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ORIGINAL ARTICLE

Outcomes of salvage haploidentical transplantation using posttransplant cyclophosphamide for graft failure following allogeneic hematopoietic stem cell transplantation

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Abstract

Haploidentical donors have emerged as an alternative donor source for salvage stem cell transplantation (SCT) after graft failure; however, data regarding salvage haploidentical SCT using posttransplant cyclophosphamide (PTCy) are limited. Using nationwide data (2011–2019), we retrospectively investigated transplant outcomes after salvage haploidentical SCT using PTCy for graft failure ($n=33$, median age 34 years). The total dose of PTCy was 75–100 mg/kg (standard dose) in 26 patients (78.8%) and 40–50 mg/kg (lower dose) in 5 patients (15.2%). The neutrophil engraftment rate at 30 days was 81.8%. One-year overall survival (OS) and non-relapse mortality (NRM) rates were 47.4% and 46.0%, respectively. The standard-dose group exhibited better OS (61.1% vs. 0.0% at 1 year, $P=0.022$) and NRM (35.1% vs. 80.0% at 1 year, $P=0.052$) than the lower-dose group. Moreover, the standard-dose group was less prone to both grades II–IV (11.5% vs. 40.0%) and III–IV (0.0% vs. 40.0%) acute graft-versus-host disease (GVHD). Use of cyclophosphamide in previous SCT and conditioning did not affect OS or NRM. In conclusion, haploidentical salvage SCT using PTCy offers promising survival outcomes. Prospective studies are required to validate the efficacy of salvage haploidentical SCT using PTCy.

Keywords Stem cell transplantation · Transplantation · Engraftment

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Introduction

Graft failure (GF) is a life-threatening complication following allogeneic stem cell transplantation (SCT) [1–4]. Between 4.0 and 7.3% of all allogeneic SCT cases exhibit GF [1–5]; a higher incidence is observed in cord blood transplantations [5]. Although salvage SCT is the only curative therapy for GF, the long-term survival rate after salvage SCT is still modest, reaching only 11–58% [1–7].

In the past decade, haploidentical donors emerged as alternative donors in salvage SCT because of rapid availability and fast neutrophil engraftment [8–16]; however, acute graft-versus-host disease (GVHD) commonly occurs after salvage SCT, occasionally hampering the success of salvage haploidentical SCT [9]. Most patients who underwent salvage haploidentical SCT received calcineurin inhibitor–based standard GVHD prophylaxis with or without antithymocyte globulin [8–10, 12–15], and data regarding the outcomes after salvage haploidentical SCT using posttransplant cyclophosphamide (PTCy) are still limited [8, 11, 12]. Currently, optimal strategies for salvage haploidentical SCT remain unestablished.

Therefore, on behalf of the Transplant Complications Working Group of the Japan Society for Transplantation and Cellular Therapy, this nationwide retrospective study aimed to evaluate the transplant outcomes and risk factors for survival after salvage haploidentical SCT using PTCy.

Materials and methods

The Transplant Registry Unified Management Program 2 of the Japanese Data Center for Hematopoietic Cell Transplantation provided the clinical data [17, 18]. Patients who were diagnosed with GF and underwent a second or higher allogeneic SCT from the haploidentical related donor (≥ 2 antigen-mismatch), using PTCy as GVHD prophylaxis, between 2011 and 2019 were included. GF diagnosis was made at the respective transplant center. Our retrospective study protocol adhered to the principles of the Declaration of Helsinki, with the approval of the institutional review board of the Tokai University School of Medicine.

In this study, overall survival (OS) was defined as the time between salvage SCT and death or the time of the last visit. Death without relapse or disease progression indicated non-relapse mortality (NRM). An absolute neutrophil count of at least 0.5×10^9/L for three consecutive times defined neutrophil engraftment. Regarding the total dose of PTCy, patients who received 75–100 mg/kg of PTCy were classified as the standard-dose group, whereas those who received 40–50 mg/kg of PTCy were classified as the lower-dose group. The dose of PTCy was at the discretion of each attending physician. The modified disease risk index was classified according to the previously reported criteria [19–21]. Acute and chronic GVHD were diagnosed and graded at each center according to the published criteria [22, 23]. Furthermore, we defined severe organ dysfunction as either ejection fraction ≤ 50%, serum creatinine ≥ 2 mg/dL, bilirubin ≥ 1.5 × upper limit of normal, or aspartate aminotransferase/alanine aminotransferase ≥ 2.5 × upper limit of normal [21, 24].

