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【 ORIGINAL ARTICLE 】

Salvage Cord Blood Transplantation Using a Short-term Reduced-intensity Conditioning Regimen for Graft Failure

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Abstract:

Objective Graft failure (GF) is a life-threatening complication of hematopoietic stem cell transplantation (HSCT). A standardized conditioning regimen and an appropriate graft source of salvage HSCT for GF have not yet been established. Some case series have shown good hematopoietic recoveries after salvage HSCT using a short-term reduced-intensity preparative regimen consisting of fludarabine (30-90 mg/m^2), cyclophosphamide (2 g/m^2), and total-body irradiation (2 Gy). However, the dose of fludarabine has varied in these reports based on the clinical condition of the patients, resulting in very limited experiences with each dose of fludarabine.

Methods We retrospectively analyzed 10 patients who developed GF after allogeneic HSCT and underwent salvage cord blood transplantation (CBT) using the above-mentioned conditioning regimen with a fixed dose (90 mg/m^2) of fludarabine.

Results Eight patients (80.0%) achieved neutrophil engraftment within 30 days from salvage HSCT with a median of 21 (range, 17-23) days. The 1-year overall survival (OS) rate after the salvage HSCT was 50.0%, and the median OS was 281 (range, 23-1,638) days. Cumulative incidences of non-relapse mortality and relapse at 1 year were 50.0% and 10.0%, respectively.

Conclusion CBT using this short-term reduced-intensity conditioning regimen may be a promising salvage therapy for GF.

Key words: graft failure, short-term reduced-intensity conditioning regimen, cord blood transplantation

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Introduction

Graft failure (GF) is a life-threatening complication of hematopoietic stem cell transplantation (HSCT). In cord blood transplantation (CBT), up to 20% of patients experience GF, while rates are lower in peripheral blood stem cell transplantation (PBSCT) and bone marrow transplantation (BMT) (1-6). There is no standard treatment for GF, and the prognosis is still poor (7). In many cases, salvage HSCT is needed. However, varied and unstable conditions among patients due to toxicities after the first transplantation make it difficult to decide on the appropriate procedure of salvage HSCT for each patient.

To reduce toxicities and shorten the duration of severe cytopenia after salvage transplantation, Goggins et al. developed a 'one-day regimen' for salvage HSCT consisting of fludarabine (Flu, 30 mg/m^2), cyclophosphamide (CY, 2 g/m^2), alemtuzumab (20 mg), and total-body irradiation (TBI; 2 Gy), administered 1 day before salvage transplantation (8).

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Favorable results with a modified version of the 'one day regimen' omitting alemtuzumab were also reported in small case series (9-12). However, in this 'modified one day regimen', the dose of Flu varied from 1 day to 3 days (30 to 90 mg/m^2 in total) according to the clinical condition of the patients, resulting in very limited actual experiences with each dose of Flu. In our institution, 3 days of Flu was uniformly adopted, and 10 GF patients were consecutively treated with this short-term reduced-intensity conditioning regimen consisting of CY, TBI, and 3 days of Flu from 2012.

We herein report the outcome of those 10 patients who received salvage CBT using this conditioning regimen.

Materials and Methods

Patients

For this retrospective cohort study, we identified 10 adult patients with hematological malignancies who received salvage CBT for primary or secondary GF at University of Tsukuba Hospital between July 2012 and August 2018. Cases who relapsed or had disease progression before salvage CBT were excluded.

Transplantation procedure

All patients received myeloablative conditioning at the first HSCT. For the nine patients who received CBT as the first HSCT, tacrolimus was used concomitantly with mycophenolate mofetil (MMF) or short-term methotrexate for prophylaxis of graft-versus-host disease (GVHD), while the one patient who received PBSCT from a haploidentical donor was administered cyclosporin and posttransplant CY instead of tacrolimus. Patients consecutively received salvage CBT using the short-term reduced-intensity conditioning regimen consisting of Flu at 30 mg/m^2 intravenously over 30 minutes on days -3, -2, and -1; CY 2 g/m^2 intravenously over 4 hours on day -1; and TBI 2 Gy on day -1 or day 0. Although the dose of Flu was determined according to the clinical condition of the patients in the original method of the modified one-day conditioning regimen (10), the dose of Flu was unified as 3 days in our institution to ensure a sufficient regimen intensity for engraftment. Cord blood was infused on day 0, at 24 hours after the administration of CY. Tacrolimus and MMF were used for prophylaxis of GVHD.

