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ORIGINAL ARTICLE

Salvage haploidentical transplantation for graft failure using reduced-intensity conditioning

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Graft failure is a major concern after cord blood transplantation (CBT) or HLA-haploidentical transplantation (haplo-SCT). As patients who undergo CBT or haplo-SCT almost always lack both matched-related and -unrelated donors, salvage transplantation would also be limited to either CBT or haplo-SCT. In this study, we assessed eight patients who received haplo-SCT as salvage therapy for graft failure. Five and three patients had received haplo-SCT and CBT, respectively, which resulted in graft failure. The median interval from the failed transplantation to salvage transplantation in six patients with primary graft failure was 33.5 days. The reduced-intensity conditioning regimen consisted of fludarabine, thiotepa, rabbit antithymocyte globulin and low-dose TBI. All eight patients achieved neutrophil engraftment, and seven patients achieved platelet recovery. The median times to neutrophil recovery and platelet recovery were 10 and 20 days, respectively. Three patients died from treatment-related causes: two from GVHD and one from rupture of carotid artery aneurysm. Five patients are alive, at a median follow-up of 946 days. The probability of overall survival at 5 years was 75%. These findings may serve as a rationale for giving precedence to haplo-SCT over CBT in salvage SCT after graft failure.
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Introduction

Graft failure is a life-threatening complication following allo-SCT. Immune rejection mediated by residual cellular immunity[1,2] or humoral immunity,[3,4] defects of the host BM microenvironment[5] and viral infections[6] are the main factors presumed to be involved in the occurrence of this complication. As immune rejection occurs as a result of the balance between residual host immunity and graft-derived immunity, the use of non-myeloablative or reduced-intensity conditioning (RIC),[7] T-cell depletion from the graft,[8] low numbers of infused progenitor cells[9,10] and immunological disparity (that is, HLA mismatch)[11] between the host and donor are known to increase the risk of graft failure. Although the overall frequency of graft failure is less than 5%, it has been reported to reach 12% for HLA-haploidentical SCT (haplo-SCT)[11] and is as high as 20% after cord blood transplantation (CBT).[12,13]

As both CBT and haplo-SCT are being increasingly performed as an alternative to HLA-matched-related or -unrelated transplantations, concerns regarding graft failure are also growing. The treatment options for graft failure are very limited. The survival rate for patients who do not receive salvage transplants are dismal (8%).[14] Salvage transplantation is generally attempted; however, the overall survival varies from 11 to 37%, with major obstacles being infections arising from prolonged neutropenia and damaged organ function as a result of previous transplantation.[14–17] Particularly, patients who undergo CBT or haplo-SCT almost always lack both matched-related and -unrelated donors during the clinically relevant period. Therefore, salvage transplantation is also limited to either CBT or haplo-SCT. We hypothesized that haplo-SCT is superior to CBT as a salvage therapy for graft failure because of the advantage of rapid neutrophil recovery, with respect to the high risk of infection in this particular setting. Therefore, we performed haplo-SCT using RIC for graft failure following CBT or haplo-SCT. Here, we describe the results for eight patients.

Patients and methods

Patients

This study is a retrospective analysis of eight consecutive patients who received a salvage transplant from an

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HLA-haploidentical related donor (2–3 Ag mismatched in the GVH vector) for primary or secondary graft failure following CBT or haplo-SCT between March 2001 and May 2010 at Osaka University Hospital or Hyogo College of Medicine Hospital. Informed consent was obtained from all the patients, and they were treated according to our institutionally approved protocols, including those for CBT and haplo-SCT.

Table 1 details the patient characteristics. Six patients had primary graft failure, whereas two had secondary graft failure. The median age of the patients was 49 years (range, 29–61 years) at the time of salvage transplantation. The stem cell sources of the previous transplantation, which failed to engraft, were cord blood in three patients, including one with double units, and haploidentical PBSC in five patients. Among these, two patients had received SCT one and two times before the failed SCT. Accordingly, they underwent salvage transplantation as their third and fourth SCT. Chimerism analysis showed no signs of donor hematopoiesis in seven patients. The remaining patient with secondary graft failure showed 100% donor chimerism in the T-cell fraction and 0% donor chimerism in the myeloid fraction.