The distribution of patient characteristics was compared using Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. We also used the Kaplan–Meier method to estimate OS probabilities, and the log-rank test to analyze differences among groups. The incidences of NRM, engraftment, acute and chronic GVHD, and Gray's test were determined using a cumulative incidence method. The competing risks included relapse in the NRM analysis; NRM in the relapse analysis; relapse and NRM in the engraftment analysis; and relapse, NRM, and recurrent GF in the acute and chronic GVHD analysis. The OS was examined by multivariate analysis using the Cox proportional hazard regression model. Factors from the univariate analysis with P values < 0.1 were included in the multivariate analysis. Covariates included in the univariate models for each analysis are the total dose of PTCy, patient age, patient sex, performance status (PS) at salvage SCT, modified disease risk index, continuation of antimicrobial treatment at salvage SCT day, severe organ dysfunction, GVHD prophylaxis other than PTCy, conditioning regimen, donor source at salvage SCT, cyclophosphamide (Cy) use at previous SCT, transplantation year, and days from SCT to salvage SCT. All P values were two-sided, and all statistical data were analyzed using EZR, a graphical user interface for R software (the R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria) [25].

Results

Patient and transplant characteristics

Table 1 shows the patient and transplant characteristics, and Table S1 describes them in detail. This study included 33 patients, with a median age of 34 (range: 2–67) years. Among them, 21 (63.6%) had a PS of 0–1. At salvage transplantation, 12 (36.4%) received treatment for active infection, and 5 (15.2%) had severe organ dysfunction. The median interval from previous SCT to salvage SCT was 49 (26–1468) days, and 22 patients (66.7%) underwent salvage SCT within 100 days from previous SCT. The total dose of PTCy was 75–100 mg/kg in 26 patients (78.8%, standard-dose group) and 40–50 mg/kg in 5

Table 1 Patient and transplant characteristics

	N = 33
Age, median [range], years	34 [2–67]
Sex (%)	
Male/ Female	19 (57.6)/ 14 (42.4)
PS (%)	
0–1	21 (63.6)
2–3	12 (36.4)
Modified disease risk index (%)	
Low/intermediate	19 (57.6)
High/very high	12 (36.4)
NA	2 (6.1)
Continuation of antimicrobial treatment at the day of salvage SCT (%)	12 (36.4)
Severe organ dysfunction (%)	5 (15.2)
The total dose of PTCy	
75–100 mg/kg	26 (78.8)
40–50 mg/kg	5 (15.2)
NA	2 (6.1)
GVHD prophylaxis (%)	
Tac + MMF	27 (81.8)
Other	6 (18.2)
Conditioning regimen (%)	
FluMel-based	10 (30.3)
FluCy-based	10 (30.3)
FluBU-based	7 (21.2)
Flu ± TBI	5 (15.2)
NA	1 (3.0)
Donor source at salvage SCT (%)	
BM/ PB	3 (9.1)/ 30 (90.9)
Cy use in previous SCT (%)	
No	16 (48.5)
Yes	17 (51.5)
Donor relation at previous SCT (%)	
Cord blood	22 (66.7)
Haploidentical donor	6 (18.2)
Matched related donor	3 (9.1)
Unrelated donor	2 (6.1)
Year of transplantation (%)	
2011–2017	17 (51.5)
2018–2019	16 (48.5)
Days from first SCT to salvage SCT, median [range]	49 [26–1,468]
≤ 100 days	22 (66.7)

PS performance status, *SCT* stem cell transplantation, *PTCy* post-transplant cyclophosphamide, *GVHD* graft-versus-host disease, *Tac* tacrolimus, *MMF* mycophenolate mofetil, *Flu* fludarabine, *Mel* melphalan, *Cy* cyclophosphamide, *BU* busulfan, *TBI* total body irradiation, *BM* bone marrow, *PB* peripheral blood