The assessment of characteristics and outcomes of the patients

For the evaluation of clinical conditions and comorbidities of the transplant recipients, the Eastern Cooperative Oncology Group-performance status (ECOG-PS) and Hematopoietic cell transplantation-comorbidity index (HCT-CI) were used (13). The time of neutrophil engraftment was defined as the first of 3 consecutive days when the absolute neutrophil count (ANC) was maintained at ≥500/μL. The day of platelet engraftment was defined as the first of 7 consecutive days of the platelet count exceeding 50,000/μL without transfusion. Primary GF was defined as failure of the ANC to exceed 500/μL or absence of donor chimerism in bone marrow cells without relapse and judged at day 28 or later from the first HSCT (14). Secondary GF was defined as a decrease in the ANC to <100/μL or the absence of donor chimerism after the initial engraftment without recovery before relapse (14). Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute and chronic GVHD were diagnosed and graded using traditional criteria (15, 16).

Statistical analyses

Wilcoxon's rank sum test or Fisher's exact test was used to analyze the differences in clinical factors between engrafted and non-engrafted patients. Two-tailed statistical tests were conducted, and a $p<0.05$ was considered statistically significant. The OS was estimated using Kaplan-Meier methods. The cumulative incidences of relapse and non-relapse mortality (NRM) were evaluated using the method of Gray. Death was treated as a competing risk for relapse. Relapse was a competing risk for NRM.

Statistical analyses were carried out using R (R Foundation for Statistical Computing, version 3.6.2) or EZR software program, version 1.51 (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (17).

Results

Patient characteristics at the first transplantation

The characteristics of the patients at the first HSCT are summarized in Table 1. The median age of the patients was 42 (range, 20-59) years old. All 10 patients received myeloablative conditioning regimens, with 4 treated with TBI-based regimens. The first grafts of stem cells were unrelated umbilical cord blood (n=9) and peripheral blood stem cells (PBSCs) from an HLA-haploidentical related donor (n=1). The median dose of total and CD34$^+$ cells in CBT was 2.53×10^7/kg (range, 2.02-4.11) and 0.90×10^5/kg (range, 0.62-1.28), respectively. Three patients had anti-HLA antibodies, none of which were donor-specific. Of the 10 patients, 9 had primary GF, and 1 (No. 9) had secondary GF. The median time after the first HSCT to the diagnosis of primary GF was 32 (range, 28-36) days. Secondary GF in No. 9 was diagnosed on day 45.

Patient characteristics and engraftment in salvage transplantation

The patient characteristics and outcomes of the salvage CBT are summarized in Tables 2 and 3. The median interval between the first HSCT and salvage CBT for primary GF was 38.5 (range, 35-46) days. The median dose of total and CD34$^+$ CB cells was 2.55×10^7/kg (range, 1.96-3.48) and 0.71×10^5/kg (range, 0.39-1.93), respectively. None of the pa-

Table 1. Characteristics of Patients at 1st HSCT.

