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Case Study

Successful Secondary Umbilical Cord Blood Transplantation for Graft Failure in Acute Myelogenous Leukemia, Treated with Modified One-Day Conditioning Regimen, and Graft-Versus-Host Disease Prophylaxis Consisting of Mycophenolate and Tacrolimus

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Although graft failure (GF) is a fatal and life-threatening complication of umbilical cord blood transplantation (CBT), the standard treatment has not been established. We describe the case of a 28-year-old man diagnosed with acute myelogenous leukemia with myelodysplasia-related changes harboring a normal karyotype. This patient underwent 2 courses of idarubicin and cytosine arabinose therapy, and 3 courses of high-dose cytosine arabinose therapy. Subsequently, he underwent high-dose chemotherapy (total body irradiation and cyclophosphamide) followed by first CBT. Primary GF occurred after post-immunological reaction and hemophagocytic lymphohistiocytosis, and was diagnosed on day 27 after the first CBT. Therefore, the patient underwent secondary CBT for GF treated with a modified one-day conditioning regimen consisting of fludarabine (30 mg/m^2, 3 days), cyclophosphamide (2 g/m^2), and total body irradiation (2 Gy), and graft-versus-host disease prophylaxis consisting of mycophenolate and tacrolimus. Consequently, the patient achieved neutrophil engraftment on day 17 after the second CBT. During the clinical course of the second CBT, the main complications were sepsis, BK virus-associated cystitis, and acute graft-versus-host disease (skin, grade 2, stage 3). After these treatments, the patient was disease-free for 39 months. Our case suggests that these treatments may be feasible, safe, and effective for the treatment of patients with GF. This case study may be helpful to physicians who directly care for GF patients, and may provide a future direction for a more efficient treatment modality. 〔*J Clin Exp Hematop 55(2) : 89-96, 2015*〕

Keywords: graft failure in umbilical cord blood transplantation, post-immunological reaction, hemophagocytic lymphohistiocytosis, modified one-day conditioning regimen, mycophenolate

INTRODUCTION

Acute myelogenous leukemia (AML) is an acute-onset hematological malignancy that is characterized by the clonal proliferation of myeloid blasts (> 20%).[1-3] With the development of diagnostic methods such as identifying chromosomal abnormalities, and the development of novel treatments, including bone marrow transplantation, dramatic improvements were achieved in the prognosis of hematological malignancy patients.[2-5] Umbilical cord blood transplantation (CBT) has been increasingly performed in recent years in patients without an HLA-identical sibling or non-sibling donor.[6,7] However, graft failure (GF) is a fatal and life-threatening complication of umbilical CBT that is characterized by a lack of donor cells (primary GF) or a loss of donor cells after

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initial engraftment (secondary GF).[8-11] Although the prognosis of GF remains poor, a standard treatment has not been established owing to the absence of randomized trials.[8-11]

Here, we report the case of a patient with successful secondary umbilical CBT for GF in AML, treated with a short-term reduced-intensity conditioning regimen consisting of fludarabine, cyclophosphamide, and total body irradiation, and graft-versus-host disease (GVHD) prophylaxis consisting of mycophenolate (MMF) and tacrolimus (FK).

CASE REPORT

A 28-year-old man with anemia and thrombocytopenia was referred to a regional hospital in October 2011. On admission, he was normotensive (108/60 mmHg) and had a heart rate of 66 beats/minute. On physical examination, he was found to have petechiae. Laboratory findings showed a hemoglobin concentration of 8.7 g/dL, platelet count of 77 × 10^9/L, and white blood cell count of 3.94 × 10^9/L with 1.0% metamyelocytes, 13.0% segmental cells, 43.0% lymphocytes, 1.0% monocytes, 0.5% eosinophils, and 41.5% blasts. Serum lactate dehydrogenase level was elevated to 339 IU/L (Table 1). Prior pancytopenia was not observed by annual health check-up.