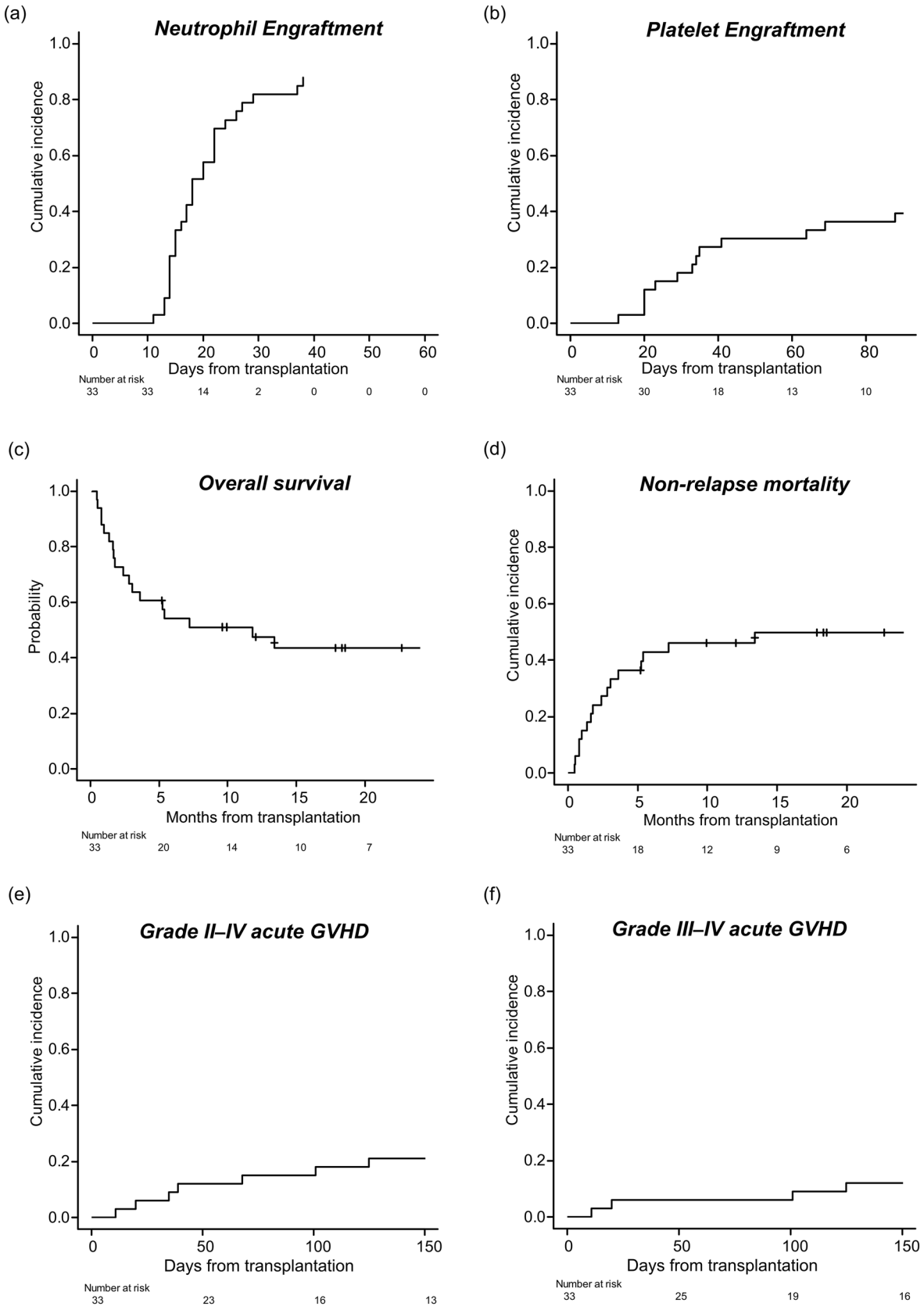
patients (15.2%, lower-dose group); however, that in 2 patients (6.1%) was unknown. Regarding previous SCT, 22 patients (67.7%) underwent cord blood transplantation and 6 patients (18.2%) had haploidentical transplantation. In the previous SCT, 17 patients (51.5%) received Cy as a conditioning regimen ($n = 14$) or GVHD prophylaxis ($n = 4$) (Table S1).

Outcomes after salvage SCT using PTCy

The median time for neutrophil engraftment after salvage SCT was 18 days, and the cumulative incidence of neutrophil engraftment at 30 days and platelet engraftment at 60 days was 81.8% (Fig. 1a) and 30.3% (Fig. 1b), respectively. Remarkably, neutrophil engraftment was successfully achieved at 22 days after salvage SCT in a patient who had donor-specific anti-HLA antibody (Table S1, case 32). The median OS was 359 days, and the OS at 1 year was 47.4% (Fig. 1c); in addition, the NRM at 1 year was 46.0% (Fig. 1d). At 100 days after salvage SCT, 15.2% and 6.1% of the patients experienced grade II–IV and III–IV acute GVHD (Fig. 1e, f), respectively.