Preparative regimen for salvage transplantation

All patients were treated with preparative regimen consisting of fludarabine 30 mg/m^2 for 3 days (days –4 to –2), thiotepa 5 mg/kg for 2 days (days –3 to –2), rabbit anti-T-lymphocyte globulin or antithymocyte globulin (ATG) and single-dose TBI 2–4 Gy. The doses of ATG and TBI in each patient are detailed in Table 2. The dose of TBI was determined according to the preparative regimen of previous transplants and the performance status of the patients at the time of salvage transplantation.

Salvage transplantation

Three of the five patients who had graft failure after haplo-SCT received salvage transplantation from the same donor. G-CSF-mobilized PBSCs were collected from the donor on days 0 and 1, with the target CD34+ cell dose of 3×10^6/kg of recipient body weight. The median number of infused CD34+ cells was 4.7×10^6/kg (range, $2.7–7.9 \times 10^6$/kg). The median interval from the failed transplantation to salvage transplantation for the six patients with primary graft failure was 33.5 days (range, 25−54 days).

Table 1 Patient characteristics

Patient no.	*Age (years)/sex*	*Diagnosis*	*Disease stage*	*No. of SCT before the failed SCT*	*SCT resulting in graft failure*				
					Stem cell source	*HLA match*		*Preparatory regimen*	*Pattern of GF*
						GVH vector	*HVG vector*		
1	29/M	MDS-AML	Refractory	0	PBSC	3/6	3/6	Flu/BU/ATG	Primary
2	54/F	CMML-AML	Refractory	2	PBSC	4/6	4/6	Flu/BU/ATG	Secondary
3	49/F	MDS-AML	Relapse after allo-SCT	1	PBSC	4/6	4/6	Flu/CA/BU/ATG	Primary
4	42/M	MDS-AML	Refractory	0	PBSC	4/6	3/6	Flu/CA/CY/TBI (8)	Primary
5	35/M	ALL	CR2	0	Double CB	5/6	5/6	CY/TBI (12)	Primary
						5/6	4/6		
6	57/M	MDS	RA	0	CB	4/6	4/6	Flu/CY/TBI (3)	Primary
7	61/M	MDS-AML	First relapse	0	CB	4/6	4/6	Flu/CY/TBI (3)	Primary
8	49/F	AML	Refractory	0	PBSC	4/6	3/6	Flu/CA/Mel/ATG	Secondary

Abbreviations: CA = cytosine arabinoside; CMML = chronic myelomonocytic leukemia; F = female; Flu = fludarabine; GF = graft failure; GVH = graft versus host; HVG = host versus graft; M = male; Mel = melphalan; MDS-AML = AML evolved from myelodysplastic syndrome.

Table 2 Information regarding salvage transplantation

Patient no.	*Interval from the failed SCT to salvage SCT (days)*	*Salvage transplantation*						
		Donor		*HLA match*		*Preparatory conditioning*		*CD34 ($\times 10^6$/kg)*
		Same as the failed SCT	*Relation*	*GVH vector*	*HVG vector*	*TBI dose (Gy)*	*ATG product/total dose (/kg)*	
1	25	Yes	Sibling	3/6	3/6	4	TMG/5	7.1
2	37	No	Daughter	4/6	3/6	2	TMG/2[a]	7.9
3	54	No	Daughter	4/6	3/6	4	ATG-F/10	4.0
4	31	Yes	Sibling	4/6	3/6	4	ATG-F/8	3.1
5	36	No	Mother	4/6	4/6	2	TMG/3	3.5
6	40	No	Daughter	3/6	3/6	3	TMG/3	5.5
7	31	No	Daughter	3/6	3/6	3	TMG/3	2.7
8	100	Yes	Daughter	4/6	3/6	4	TMG/3	5.3

Abbreviations: ATG-F = anti-T-lymphocyte globulin-Fresenius; GVH = graft versus host; HVG = host versus graft; TMG = thymoglobulin.
[a]Only patient no. 2 received ATG after transplantation (on days 10, 14 and 19).

GVHD prophylaxis and treatment
GVHD prophylaxis and treatment followed the institutional haplo-RIC protocol, which has been detailed elsewhere.[18] Briefly, GVHD prophylaxis consisted of continuous i.v. infusion of tacrolimus with target levels of 10–12 ng/mL and methylprednisolone 1 mg per kg per day. After patients achieved neutrophil engraftment and acute GVHD was considered absent, tacrolimus and methylprednisolone were tapered.

