioning regimen revealed that TRM in MAC was higher than in RIC and that RIC was more significantly associated with ATL-related mortality than MAC, although no significant difference in OS between MAC and RIC recipients was observed [10]. RIC might provide long-term survival by reducing TRM.

It was previously reported that GvATL effect might affects long-term survival of patient with ATL after allo-HSCT from related marrow and peripheral blood and unrelated marrow donors [1, 3, 5]. Recent report by Kanda et al. demonstrated that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival in allografted patients with ATL [9], which was in accordance with previous data [1, 3, 5]. In the present study, one patient that relapsed after CBT had achieved another CR only by local radiation therapy, and survived more than two years. With a suggestive anti-lymphoma effect after CBT for a patient with peripheral T-cell lymphoma and mycosis fungoides [19], CvATL effect could also work after CBT for ATL.

Our results suggested that CBT could be feasible treatment for selected patients with ATL, probably those with chemosensitivity. Further clinical studies for the development of proper indication of CBT, an effective transplant procedure including a preconditioning regimen are needed. For this purpose, a clinical trial of CBT with FLU, MEL, and TBI 4 Gy for chemosensitive ATL are underway in Japan.

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Conflict of interest: The authors declare that they have no conflict of interest.

Figure 1. Kaplan-Meier estimates of overall survival after cord blood transplantation for all patients with ATL.

Figure 2. Kaplan-Meier estimates of overall survival after cord blood transplantation according to chemosensitivity.

Figure 3. Kaplan-Meier estimates of overall survival after cord blood transplantation according to conditioning type.

Figure 1

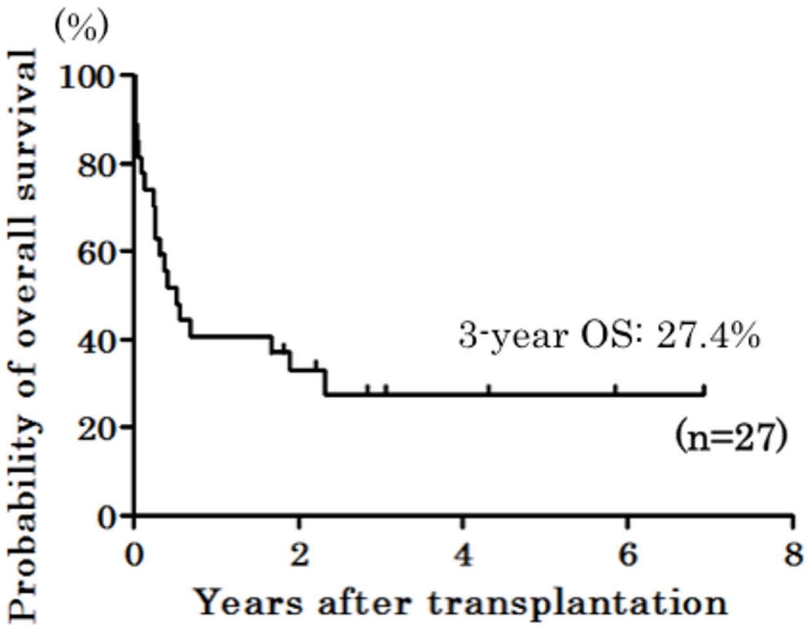
(%)
100
80
60
40
20
0
Probability of overall survival
3-year OS: 27.4%
(n=27)
0
2
4
6
8
Years after transplantation