Prognostic effects of the total dose of PTCy

We investigated the prognostic effects of the total dose of PTCy for transplant outcomes after salvage SCT. No significant differences in patient characteristics were found between the standard-dose and lower-dose groups (Table S2). In the univariate analysis, the neutrophil engraftment was similar between the standard-dose and lower-dose groups (80.8% and 80.0%, respectively, at 30 days; $P = 0.52$; Fig. 2a), as was the case with platelet engraftment (34.6% and 20.0%, respectively, at 60 days; $P = 0.28$; Fig. 2b). Notably, the standard-dose group had a significantly better OS than the lower-dose group (61.1% vs. 0.0% at 1 year; $P = 0.022$; Table 2; Fig. 2c). In the multivariate analysis for OS adjusting for PS, lower-dose PTCy was significantly associated with a worse OS (hazard ratio, 3.03; 95% CI, 1.00–9.15; $P = 0.049$; Table 2). The standard-dose group had a lower NRM than the lower-dose group, but the difference was not significant (35.1% vs. 80.0% at 1 year; $P = 0.052$; Fig. 2d). Moreover, the standard group was less likely to experience both grades II–IV (11.5% vs. 40.0% at 100 days; $P = 0.010$; Fig. 2e) and III–IV of acute GVHD (0.0% vs. 40.0% at 100 days; $P < 0.001$; Fig. 2f) than the lower-dose group. Figure S1 shows the forest plot for OS stratified by patient characteristics. The beneficial effects of standard-dose PTCy was more evident in younger patients or those with good PS (Figure S1).


(a)
Neutrophil Engraftment
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 10 20 30 40 50 60
Days from transplantation
Number at risk
33 33 14 2 0 0 0
(b)
Platelet Engraftment
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 20 40 60 80
Days from transplantation
Number at risk
33 30 18 13 10
(c)
Overall survival
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 5 10 15 20
Months from transplantation
Number at risk
33 20 14 10 7
(d)
Non-relapse mortality
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 5 10 15 20
Months from transplantation
Number at risk
33 18 12 9 6
(e)
Grade II–IV acute GVHD
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 50 100 150
Days from transplantation
Number at risk
33 23 16 13
(f)
Grade III–IV acute GVHD
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 50 100 150
Days from transplantation
Number at risk
33 25 19 16

◂**Fig. 1** Transplant outcomes after salvage haploidentical SCT using PTCy. The neutrophil (**a**) and platelet recovery rates (**b**), overall survival (**c**), non-relapse mortality (**d**), and the incidence of grade II–IV (**e**) and III–IV (**f**) acute GVHD. *SCT* stem cell transplantation, *PTCy* posttransplant cyclophosphamide, *Cy* cyclophosphamide, *GVHD* graft-versus-host disease

Effects of Cy use in previous SCT and conditioning regimen

To elucidate the safety of successive Cy administration in a short period, we focused on patients who received Cy in previous SCT ($n=17$) and those who received Cy-based conditioning regimen in salvage SCT ($n=10$). The median total dose of Cy was 120 (50–130) and 30 (30–50) mg/kg in previous SCT and in the Cy-based conditioning regimen, respectively. Remarkably, the OS was comparable between patients with and without Cy administration in previous SCT (52.3% in patients with Cy in previous SCT vs. 43.8% in those without at 1 year; $P=0.83$; Fig. 3a); the NRM was also comparable between these patients (47.8% in patients without Cy in previous SCT vs. 43.8% in those without at 1 year; $P=0.89$; Fig. 3b). Regarding the conditioning regimen in the salvage SCT, fludarabine plus cyclophosphamide (FluCy)-based conditioning did not affect the OS (40.0% in patients with FluCy-based conditioning vs. 52.9% in those without at 1 year; $P=0.98$; Fig. 3c). Although patients with FluCy-based conditioning had higher NRM than those without, the difference was still not significant (60.0% vs. 36.8% at 1 year; $P=0.51$; Fig. 3d).