Bone marrow aspirate was hypercellular and had abnormal blast cells (27.0%) (Fig. 1A-1E). Blast cells were positive for myeloperoxidase (MPO) stain (Fig. 1F). Dysplastic features were present in all 3 hematopoietic lineages (Fig. 1A-1E).

Flow cytometric analysis performed on admission revealed the presence of surface markers for CD13, CD33, CD34, and HLA-DR. Chromosomal analysis showed a normal karyotype: 46, XY. Other screening molecular analyses of the leukemia were performed, such as PML-RARA, AML1-MTG8, CBFb-MYH11, NUP98-HoxA9, ETV6-AML1, E2A-HLF, SIL-TAL-1, MLL-AF4, MLL-AF6, MLL-AF9, and MLL-EML. All of these molecular analyses of the leukemia resulted in negative findings. On the basis of these cytogenetic and flow cytometric findings, we finally diagnosed the patient with AML with myelodysplasia-related changes.

Therefore, we immediately started idarubicin and cytosine arabinose (IDA/Ara C) therapy on admission. After these treatments, the patient showed induction failure, which was suggested by the presence of residual myeloid blasts (13.0%) in the bone marrow. Subsequently, we repeatedly administered IDA/Ara C therapy as a re-remission induction therapy. After repeated IDA/Ara C therapy, the patient showed a complete response in December 2012. Post-remission therapy consisted of 3 courses of high-dose cytosine arabinose therapy. After this treatment, the patient retained a complete response. Subsequently, the patient underwent high-dose chemotherapy and allogeneic bone marrow transplantation because a poor outcome was reported under 2 courses of induction therapy for complete remission, as well as the presence of the morphologic myelodysplastic features at diagno-

Table 1. Laboratory findings at admission

(Peripheral cell count)			(Serum Chemistry)			(Coagulation)		
WBC	3.94	× 10^3/μL	T. Bil	0.8	mg/dL	PT	77.8	%
PROMYE	0.0	%	AST	64	IU/L	PT(INR)	1.14	
MYE	0.0	%	ALT	104	IU/L	APTT	32.9	sec
META	1.0	%	ALP	274	IU/L	Fib	240.1	mg/dL
STAB	0.0	%	LDH	339	IU/L	FDP	3.7	mg/dL
SEG	13.0	%	CK	58	IU/L			
LYMPH	43.0	%	Na	142	mEq/dL			
MONO	1.0	%	K	3.7	mEq/dL			
EOSIN	0.5	%	Cl	108	mEq/dL			
BASO	0.0	%	Ca	9.2	mg/dL			
BLAST	41.5	%	BUN	10.2	mg/dL			
RBC	268	× 10^4/μL	Cr	0.6	mg/dL			
Hb	8.7	g/dL	UA	5.3	mg/dL			
Hct	23.9	%	Ferri	870	ng/mL			
MCV	89.2	fL	TP	7.1	g/dL			
MCHC	36.4	%	ALB	4.9	g/dL			
PLT	7.7	× 10^4/μL	CRP	0.02	mg/dL			
Ret	1.0	%						

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin concentration; Plt, platelet count; T. Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; Ferri, ferritin; TP, total protein; ALB, albumin; CRP, C-reactive protein; PT, prothrombin time; PT (INR), prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin/fibrinogen degradation products