Figure 2

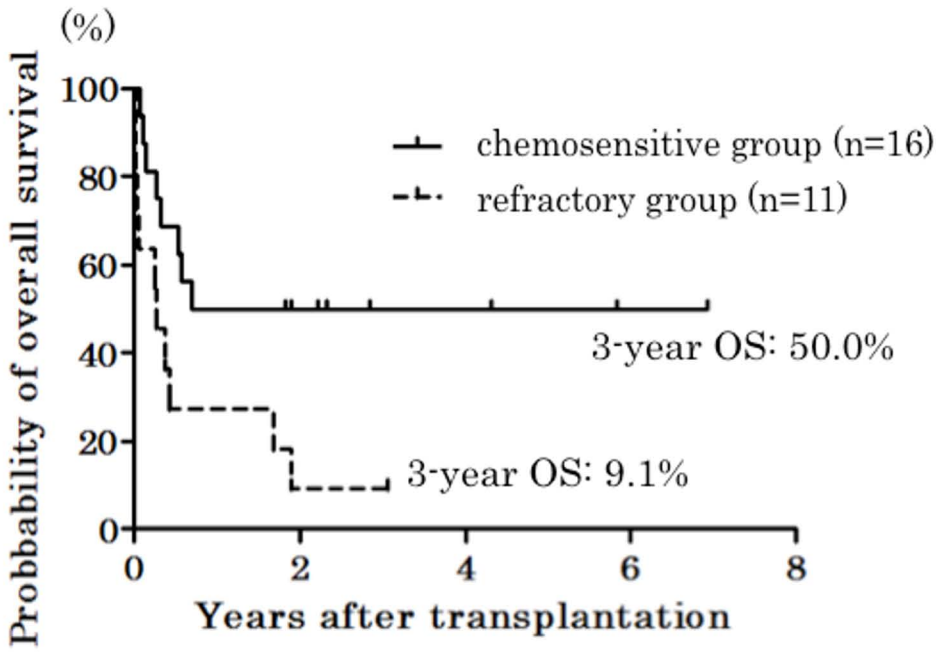
(%)
100
80
60
40
20
0
Probbability of overall survival
chemosensitive group (n=16)
refractory group (n=11)
3-year OS: 50.0%
3-year OS: 9.1%
0
2
4
6
8
Years after transplantation

Figure 3

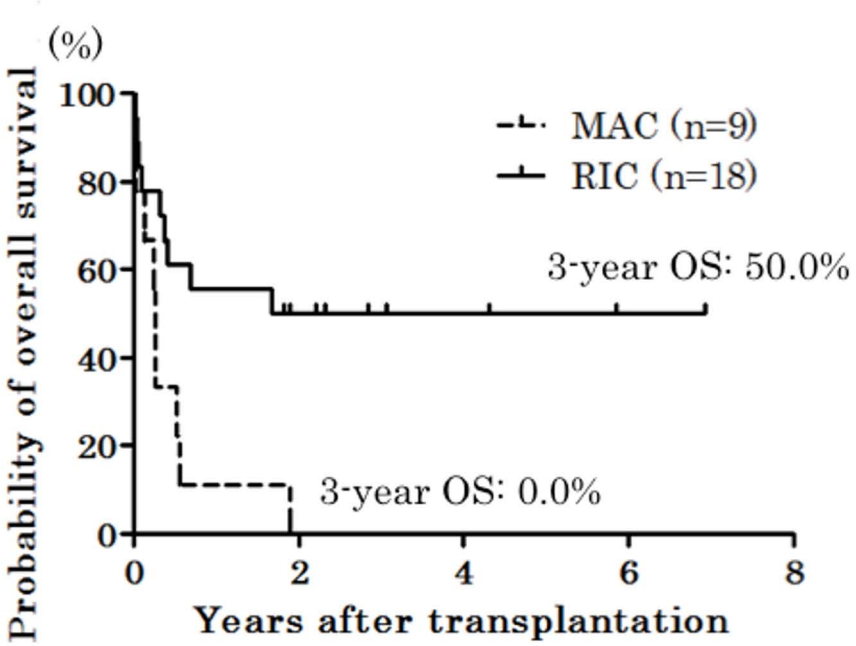
(%)
Probability of overall survival
100
80
60
40
20
0
0
2
4
6
8
Years after transplantation
MAC (n=9)
RIC (n=18)
3-year OS: 50.0%
3-year OS: 0.0%

Table 1.Patinet characteristics and transplant condition

Sex (male/female)	18/9
Median age at transplant (range)	52 (41-63)
Subtype of ATL	
Acute	17
Lymphoma	10
Disease status at transplantation	
CR1	5
PR1	10
PR2	1
PIF	5
REL	6
Conditioning regimen	
CY 120mg/kg, BU 16 or 12.8mg/kg	3
CY 120mg/kg, TBI 12Gy with or without CA 8g/m^2	6
FLU 125mg/m^2, MEL 80mg/m^2, TBI 4Gy	13
FLU 125mg/m^2, MEL 80mg/m^2	4
FLU125mg/m^2, BU 6.4mg/kg, TBI 2Gy	1
Prophylaxis against GVHD	
CsA	1
TCR	12
CsA + sMTX	7
TCR + sMTX	7
HLA compatibility	
Matched	1
One-antigen mismatch	4
Two-antigen mismatch	22
Nucleated-cell dose/kg of body weight-x 10^7	2.75 (2.00-4.28)