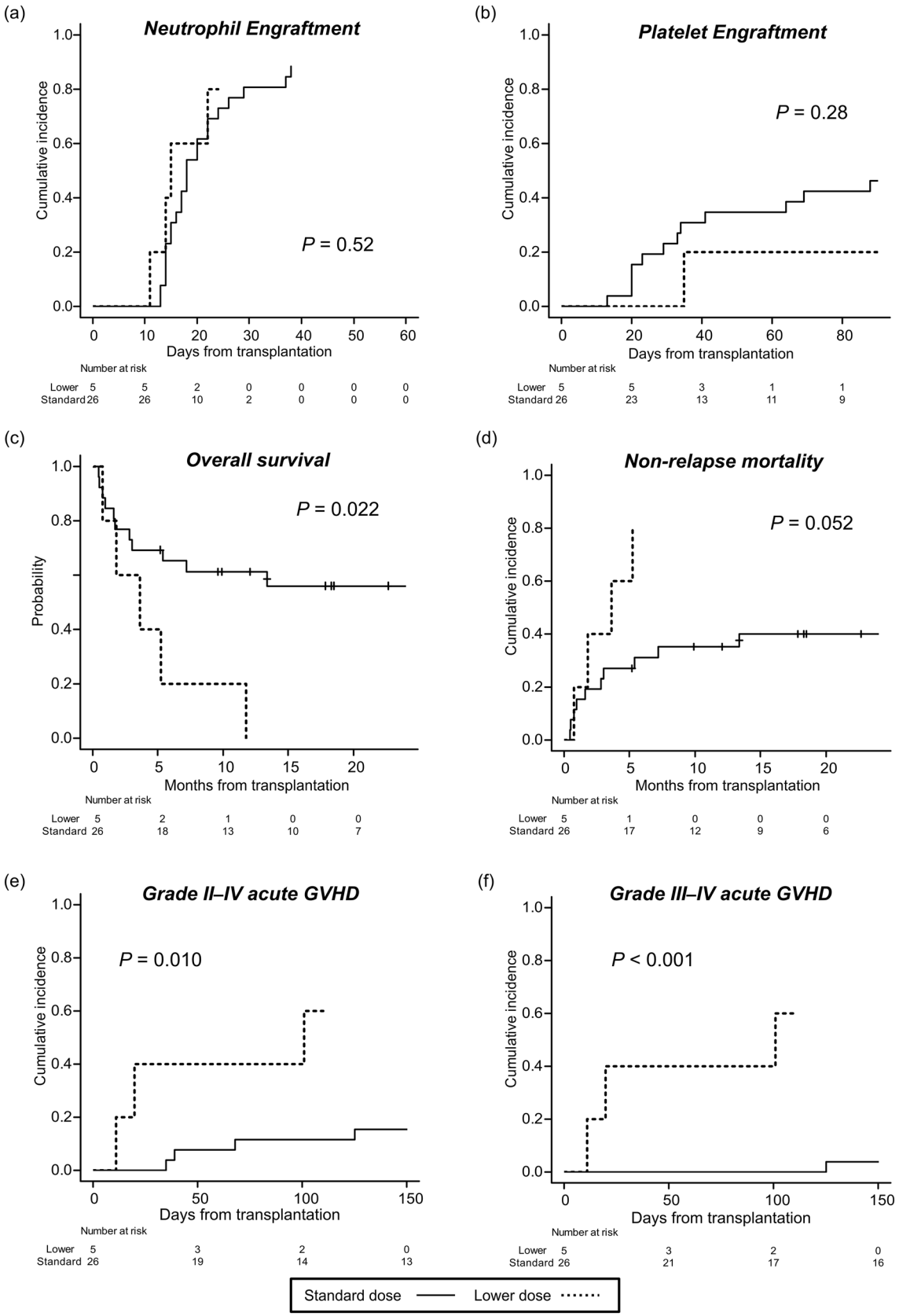
Discussion

This study demonstrated that salvage SCT using PTCy can lead to promising transplant outcomes and that administering the standard dose of PTCy can prevent severe acute GVHD and ensure long-term survival.

The feasibility of salvage haploidentical SCT has already been extensively studied [8–16]. However, reports about salvage haploidentical SCT using PTCy remain limited [8, 9, 11, 12]. Thus, this nationwide retrospective study investigated the transplant outcomes of salvage haploidentical SCT using PTCy. Salvage cord blood transplantation for GF entails the risks of recurrent GF and early mortality caused by the delayed neutrophil engraftment [4, 9, 16, 26], whereas salvage haploidentical SCT using antithymocyte globulin is associated with severe acute GVHD [9]. These problems can substantially hinder long-term survival after salvage SCT. Nevertheless, our study showed that haploidentical salvage SCT using PTCy offered fast neutrophil engraftment (81.8% at 30 days) and effectively prevented severe acute GVHD after salvage SCT (Grade III–IV; 6.1% at 100 days), leading to promising survival outcomes (47.4% at 1 year). Our results are similar to those of a French study, which reported an OS rate of 56% at 1 year and a neutrophil engraftment rate of 79% [11]. Given that 1-year OS after salvage cord blood transplantation reported so far was only 16.7–34.6% [9, 12, 16], our study further supports the idea that the strategy of salvage haploidentical SCT using PTCy can be a promising option for GF after allogeneic SCT. However, prospective studies are still required to investigate the efficacy and safety of salvage haploidentical SCT using PTCy.