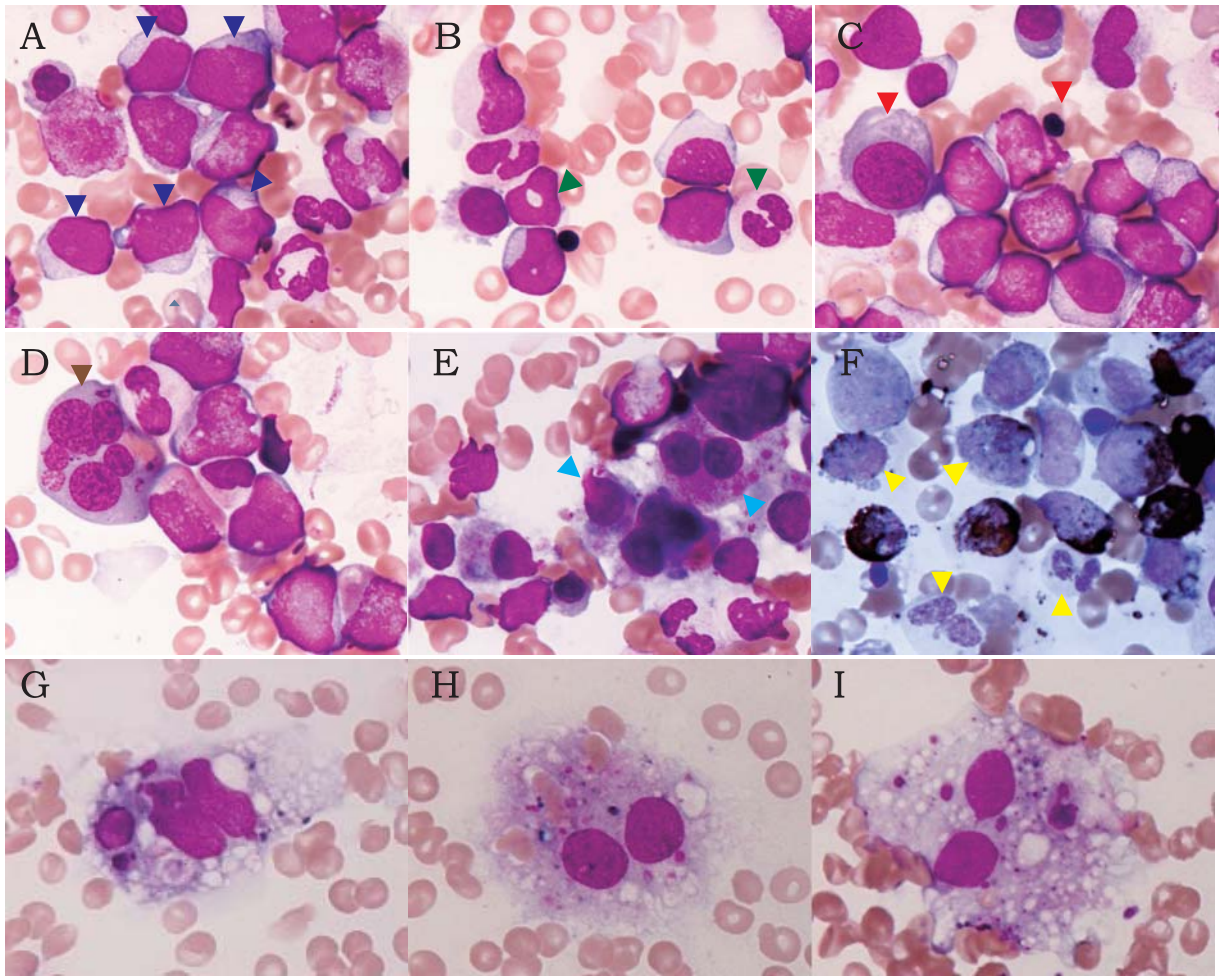

Fig. 1. Bone marrow findings at diagnosis (*1A-1F*) and at first transplantation on day 18 (*1G-1I*). A bone marrow smear showing the proliferation of blasts with dysplastic features in all 3 hematopoietic lineages. Bone marrow aspirate demonstrating a hypercellular bone marrow and abnormal blast cells (27.0%) (black arrow heads) (*1A-1D*). Blast cells were positive for myeloperoxidase (MPO) stain (*1F*). Dysplastic features were present in all 3 hematopoietic lineages (*1A-1C*). In the myeloid series, dysgranulopoiesis in abnormal cytoplasmic granules and pleomorphic nuclear forms were detected (green arrow heads) (*1B*). In the erythroid series, dyserythropoiesis was observed in pleomorphic nuclear forms, ringed sideroblasts, and nuclear-cytoplasmic dyssynchrony (red arrow heads) (*1C-1E*). In the megakaryocyte series, bizarre nuclear figures, decreased ploidy, separated nuclei (so-called nuclear dispersion), and small micromegakaryocytes were present (blue arrow heads) (*1E*). Cells were positive for MPO stain; > 3% of the blast cells stained positive for MPO (yellow arrow heads) (*1F*). Bone marrow examination showed a dominance of lymphocytes and 7% hemophagocytosis with hypocellular bone marrow (NCC 1,500/μL) at the first transplantation on day 18 (*1G-1I*).