Supportive care
Patients were hospitalized in single rooms ventilated with high-efficiency particulate air filtration systems. All patients received broad-spectrum antibiotics and azoles (itraconazole or voriconazole) at the time of salvage transplantation. Following engraftment, patients received trimethoprim-sulfamethoxazole or aerosolized pentamidine for prophylaxis against pneumocystis pneumonia for at least 12 months post transplantation. Acyclovir was continued at 200 mg per day until the discontinuation of immunosuppressant. Patients received i.v. Ig 100 mg/kg weekly for 2 months after transplantation. CMV was monitored weekly by a pp65 antigenemia test. In addition, human herpesvirus-6 was monitored bi-weekly by PCR for virus DNA. Documented CMV or human herpesvirus-6 reactivation was treated with either ganciclovir or foscarnet. G-CSF 300 $\mu g/m^2$ was administered from day 1 or day 5 until the neutrophil count was greater than 2500/μL for two consecutive tests.

Chimerism analysis
Donor chimerism was determined serially in the T-cell- or neutrophil-enriched cell fractions of peripheral blood and BM. The methodology used for cell separation and chimerism analysis has been detailed elsewhere.[18,19] Briefly, T cells were enriched by a negative selection system (RosetteSep; StemCell, Vancouver, Canada) to a purity of $>95\%$, and granulocytes were recovered from the Ficoll-red blood cell interface with a purity of $>99\%$. Chimerism analysis involved quantitative PCR of informative STRs in the recipient and donor. DNA was amplified with fluorescent PCR primers for markers that would distinguish the donor and recipient alleles. Fluorescent PCR products were separated with an Applied Biosystems 310 Genetic Analyzer (Applied Biosystems, Carlsbad, CA, USA), and GeneScan software (Applied Biosystems) was used to correlate allele peak areas with the percentage of donor or recipient DNA.

Definitions and statistical analysis
Neutrophil engraftment was defined by an ANC of at least 500/μL for three consecutive tests, whereas platelet recovery was defined by a platelet count of at least 20 000/μL without transfusion support. Primary graft failure was defined by an absence of neutrophil recovery associated with no appearance or complete loss of donor cells using STR chimerism analysis by day 18 or an absence of neutrophil recovery by day 60. Secondary graft failure was defined as a recurrent neutropenia less than 500/μL after initial recovery. Diagnosis of acute and chronic GVHD was based on standard clinical criteria,[20] with histopathological confirmation where possible. Overall survival and disease-free survival were calculated using the Kaplan–Meier method.

Results

Engraftment and chimerism
All eight patients achieved neutrophil engraftment, and seven patients achieved platelet recovery following salvage haplo-SCT (Table 3). The median times to neutrophil recovery and platelet recovery were 10 days (range, 8–11 days) and 20 days (range, 17–97 days), respectively. Chimerism analysis showed that all patients achieved complete donor chimerism in both the T-cell and myeloid fractions within 4 weeks after transplantation.

GVHD
Four patients had no clinical acute GVHD. During the tapering of immunosuppressants, two patients developed grade II GVHD, whereas two patients developed grade III GVHD. Although both patients with grade II GVHD were successfully treated with increased doses of steroid therapy, the two patients with grade III GVHD (both with stage 2 liver involvement) were resistant to steroid therapy and subsequently died. None of the evaluable six patients developed chronic GVHD clinically.

Toxicity, relapse and cause of death
In all, three of the eight patients died from treatment-related causes: two from GVHD and one from rupture of

Table 3 Outcomes of salvage transplantation

Patient no.	*Time to engraftment (days)*		*GVHD*		*Relapse*	*Current status*	*Cause of death*
	Neutrophil	*Platelet*	*Acute*	*Chronic*			
1	10	17	0	No	No	Alive, day 3468	
2	8	97	II	No	No	Dead, day 2395	Rupture of carotid artery aneurysm
3	8	35	0	No	No	Alive, day 936	
4	10	17	0	No	Yes (day 718)	Alive, day 916	
5	10	20	II	No	No	Alive, day 459	
6	9	18	0	No	No	Alive, day 246	
7	11	24	III	NE	No	Dead, day 112	GVHD
8	11	NA	III	NE	No	Dead, day 91	GVHD, leukoencephalopathy

Abbreviations: NA = not achieved; NE = not evaluable.

carotid artery aneurysm, possibly related to thrombotic microangiopathy. One patient relapsed 718 days after salvage transplantation and received a third transplantation from a haploidentical related donor.