No.	Age	Sex	Disease	Disease status	ECOG-PS	HCT-CI	Anti-HLA Ab (donor-specificity)	1st donor	Matched HLA (/6 antigens)	TNC ($\times10^7$/kg)	CD34$^+$cells ($\times10^5$/kg)	Conditioning regimen	Classification of GF	Days from 1st HSCT to diagnosis of GF
1	59	W	AML	NR	1	3	-	CB	5	2.91	1.28	CY-Flu-Bu	Primary	34
2	32	M	ALL	CR1	0	2	NA	CB	5	2.16	0.70	CY-TBI	Primary	28
3	20	M	ALL	CR1	1	0	-	Haplo-PB	3	42.64	32.8	Flu-TBI	Primary	34
4	31	W	CML	CR2	0	3	-	CB	5	2.73	1.12	Flu-Bu-TBI	Primary	21
5	42	W	ALL	CR1	0	2	+ (No)	CB	5	3.23	0.62	CY-TBI	Primary	32
6	30	M	AML	NR	0	0	-	CB	4	2.38	0.90	CY-TBI	Primary	32
7	42	M	MPAL	CR2	0	0	-	CB	6	2.26	0.68	CY-Bu	Primary	28
8	55	W	AML	CR1	0	0	+ (No)	CB	4	4.11	0.69	Flu-Bu-TBI	Primary	36
9	56	W	ATL	CR1	0	3	-	CB	4	2.53	1.01	Flu-Bu-TBI	Secondary	45
10	53	W	AML	CR2	1	2	+ (No)	CB	5	2.02	0.94	CY-Bu	Primary	32

Ab: antibody, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, ATL: adult T-cell leukemia, Bu: busulfan, CB: cord blood, CML: chronic myeloid leukemia, CR: complete remission, CY: cyclophosphamide, CY-Bu: CY 120 mg/kg and Bu 12.8 mg/kg, CY-Flu-Bu: CY 100 mg/kg, Flu 30 mg/m^2 and Bu 12.8 mg/kg, CY-TBI: CY 120 mg/kg and TBI 12 Gy, ECOG-PS: Eastern Cooperative Oncology Group-performance status, Flu: fludarabine, Flu-Bu-TBI: Flu 180 mg/m^2, Bu 12.8 mg/kg and TBI 2 Gy, Flu-TBI: Flu 150 mg/m^2 and TBI 12 Gy, GF: graft failure, haplo-PB: haploidentical related peripheral blood stem cell, HCT-CI: hematopoietic cell transplantation-comorbidity index, HLA: human leucocyte antigen, HSCT: hematopoietic stem cell transplantation, M: man, MPAL: mixed phenotype acute leukemia, NA: not available, NR: non-remission, TBI: total-body irradiation, TNC: total nucleated cells, W: woman

Table 2. Characteristics at the Salvage CBT.

No.	Days from 1st HSCT to salvage CBT	Donor chimerism	ECOG-PS	HCT-CI	Anti-HLA Ab (donor-specificity)	Matched HLA (/6 antigens)	TNC ($\times10^7$/kg)	CD34$^+$cells ($\times10^5$/kg)	Organ toxicities at the salvage CBT (grade)	Infection at the salvage CBT
1	46	0%	2	4	NA	5	2.75	0.58	No	CNS bacteremia
2	36	0%	0	3	NA	4	2.40	0.39	No	FN
3	38	95.7%	2	1	+(No)	5	2.50	0.71	No	FN
4	35	NA	1	4	NA	4	2.89	0.90	No	*Capnocytophaga* sp. bacteremia
5	39	21-29%	2	3	NA	4	1.96	0.73	No	FN
6	36	NA	1	0	NA	4	2.40	0.70	No	No
7	37	NA	3	2	NA	3	3.19	1.93	Liver injury (3)	FN
8	41	NA	2	2	NA	4	2.23	0.57	Liver injury (1)	FN
9	49	NA	1	4	NA	4	3.48	0.90	Respiratory dysfunction (3)	FN
10	39	0%	2	3	+(No)	4	2.60	0.67	Liver injury (2)	*S. epidermidis* bacteremia

Ab: antibody, *Capnocytophaga* sp.: *Capnocytophaga* species, CBT: cord blood transplantation, CNS: coagulase-negative *Staphylococcus*, ECOG-PS: Eastern Cooperative Oncology Group-performance status, FN: febrile neutropenia, HCT-CI: hematopoietic cell transplantation-comorbidity index, HLA: human leucocyte antigen, HSCT: hematopoietic stem cell transplantation, NA: not available, *S. epidermidis*: *Staphylococcus epidermidis*, TNC: total nucleated cells

tients had donor-specific anti-HLA antibodies. Compared to the first HSCT, nine patients had a worse ECOG-PS and HCT-CI at salvage CBT. One patient (No. 7) had grade 3 liver injury, and another (No. 9) had grade 3 respiratory dysfunction.