sis. As the patient had no HLA-identical sibling or non-sibling donor, we selected umbilical CBT (Table 2). Anti-HLA antibody was not present in this case. The patient underwent high-dose chemotherapy with a conditioning regimen in the first complete remission, including total body irradiation (12 Gy) and cyclophosphamide (120 mg/kg) on days 2 to 6, and the first allogeneic bone marrow transplantation from an HLA-2-locus-mismatched cord blood donor, containing 2.7×10^7 cells/kg and 1.6×10^5 $CD34^+$ cells/kg, in June 2012. Acute GVHD (aGVHD) prophylaxis included short-term methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) and cyclosporine treatment. Fever and skin rash were observed on day 13. Subsequently, elevation of lactate dehydrogenase (903 IU/L) and ferritin (11,000 ng/mL) occurred on day 17. Bone marrow examination showed a dominance of lymphocytes and 7% hemophagocytosis with hypocellular bone marrow (NCC 1,500/μL) on day 18 (Fig. 1G-1I). Moreover, bone marrow chimerism analysis showed recipient chimerism (> 95%) by polymerase chain reaction amplification using polymorphic non-coding DNA sequences of short tandem repeat-polymerase chain reaction. Peripheral blood DNA analysis did not detect human herpesvirus-6

Table 2. HLA profile of sibling donor and cord blood using 1st CBT and 2nd CBT

	HLA-A		HLA-B		HLA-C		HLA-DR		TNC	$CD34^+$ cells
Patient	0201	2601	5101	6701	0304	0701	1201	1454		
CB1	0201	0207	5101	5603	0102	0304	1201	1454	2.7×10^7/kg	1.6×10^5/kg
CB2	0201	2602	4801	5401	0102	0803	1201	1405	2.6×10^7/kg	1.2×10^5/kg
Sister	0201	3101	0702	6701	0701	0701	1201	1454		

HLA, human leukocyte antigen; CBT, umbilical cord blood transplantation; TNC, total nucleated cells; CB, cord blood