CR1 first complete remission, PR1 first partial remission, PR2 second partial remission, PIF primary induction failure, REL refractory after relapse, CY cyclophosphamide, BU busulfan, CA cytarabine, FLU fludarabine, MEL melphalan, TBI total body irradiation, CsA cyclosporine, TCR tacrolimus, sMTX short term methotrexate

Table 2. Characteristics and results of hematopoietic stem cell transplantation of the 27 patients with ATL

No.	age	sex	subtype	Disease status at transplant	Conditioning regimen	GVHD prophylaxis	aGVHD	cGVHD	Relapse from transplant (year)	Survival time from transplant (year)
1	45	male	acute	PR1	FLU+MEL+TBI	CsA+sMTX	-	-	-	6.9[a]
2	59	female	acute	PR1	FLU+MEL+TBI	TCR	-	-	3.8	5.8[a]
3	61	male	lymphoma	CR1	FLU+MEL+TBI	TCR	I	-	-	4.3[a]
4	55	female	lymphoma	PIF	FLU+MEL+TBI	TCR+sMTX	-	-	-	3.1[a]
5	54	female	acute	PR1	FLU+MEL	TCR+sMTX	-	-	-	2.8[a]
6	54	male	acute	CR1	FLU+MEL+TBI	TCR	II	extensive	-	2.2[a]
7	53	male	acute	PR1	FLU+MEL+TBI	TCR+sMTX	-	-	-	1.9[a]
8	52	male	acute	PR1	FLU+MEL+TBI	TCR+sMTX	I	limited	-	1.8[a]
9	41	male	lymphoma	CR1	FLU+MEL+TBI	TCR	II	extensive	1.6	2.3 (PD)
10	51	female	lymphoma	relapse	FLU+MEL+TBI	TCR	-	-	0.8	1.7 (PD)
11	58	male	acute	PR1	FLU+MEL+TBI	TCR+sMTX	-	-	0.4	0.7 (PD)
12	56	female	lymphoma	relapse	FLU+MEL	CsA+sMTX	II	-	0.2	0.4 (PD)
13	53	male	lymphoma	PIF	FLU+MEL+TBI	CsA+sMTX	-	-	0.2	0.4 (PD)
14	52	male	lymphoma	PR1	FLU+MEL+TBI	TCR+sMTX	-	-	-	0.3 (TRM)
15	63	male	acute	PR1	FLU+BU+TBI	TCR	-	-	-	0.1 (TRM)
16	59	male	acute	PR1	FLU+MEL	TCR	-	-	-	0.1 (TRM)
17	59	male	lymphoma	PIF	FLU+MEL	TCR+sMTX	NE	NE	NE	0.1 (TRM)
18	55	female	lymphoma	PIF	FLU+MEL+TBI	TCR	NE	NE	refractory	0.1 (PD)
19	44	male	acute	relapse	CY+CA+TBI	TCR	-	-	0.3	1.9 (PD)
20	43	male	acute	CR1	CY+TBI	CsA+sMTX	-	-	-	0.6 (TRM)
21	52	female	acute	CR1	CY+TBI	TCR	IV	-	0.4	0.5 (PD)
22	46	male	acute	PR2	BU+CY	CsA+sMTX	NE	NE	refractory	0.3 (PD)
23	44	female	acute	relapse	CY+TBI	CsA+sMTX	-	-	-	0.3 (TRM)
24	48	male	acute	relapse	BU+CY	CsA+sMTX	-	-	-	0.2 (TRM)
25	45	male	lymphoma	PR1	BU+CY	TCR	I	-	-	0.1 (TRM)
26	50	male	acute	relapse	CY+TBI	TCR	-	-	-	0.1 (TRM)
27	47	female	lymphoma	PIF	CY+CA+TBI	CsA+sMTX	NE	NE	NE	0.1 (TRM)

aGVHD acute graft-versus-host disease, cGVHD chronic GVHD, NE not evaluated, PD progressive disease, TRM transplant-related mortality, [a] patient still alive