Survival

Five patients are alive at a median follow-up of 946 days (range, 276–3498 days). The probability of overall survival and disease-free survival at 5 years was 75 and 56%, respectively.

Discussion

We showed that salvage haplo-SCT for graft failure using RIC regimen allowed rapid neutrophil engraftment in all our patients, which translated into no mortality from infectious complications and favorable long-term survival (5-year overall survival = 75%).

Recently, the result of a Japanese nationwide survey of salvage CBT for graft failure was reported by Waki *et al*.[21] Of 80 patients who received salvage CBT, 61 patients who survived for more than 28 days were evaluated for hematopoietic recovery. Among them, 45 patients (74%) achieved neutrophil engraftment at a median of 21 days, and 31 patients (51%) achieved platelet recovery. Thirteen patients developed primary graft failure again. The rate of TRM at day 100 was 45%, with 60% related to infectious complications. The probability of overall survival at 1 year after CBT was 33%. Although the number of patients in this study is too small to draw any conclusions, we found a clear advantage of haplo-RIC over CBT in terms of neutrophil engraftment. Meanwhile, the major drawback of haplo-SCT is the risk of GVHD. Although the rate of severe GVHD was limited, two patients developed fatal GVHD in this study. Optimization of GVHD prophylaxis, such as the use of higher doses of ATG, may further improve the outcome of haplo-SCT for graft failure. To date, reports describing salvage transplantation from haploidentical donors in adult patients are few.[22,23] In the pediatric setting, Lang *et al*.[24] described 11 patients who received haplo-SCT for graft failure, with findings consistent with this report with respect to rapid neutrophil engraftment at a median of day 9, associated with favorable survival (1-year event-free survival = 72%). Although the number of reported cases is limited, double-unit CBT also appears promising.[25]

This study also showed the relative safety and effectiveness of the preparative regimen, consisting of fludarabine, thiotepa, low-dose TBI and ATG. In the majority of recent studies concerning salvage transplantation for graft failure, fludarabine and either ATG or alemtuzumab were included in the preparative regimen.[26–29] These agents are highly immunosuppressive and expected to suppress host immunocompetent cells, including T and NK cells, which are involved in the mechanism of immune-mediated graft rejection. Moreover, the use of ATG or alemtuzumab reduces the risk of GVHD after salvage transplantation. Of note, the aforementioned study by Waki *et al*.[21] showed that the incidence of neutrophil engraftment was higher in patients who received alkylating agents, including melphalan, busulfan and cyclophosphamide, as part of conditioning. Furthermore, the effect of low-dose TBI in promoting donor engraftment in the settings of the first transplantation has been reported by several studies.[14,30] Collectively, the preparative regimen used in this study has a powerful potential in enabling successful donor engraftment with limited toxicity in salvage transplantation for graft failure.

Theoretically, it could be argued that the donor in salvage transplantation should be altered from the previous failed transplantation, as previous studies have shown that cytotoxic T cells targeting mismatched HLA possessed by the donor are aroused at the time of immune rejection.[1] However, in this study, all three patients who received salvage transplantation from the same donor as the previous failed transplantation achieved engraftment. Nevertheless, considering the possible risk to a healthy donor of the administration of high doses of G-CSF twice in a short period of time as well as of poor mobilization, the donor for the salvage transplantation should be chosen cautiously.

This study has several inherent limitations. First, as a retrospective review, our case series is subject to a possible selection bias. In the study period, 12 patients developed graft failure after CBT or haplo-SCT, including eight patients who received salvage haplo-SCT, and thus were analyzed in this study. Of the remaining four patients, two patients received salvage transplantation from HLA one-locus mismatched donors. The other two patients could not receive salvage SCT, as they died as early as on days 20 and 25. Thus, we do not consider this study to be biased. Second, the number of the patients was small and the duration of follow-up for some of them was short. Nevertheless, our case series suggest the usefulness of this approach, indicating the need for further clinical study.

In conclusion, we showed that salvage haplo-SCT for graft failure allowed rapid engraftment in all patients, which translated into favorable overall survival. This study may serve as a rationale for giving precedence to haplo-SCT over CBT in the settings of salvage SCT after graft failure.

Conflict of interest

The authors declare no conflict of interest.

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