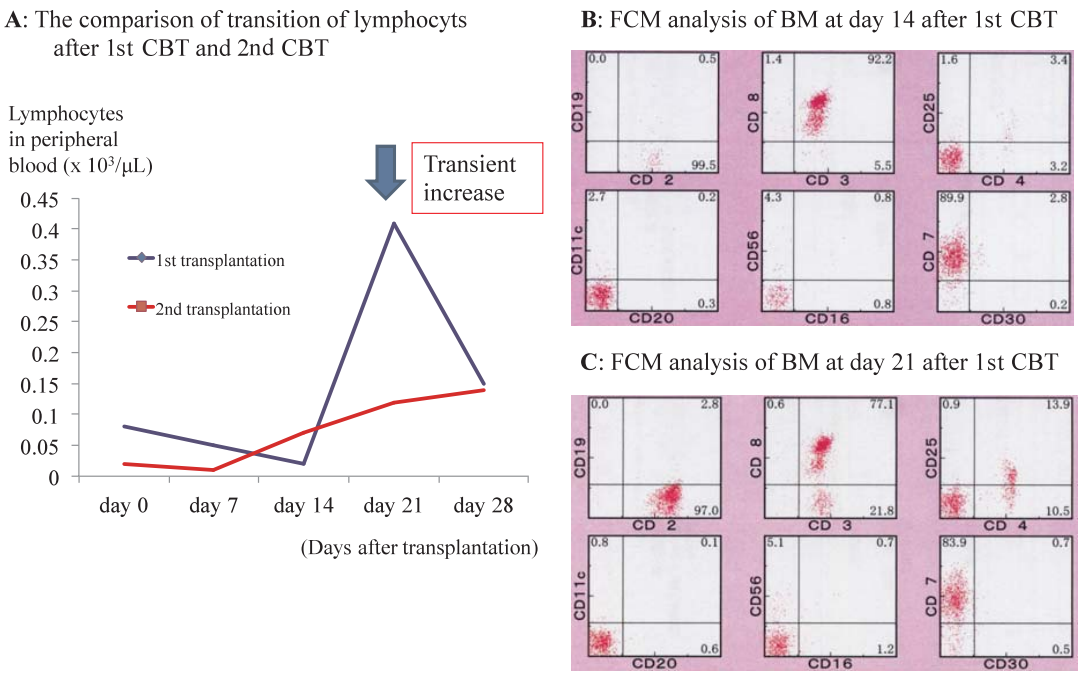

Fig. 2. Comparison of lymphoid transition between 1st cord blood transplantation (CBT) and 2nd CBT. In the 1st CBT of our case, the lymphocytes in peripheral blood transiently increased in number at 3 weeks after CBT. However, in the 2nd CBT, the lymphocytes did not increase at 3 weeks after CBT (*2A*). Furthermore, in bone marrow examination of the 1st CBT, host-derived $CD8^+$ T cells increased in number by 92% and 77% at 2 week and 3 weeks, respectively (*2B* & *2C*). HSCT, hematopoietic stem cell transplantation; FCM, flow cytometry; BM, bone marrow

(HHV-6), Epstein-Barr virus, cytomegalovirus (CMV), herpes simplex virus, or varicella-zoster virus DNA. Together, these findings supported a diagnosis of pre-engraftment immunological reaction (PIR) and hemophagocytic lymphohistiocytosis (HLH).

Next, we administered prednisolone to treat the PIR and HLH. This treatment led to resolution of the fever and skin rash. However, the neutrophil count did not exceed 500/μL during the first CBT clinical course. Subsequent bone marrow examination still showed a dominance of lymphocytes and 2% hemophagocytosis, with hypocellular bone marrow (NCC 1,100/μL) on day 27. Moreover, bone marrow chimerism analysis showed recipient chimerism of > 95%. Consequently, we made a diagnosis of primary GF on day 27. At this time, the patient showed a good performance status (PS: 0), an absence of liver and renal dysfunction, and no infection. Thus, in our case, risk assessment using the Hematopoietic Cell Transplantation-Specific Comorbidity Index was zero.[12] Therefore, the patient underwent a second CBT from an HLA-2-locus-mismatched cord blood donor, containing 2.6×10^7 cells/kg and 1.2×10^5 $CD34^+$ cells/kg (Table 2). To prevent GF, the patient underwent a short-term reduced-intensity conditioning regimen, consisting of fludarabine (30 mg/m^2, 3 days), cyclophosphamide (2 g/m^2), and total body irradiation (2 Gy), and GVHD prophylaxis consisting of MMF and FK on day 38 after the first CBT. Neutrophil engraftment (> 0.5×10^9/L) and platelet engraftment (> 50×10^9/L without transfusion) were achieved on days 17 and 28, respectively.