Patient No. 9 was a heavy smoker (>40 pack-years) and had a severely decreased pulmonary diffusion capacity [diffusing capacity for carbon monoxide (DL_{CO}), 39.6%] and mild obstructive disorder [percent predicted forced expiratory volume in one second ($FEV_{1.0}$), 60.4%] before the first transplantation. Although a non-TBI conditioning regimen was selected at the first HSCT to avoid causing pulmonary toxicity due to TBI, the respiratory status worsened from day 43 of the first HSCT, requiring 4 L/min oxygen administration. Chest computed tomography (CT) performed on day 0 of salvage CBT showed diffuse ground-glass opacity (GGO) in both lungs, so infectious diseases, such as pneumocystis pneumonia and cytomegalovirus (CMV) pneumonia, interstitial pneumonia, and drug-induced lung injury, were suspected. Screening tests for infectious diseases, such as CMV polymerase chain reaction (PCR), β-D-glucan, and bacterial culture tests, were negative. Although drug-induced

Table 3. Outcomes after the Salvage CBT.

No.	Engrafted	Donor chimerism	Days until neutrophil engraftment	Days until platelet engraftment	aGVHD (grade)	cGVHD (grade)	Relapse (month)	Survival (month)	Cause of death
1	Yes	100%	21	70	Yes (II)	Yes (limited)	Yes (34.9)	Died (38.5)	Relapse
2	No	NA	Failure	Failure	Yes* (III)	NA	No	Died (1.0)	Hemorrhage
3	Yes	100%	21	72	Yes (I)	No	Yes (4.7)	Died (15.3)	Relapse
4	Yes	NA	21	38	Yes (II)	Yes (limited)	No	Died (3.4)	Infection
5	Yes	NA	20	49	Yes (I)	Yes (extensive)	No	Alive (54.6)	NA
6	Yes	99.5%	19	45	Yes (I)	Yes (extensive)	No	Alive (50.1)	NA
7	No	NA	Failure	Failure	NA	NA	No	Died (0.7)	Infection
8	Yes	NA	23	Failure	No	NA	No	Died (1.5)	ARDS
9	Yes	NA	22	Failure	No	NA	No	Died (1.7)	Respiratory failure
10	Yes	NA	17	38	Yes (II)	NA	No	Alive (22.2)	NA

*hyperacute GVHD on day 7 of the salvage HSCT without neutrophil engraftment

aGVHD: acute graft-versus-host disease, ARDS: acute respiratory distress syndrome, CBT: cord blood transplantation, cGVHD: chronic graft-versus-host disease, GVHD: graft-versus-host disease, HSCT: hematopoietic stem cell transplantation, NA: not applicable or available

lung injury and the complex factors associated with the original lung dysfunction could not be ruled out, no diagnosis was confirmed.

All patients but No. 6 were complicated with active infection and treated with antibiotics at the start of the conditioning regimen for salvage CBT (infection details described in Table 2). Five patients (No. 2, 3, 5, 7, 9) had a fever over 37.5℃ before conditioning for salvage CBT. No patients except for No. 9 mentioned above were receiving oxygen inhalation or vasoactive agents.

Although 2 patients died before engraftment within 30 days (described in detail in "Toxicities and complications" below), all 8 other patients achieved neutrophil engraftment. The median interval from salvage CBT to neutrophil engraftment was 21 (range, 17-23) days. Six patients achieved platelet engraftment, and the median interval from salvage CBT to platelet engraftment was 47 (range, 38-72) days. Four other patients died without platelet engraftment within 60 days.