Considering Cy toxicity, haploidentical SCT using lower-dose PTCy has been examined for years [27, 28]. A multicenter prospective study revealed that the 80 mg/kg of PTCy is feasible [27]. The incidence of acute and chronic GVHD in patients receiving 80 mg/kg of PTCy seemed comparable to the historical data using 100 mg/kg of PTCy (grade III–IV acute GVHD, 1–5%; chronic GVHD, 28–35%) [27, 29, 30]. However, patients receiving 25–50 mg/kg concentration of PTCy have a nonnegligible risk of developing severe acute GVHD (grade III–IV; 9.1–33%) [28]. Patients who developed GF are likely to suffer from concomitant infection [16] and severe organ dysfunction [5, 31] caused by the predisposed conditioning regimen, leading to a poor PS [21]. Therefore, the administration of lower-dose PTCy has been attempted. Our study included the largest number of patients who underwent salvage haploidentical SCT using PTCy for GF, enabling us to examine the prognostic factors for survival. We, for the first time, examined the prognostic impact of Cy dose in salvage SCT using PTCy. Unfortunately, lower-dose PTCy was significantly associated with worse OS. Patients who received lower-dose PTCy demonstrated similar neutrophil engraftment rate after salvage SCT. Nevertheless, lower-dose PTCy resulted in a significantly poor OS, which would be attributed to the higher incidence of severe acute GVHD after salvage SCT. Although frail patients could also be included in the lower-dose PTCy group, poor OS was also found in a multivariate analysis adjusting for PS. Given that three out of five patients in the lower-dose group succumbed to acute GVHD, standard-dose PTCy might be indispensable to effectively prevent the development of acute GVHD after salvage SCT.

Another clinical concern for salvage SCT using PTCy is whether patients who had received Cy as a conditioning regimen or GVHD prophylaxis in previous SCT can tolerate the successive Cy administration in a short period. The original method of haploidentical SCT using PTCy reported in 2008 included the Cy-containing conditioning regimen [32]; however, the incidence of Cy-induced cardiomyopathy reached 8.5% in patients who received a conditioning regimen with 200 mg/kg of Cy [33]. Even in patients who received 100–120 mg/kg of Cy, 1.4% experienced Cy-induced cardiomyopathy [33, 34]. Moreover, Cy-induced cardiomyopathy occurred after haploidentical SCT using


(a)
Neutrophil Engraftment
Cumulative incidence
P = 0.52
Days from transplantation
Number at risk
Lower 5 5 2 0 0 0 0
Standard 26 26 10 2 0 0 0
(b)
Platelet Engraftment
Cumulative incidence
P = 0.28
Days from transplantation
Number at risk
Lower 5 5 3 1 1
Standard 26 23 13 11 9
(c)
Overall survival
Probability
P = 0.022
Months from transplantation
Number at risk
Lower 5 2 1 0 0
Standard 26 18 13 10 7
(d)
Non-relapse mortality
Cumulative incidence
P = 0.052
Months from transplantation
Number at risk
Lower 5 1 0 0 0
Standard 26 17 12 9 6
(e)
Grade II–IV acute GVHD
Cumulative incidence
P = 0.010
Days from transplantation
Number at risk
Lower 5 3 2 0
Standard 26 19 14 13
(f)
Grade III–IV acute GVHD
Cumulative incidence
P < 0.001
Days from transplantation
Number at risk
Lower 5 3 2 0
Standard 26 21 17 16
Standard dose
Lower dose

◂**Fig. 2** Transplant outcomes after salvage haploidentical SCT using PTCy stratified by the total dose of Cy. The neutrophil (**a**) and platelet recovery rates (**b**), overall survival (**c**), non-relapse mortality (**d**), and incidence of grade II–IV (**e**) and III–IV (**f**) acute GVHD. *SCT* stem cell transplantation, *PTCy* posttransplant cyclophosphamidem, *Cy* cyclophosphamide, *GVHD* graft-versus-host disease

PTCy was also reported.[34]. Thus, we evaluated the prognostic risk of Cy use in previous SCT and in the conditioning regimen. In previous SCT, 13 patients received Cy-based conditioning regimen, 3 received PTCy, and 1 received both Cy-based conditioning regimen and PTCy (Table S1). As