During the clinical course of the second CBT, the main

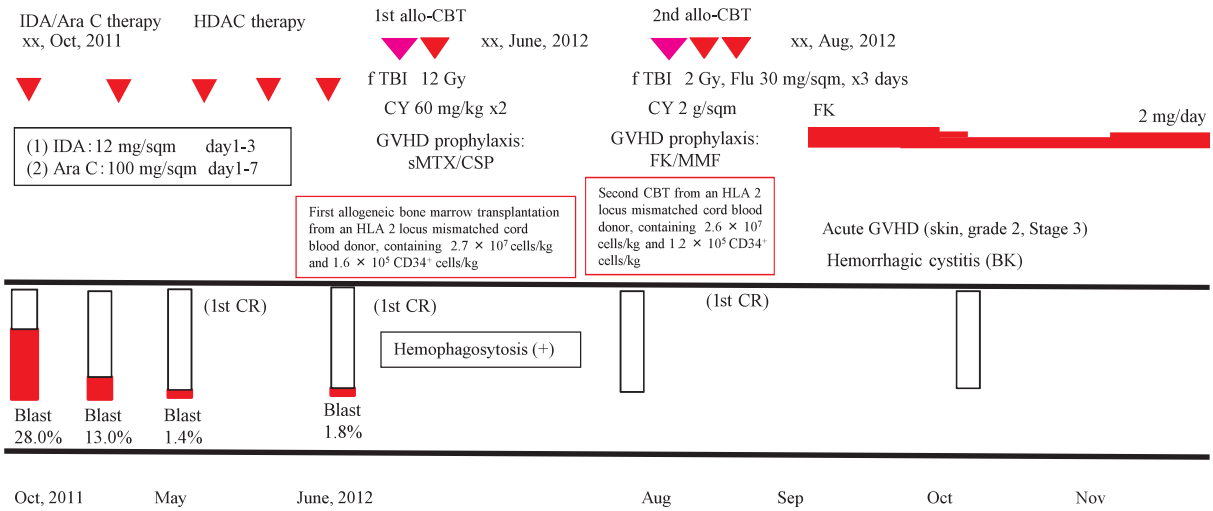

Fig. 3. Clinical course of the present case. We presented a 28-year-old man, diagnosed with acute myelogenous leukemia with myelodysplasia-related changes. On the basis of poor prognosis factors, the patient underwent a myeloablative conditioning regimen, followed by cord blood transplantation (CBT) in the first complete remission. After primary graft failure was diagnosed on day 27, the patient underwent secondary CBT with a short-term reduced-intensity conditioning regimen, consisting of fludarabine, cyclophosphamide, and total body irradiation, and graft-versus-host disease prophylaxis consisting of mycophenolate and tacrolimus. Consequently, engraftment was achieved on day 17, and the patient remained disease-free for 39 months.
IDA, idarubicin; Ara C, cytosine arabinose; HDAC, high-dose cytosine arabinose; CBT, umbilical cord blood transplantation; TBI, total body irradiation; GVHD, graft-versus-host disease; CY, cyclophosphamide; sMTX, short-term methotrexate; CSP, cyclosporine; Flu, fludarabine; MMF, mycophonolate; FK, taclolimus; HLA, human leukocyte antigen; CR, complete remission