Toxicities and complications

Early death before engraftment within 30 days was seen in 2 patients. One patient (No. 7) developed disseminated candidiasis caused by *Candida famata* and died on day 23 after salvage CBT. Patient No. 2 presented with elevated bilirubin and biliary enzyme levels as well as a rash on his trunk from day 7 without neutrophil engraftment. A skin biopsy showed apoptosis, liquefaction degeneration, and incontinentia pigmenti in the epidermal basal layer, no inclusion bodies suggestive of viral infection, and negative findings for CMV immunostaining. Based on these findings, he was diagnosed with hyperacute GVHD. His GVHD progressed to Grade III (skin stage 2, liver stage 2, gut stage 0), and he was treated with 2 mg/kg/day of methylprednisolone but died on day 29 from intracranial hemorrhaging. The other 8 patients tolerated the conditioning regimen well and ultimately achieved neutrophil engraftment. Clinical factors at the start of conditioning of salvage CBT were compared between engrafted and non-engrafted patients, but none of following factors significantly affected the achievement of engraftment: CRP level (p=0.40), duration of neutropenia (p=0.93), presence of a fever (>37.5℃) (p=0.44), oxygen administration (p=1.00), or infectious diseases under antibacterial treatment (p=1.00). Among the eight patients who achieved engraftment, some cases of severe infectious disease were observed. Two patients experienced documented bacterial infections during the neutropenic period before engraftment, one (No. 1) with *Stenotrophomonas maltophilia* bacteremia and the other (No. 6) with *Staphylococcus epidermidis* bacteremia, and both were successfully treated with antibiotics. Severe viral infections occurred in two patients. Patient No. 3 developed cytomegalovirus retinitis and was treated with ganciclovir. Patient No. 6, who developed adenovirus cystitis and pneumonia and was successfully treated with cidofovir. Patient No. 9, who had had grade 3 respiratory dysfunction and bilateral diffuse GGO before salvage CBT, developed CMV antigenemia on day 14 after salvage CBT. CMV pneumonia was suspected, and she was treated with foscarnet, but her respiratory condition continued to deteriorate. Although she achieved neutrophil engraftment on day 22, intratracheal intubation was performed on day 25 due to her worsening respiratory condition. Pulmonary alveolar proteinosis was also suspected because of crazy-paving pattern and subpleural sparing on additional CT, but bronchoalveolar lavage showed no notable findings other than mild neutrophil elevation (12.7%), and a bacterial culture test was also negative. She did not respond to steroid pulse therapy or immunoglobulin administration and died of respiratory failure on day 52. Due to the lack of family consent, a pathological autopsy was not performed, and the cause of respiratory failure remained unknown.

GVHD

Of the eight individuals who achieved neutrophil engraftment, three developed Grade I acute GVHD, and three developed Grade II acute GVHD (Table 3). No patients devel-