Table 2 Univariate and multivariate analysis for OS

Factor	Univariate			Multivariate	
	N	Probability at 1 year (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
The total dose of PTCy					
75–100 mg/kg	26	61.1 (39.7–76.9)	0.022	Reference	
40–50 mg/kg	5	0.0 (NA)		3.03 (1.00–9.15)	0.049
Age					
< 55 years	26	44.5 (24.7–62.6)	0.45		
≥ 55 years	7	57.1 (17.2–83.7)			
Sex					
Male	19	41.4 (19.6–62.1)	0.59		
Female	14	57.1 (28.4–78.0)			
PS at salvage SCT					
0–1	21	61.1 (36.9–78.4)	0.094	Reference	
2–3	12	25.0 (6.0–50.5)		2.64 (0.94–7.43)	0.067
Modified disease risk index					
Low/intermediate	19	47.4 (24.4–67.3)	0.78		
High/very high	12	45.7 (16.0–71.6)			
Continuation of antimicrobial treatment at the day osf salvage SCT					
No	21	61.2 (37.1–78.4)	0.11		
Yes	12	22.2 (4.1–49.2)			
Severe organ dysfunction					
No	28	52.2 (32.1–69)	0.10		
Yes	5	20.0 (0.8–58.2)			
GVHD prophylaxis					
Tac + MMF	27	50.3 (30–67.6)	0.39		
Other	6	33.3 (4.6–67.6)			
Conditioning regimen					
FluCy-based	10	40.0 (12.3–67.0)	0.98		
Other combination	22	52.9 (29.8–71.5)			
Donor source at salvage SCT					
BM	3	66.7 (5.4–94.5)	0.43		
PB	30	45.3 (26.8–62.1)			
Cy use in previous SCT					
No	16	43.8 (19.8–65.6)	0.83		
Yes	17	52.3 (26.8–72.7)			
Year of transplantation					
2011–2017	17	46.3 (22.1–67.6)	0.64		
2018–2019	16	48.1 (22.4–69.9)			
Days from first SCT to salvage SCT					
< 100 days	22	44.4 (23.2–63.8)	0.92		
≥ 100 days	11	53.0 (20.9–77.3)			
< 60 days	20	38.6 (17.6–59.3)	0.36		
≥ 60 days	13	60.6 (29.4–81.4)			