complications were methicillin-resistant *Staphylococcus capitis* (MRS) bacteremia, HHV-6 DNAemia, CMV antigenemia, BK virus-associated cystitis, and aGVHD (skin, stage 3, grade 2). MRS was detected on day 3, and vancomycin was administered to control the bacteremia. Prophylactic treatment with foscarnet sodium (PFA) (180 mg/kg/day, weekly) was administered under the monitoring of HHV-6 DNA in peripheral blood on a weekly basis due to the high risk of HHV-6 infection during the 2nd CBT. However, HHV-6 DNAemia and CMV antigenemia were detected on day 14 and day 23, respectively. Thus, pre-emptive treatment with PFA (180 mg/kg/day, daily) was started and controlled. aGVHD of the skin (stage 3, grade 2) was observed on day 40, and was treated through the external administration of prednisolone. BK virus-associated cystitis developed on day 60, and hydration and ciprofloxacin (600 mg/day) were administered. These treatments led to resolution of the MRS bacteremia, HHV-6 DNAemia, CMV antigenemia, BK virus-associated cystitis, and aGVHD. We retrospectively compared the lymphocyte transition between 1st CBT and 2nd CBT. Consistent with a previous report of a transient lymphocyte increase before GF in a mouse model and in hematopoietic stem cell transplantation (HSCT) patients,[13] in our case of 1st CBT, a transient lymphocyte increase occurred before GF (Fig. 2). However, during the clinical course of 2nd CBT, a transient lymphocyte increase did not occur before successful engraftment (Fig. 2). Finally, the patient was discharged on day 120. For 39 months after the treatment, the patient remained disease-free, and did not require further treatment for AML (Fig. 3). Our findings in this case suggest that these treatments may be feasible, safe, and effective for the treatment of patients with GF in CBT.

DISCUSSION

The results of a second transplantation for GF are still poor at approximately 1 year, with an 11% survival rate among 122 patients having been reported.[14] In particular, half of patients who underwent a second transplantation died within 100 days following second transplantation.[15] The major causes of death in these patients were infection, multi-organ failure, and GF.[14,15] Therefore, elucidation of the pathogenesis of GF and the establishment of an appropriate HSCT source, conditioning regimen, and GVHD prophylaxis are essential for overcoming the poor outcome of second transplantations.

In our case, the dysfunction of host cells by PIR and HLH may have been associated with the pathogenesis of primary-type GF in the 1st CBT. Furthermore, the patient successfully underwent secondary CBT with a modified one-day

conditioning regimen consisting of fludarabine, cyclophosphamide, and total body irradiation, and GVHD prophylaxis consisting of MMK and FK. Our case suggests that these treatments may be feasible, safe, and effective for the treatment of patients with GF in CBT. We speculate that a modified one-day conditioning regimen and GVHD prophylaxis contribute to suppression of the activation of donor cells that play a major role in the pathogenesis of GF, and may be reasonable therapeutic modalities. GF is classified into primary GF by an initial lack of donor cells or secondary GF by a loss of donor cells after initial engraftment.[8-11,14] Moreover, primary GF can be subdivided into a rejection or a dysfunction of donor cells.[8-11,14] However, the pathogenesis in the disease progression of GF in CBT is not fully understood. One of the pathogeneses of GF in CBT was reported to be associated with PIR or HLH.[16-18] Recently, Koyama *et al*. reported that a transient increase of lymphocytes before GF may play an important role in the pathogenesis of GF in a mouse model and clinical HSCT patients.[13] Moreover, Kuriyama *et al*. reported that the CD47-signal regulatory protein α antiphagocytic system plays a key role in the maintenance of hematopoietic stem cells, and that its disruption by hematopoietic stem cell-specific CD47 down-regulation may be critical for HLH development.[19] Consistent with previous reports,[16-19] the findings in our case suggested that PIR and HLH may be associated with the pathogenesis of GF in the 1st CBT.

To achieve a successful 2nd HSCT, it should be essential to consider the source of HSCT, the conditioning regimen, and GVHD prophylaxis based on the pathogenesis of GF. As for the source of HSCT, urgent and appropriate preparation of this should be essential. Thus, we selected the 2nd CB containing total nucleated cells at over 2×10^7 cells/kg and $CD34^+$ cells at over 1×10^5 cells/kg because of the absence of an appropriate HLA-identical sibling donor or non-sibling donor.