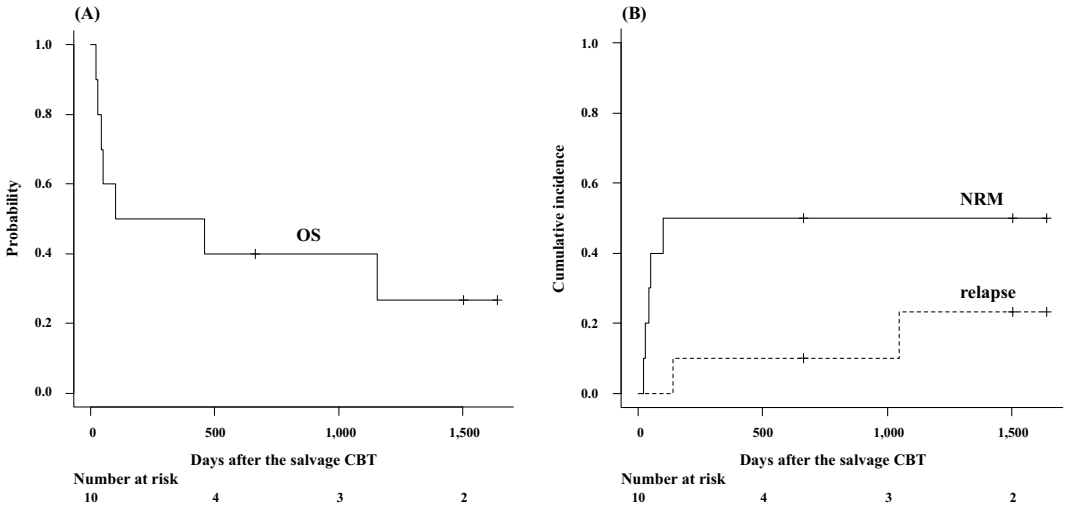

Figure. **The OS, NRM, and relapse after salvage CBT. (A) The median OS after salvage CBT was 281 (range, 23-1,638) days. The 1-year OS rate after salvage CBT was 50.0% (95% CI, 18.4-75.3%). (B) The cumulative incidences of NRM (solid line) and relapse (dotted line) at 1 year were 50.0% and 10.0% (95% CI, 16.3-76.8% and 0.3-39.2%), respectively. CBT: cord blood transplantation, NRM: non-relapse mortality, OS: overall survival**

oped Grade III or IV acute GVHD. Two patients (No. 5 and 6) developed lung complications, possibly caused by extensive chronic GVHD, and both were treated by prednisolone. Two other patients (No. 1 and 4) developed limited chronic GVHD.

The survival

At the last follow-up, 3 (No. 5, 6, and 10) of the 10 patients were alive, and all of them were in remission. The median OS after salvage CBT was 281 days [range, 23-1,638 days; 95% confidence interval (CI), 23 days to not reached], and the OS rate at 1 year was 50.0% (95% CI, 18.4-75.3%) (Figure A). The cumulative incidences of NRM and relapse at 1 year were 50.0% (95% CI, 16.3-76.8%) and 10.0% (95% CI, 0.3-39.2%), respectively (Figure B). The causes of death except for the above-mentioned early deaths were relapse of primary diseases (n=2), infectious diseases (n=1), and acute respiratory distress syndrome (n=1).

Discussion

We herein report 10 patients with primary or secondary GF who received salvage CBT using a short-term reduced-intensity conditioning regimen consisting of CY, TBI, and 3 days of Flu. Despite advances in HSCT methods and investigations into the cause of GF, GF has not yet been eliminated and remains a significant cause of morbidity and mortality following allogeneic HSCT. Salvage HSCT is usually performed for GF, but the appropriate choice of graft source and conditioning regimens remains difficult, and the outcome of salvage HSCT for GF is poor.

Regarding the conditioning regimen for salvage HSCT, several studies have reported favorable results of Flu-based reduced-intensity conditioning regimens with acceptable toxicity (18-20). Furthermore, two Japanese studies showed that the use of a Flu-based regimen with alkylating agents was associated with a high neutrophil engraftment rate (21, 22). Goggins et al. reported the usefulness of a short-term reduced-intensity conditioning regimen, known as a 'one-day regimen', for allogeneic non-myeloablative stem cell transplantation using HLA-mismatched related donors (8). This original one-day regimen included alemtuzumab to increase immunosuppression by T-cell depletion. However, the use of alemtuzumab is considered to increase the risk of infectious complications. Sumi et al. performed salvage transplantation from cord blood (n=5) and matched sibling (n=1) for patients with GF using a 'modified one-day conditioning regimen', which involved excluding alemtuzumab and altering the dose of Flu according to the patient condition (10). All patients achieved stable neutrophil engraftment with this modified one-day conditioning regimen. At the second HSCT, the host immune system have already been weakened sufficiently by the first conditioning, so Flu and low-dose TBI without alemtuzumab might be sufficient to suppress the immune system for salvage HSCT.