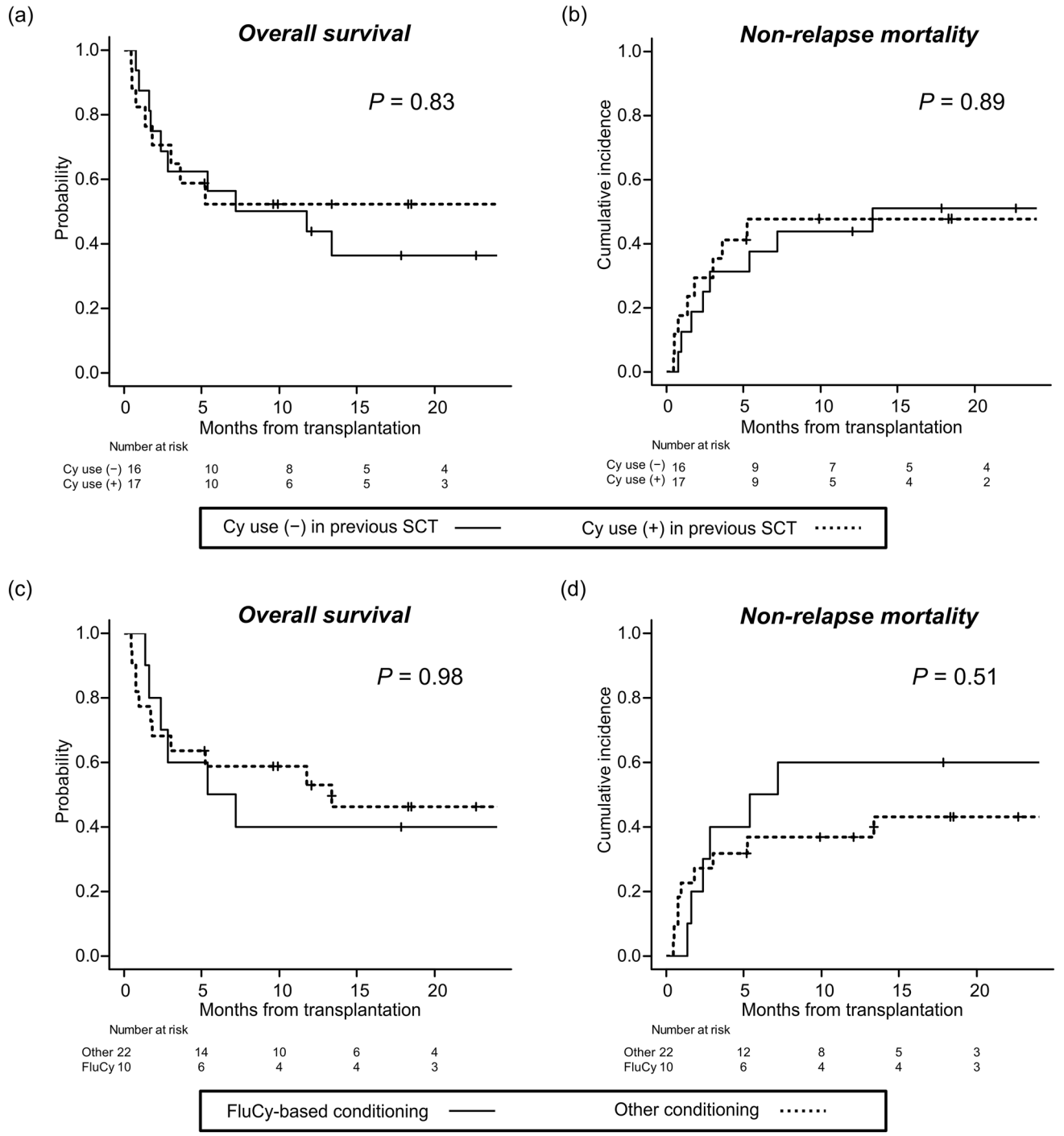


Fig. 3 Subgroup analyses for transplant outcomes after salvage haploidentical SCT using PTCy stratified by Cy use in previous SCT and as the conditioning regimen. Overall survival (**a**) and non-relapse mortality (**b**) according to Cy use in previous SCT. Overall survival (**c**) and non-relapse mortality (**d**) according to the conditioning regimen. *SCT* stem cell transplantation, *PTCy* posttransplant cyclophosphamide, *Cy* cyclophosphamide

for the conditioning regimen in salvage SCT, 10 patients used FluCy-based conditioning. Notably, OS and NRM were not significantly different with respect to the Cy use in previous SCT and in the conditioning regimen. One possible explanation for these results is that the duration from the previous SCT to salvage SCT (median 49 days) could mitigate toxicity associated with successive Cy administration. In fact, only one patient succumbed to organ failure after

salvage SCT in our study (Table S1). Considering the low incidence of Cy-induced cardiomyopathy, the study's small sample size precludes the definitive conclusion for the safety of successive Cy administration. Hence, our results should be carefully validated in larger cohorts.

This study has some limitations. First, this study is a retrospective study based on the registry database in Japan. Thus, the dose of PTCy was at the discretion of each attending physician or institution, possibly resulting in some biases. Moreover, our database does not include data on whether the GF was primary or secondary. Although the univariate analysis showed that the number of days from SCT to salvage SCT (cut-off points of 100 or 60 days) was not a significant prognostic factor, our results should still be carefully interpreted. Furthermore, the prognostic impact of PTCy dose focusing on the primary graft failure should be evaluated in a larger study. Second, the sample size is small for detecting the significant association between PTCy total dose and NRM. However, this study still demonstrated that the incidence of severe acute GVHD was significantly higher in the lower-dose PTCy group. Considering the dismal outcomes of patients who developed severe acute GVHD [35], the higher incidence of severe acute GVHD in the lower-dose PTCy group seemed unacceptable. Third, some data regarding patient characteristics were lacking, particularly the detailed information on anti-HLA antibody titers [36], suggesting the possibility of some biases. Despite these limitations, our study further supports the efficacy and safety of salvage SCT using PTCy for GF after allogeneic SCT. We believe that our results provide useful information for the prevention and treatment strategies for GF.

In conclusion, salvage haploidentical SCT using PTCy offers promising survival outcomes and could be a crucial option for GF after allogeneic SCT. An adequate dose of PTCy (i.e., 75–100 mg/kg) might be indispensable to achieve long-term survival. We plan to conduct a prospective study to further clarify the efficacy of salvage SCT using PTCy for GF after allogeneic SCT.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12185-022-03405-w.

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Data availability Clinical data were provided by the Transplant Registry Unified Management Program 2 of the Japanese Data Center for Hematopoietic Cell Transplantation. Restrictions are applicable to the availability of the data, which were used under license for this study.

Declarations

Conflict of interest The authors declare no competing financial interests.

Ethics approval Our study protocol was approved by the institutional review board of the Tokai University School of Medicine.

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