As for the conditioning regimen, to overcome the poor survival of GF, Goggie *et al*. and Sumi *et al*. reported some success by an innovative conditioning regimen in the treatment of 2nd CBT.[8,9] In particular, Sumi *et al*. reported a modified one-day regimen consisting of fludarabine (30 mg/m^2, days 1-3), cyclophosphamide (2 g/m^2), and total body irradiation (2 Gy).[9] In our case, we administered 3 consecutive days of fludarabine to control the host immune system due to the presence of persistent HLH before a second HSCT. Furthermore, additional low-dose total body irradiation may assist in successful engraftment, consistent with a previous report regarding the eradication of residual host immune cells in GF by low-dose total body irradiation.[20] Among previously reported HSCT patients undergoing a second HSCT with a modified one-day conditioning regimen, the result of the second HSCT for GF was excellent at approximately 1 year, with an 80% survival rate (Table 3). Consequently, we performed the modified one-day conditioning regimen as the conditioning regimen of 2nd HSCT.

As for the GVHD prophylaxis, Uchida *et al*. reported that a combination of MMF and FK was well tolerated and decreased early non-relapse mortality, possibly through improved control of PIR.[18] In our case, we selected the GVHD prophylaxis as a combination of MMF and FK because of the presence of PIR by a transient lymphocyte increase during the 1st CBT. The modified one-day conditioning regimen and GVHD prophylaxis of MMF and FK led to successful second CBT.

Finally, the control of infectious complications was a critical factor in patient outcome. Indeed, during the second

Table 3. Previously published reports regarding the one day conditioning regimen in the second transplantation for graft failure

Reference (year)	Age/Disease	Status at retransplantation	Source of HSCT	Engraftment	Treatment outcome
Yamashita T, *et al*. (2009)	56/ML	Rejection/ febrile neutropenia	CB → CB	19 days	Alive, > 60 mon
Yamashita T, *et al*. (2009)	66/AML	Relapse/ pulmonary aspergillosis	CB → CB	17 days	Alive, > 53 mon
Sumi M, *et al*. (2010)	42/AML	Rejection/ *P*. aeruginosa sepsis	CB → CB	25 days	Alive, > 53 mon
Sumi M, *et al*. (2010)	20/ALL	Rejection/MRSE sepsis	BM → CB → CB	26 days	Dead (relapse), 13 mon
Sumi M, *et al*. (2010)	34/CML	Rejection	CB → CB	18 days	Alive, > 28 mon
Sumi M, *et al*. (2010)	37/AML	Rejection/ streptococcosis sepsis	CB → PB	10 days	Alive, > 27 mon
Sumi M, *et al*. (2010)	53/AML	MRSE sepsis	CB → CB	20 days	Dead (HLH), 2 mon
Sumi M, *et al*. (2010)	68/AA	MRSE sepsis	CB → CB	24 days	Alive, > 14 mon
Present case	28/AML	Rejection	CB → CB	17 days	Alive, > 39 mon

ML, malignant lymphoma; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; AA, aplastic anemia; MRSE, methicillin-resistant *Staphylococcus epidermidis*; HSCT, hematopoietic stem cell transplantation; BM, bone marrow; PB, peripheral blood; CB, cord blood; HLH, hemophagocytic lymphohistiocytosis

CBT, there was a high risk of the development of HHV-6 encephalitis.[18-20] Therefore, we monitored HHV-6 DNA in peripheral blood on a weekly basis. Moreover, PFA (180 mg/kg) was administered on a weekly basis, in a prophylactic therapeutic manner. Moreover, when CMV antigenemia occurred, we administered PFA (180 mg/kg) on a daily basis, in a pre-emptive therapeutic manner. Consistent with previous reports,[21,22] PFA, with less toxicity than myelosuppression, may be an effective and reasonable therapeutic strategy for the control of CMV and HHV-6 infections in the second setting of CBSCT.

In conclusion, our findings in this case suggest that these treatments may be a feasible, safe, and effective strategy for patients with GF in CBT. A randomized study and longer follow-up period will be necessary for the assessment of this therapeutic modality. This case study may be helpful to physicians who directly care for GF patients, and may provide a future direction for a more efficient treatment modality.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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