Regarding donor sources, a Spanish group reported the outcome of 89 patients with GF, in which most (61 cases) received salvage PBSCT (23). Other patients received CBT (8 cases), BMT (6 cases), autologous peripheral blood infusion (5 cases), or conservative therapy without stem cell infusion (9 cases). Neutrophil engraftment was achieved in 80% of patients who received salvage HSCT with a median time for neutrophil recovery of 15 days. For the 48 evaluable patients who achieved engraftment after salvage HSCT, the 5-year OS was 28%. In Japan, however, CBT is used most frequently for the salvage HSCT. A Japanese retrospective study compared feasibilities of graft sources for salvage HSCT by analyzing 220 patients who developed GF after

the first CBT procedure (21). Among them, 180 received CBT, 24 received PBSCT, and 16 received BMT. The cumulative incidence of neutrophil engraftment on day 30 after salvage HSCT was 39% with CBT, 71% with PBSCT, and 75% with BMT. The median intervals of neutrophil engraftment and salvage HSCT were 21 days after CBT, 14.5 days after PBSCT, and 18 days after BMT. The probability of a 1-year OS after salvage HSCT was 28% with CBT, 58% with PBSCT, and 38% with BMT. They concluded that PBSCs were the preferable source of stem cells in salvage HSCT for GF after CBT. Another Japanese group showed a similar outcome of salvage CBT for GF (22). In that report, 80 patients with GF underwent salvage CBT, and 45 achieved neutrophil engraftment at a median of 21 days, with a 1-year OS rate of 33%. Based on these previous findings, PBSCT may provide a higher engraftment rate with a shorter interval than CBT as salvage for GF in heterogenous backgrounds.

However, the retrospective nature of the analyses hampers the comparison of these graft sources in practice. Indeed, finding HLA-matched healthy donors and harvesting PBSCs from them is often difficult and time-consuming, leading to a delay in performing salvage HSCT. Therefore, in actual clinical settings, it is sometimes difficult to prepare graft PBSCs for salvage HSCT. In this respect, cord blood is readily available and frequently used for salvage HSCT in Japan. In our study, salvage CBT using the short-term reduced-intensity conditioning regimen showed a favorable engraftment rate and OS potentially comparable to the outcomes of salvage PBSCT in previous reports (21, 23). Thus, with the relative availability of cord blood as a stem cell source, CBT using the short-term reduced-intensity conditioning regimen presented in our study may be a suitable salvage therapy for GF.

The high NRM remains a major problem in salvage CBT for GF. In the 2 above-mentioned Japanese studies, the NRM (21) and therapy-related mortality (22) were 60% and 56% at 1 year after salvage CBT, respectively. In our study, the NRM was 50% at 1 year, mainly because of infectious complications. In the original report of the modified one-day conditioning regimen (10), the dose of Flu was adjusted according to the clinical condition of the patients from 1 day to 3 days (30 mg/m^2 to 90 mg/m^2 in total). In the present study, 2 of 3 patients who received Flu at 90 mg/m^2 developed severe viral infections, while 3 patients who received 30 or 60 mg/m^2 of Flu developed no severe viral infections. All patients achieved neutrophil engraftment regardless of the dose of Flu. They considered that the dose of Flu might be a significant factor influencing the risk of viral infections following salvage HSCT. In the present study, the dose of Flu was unified at 90 mg/m^2 to ensure a sufficient intensity for engraftment, although 9 out of 10 patients were complicated with active infections at salvage CBT. Reducing Flu might lead reduce the risk of infectious death while ensuring effective engraftment, although this strategy must be confirmed in further studies.

Some limitations to our study warrant mention, due to its retrospective nature. The selected patients may have been those who were considered to be able to tolerate the regimen and willing to undergo salvage transplantation. Although our study included a relatively large number of patients compared with previous reports using this short-term conditioning regimen with Flu-CY-TBI, the cohort is still small. Further analyses of larger cohorts or prospective studies are expected to confirm the effectiveness of salvage CBT with this short-term, reduced-intensity conditioning regimen for GF.

In conclusion, our study demonstrated the feasibility of salvage CBT for GF using a short-term reduced-intensity conditioning regimen consisting of CY, TBI, and 3 days of Flu. Favorable engraftment and a good OS were achieved using this regimen, but high NRM was still a problem after salvage CBT.

The authors state that they have no Conflict of Interest (COI).

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