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Haploidentical

Outcomes of Salvage Haploidentical Transplant with Post-Transplant Cyclophosphamide for Rescuing Graft Failure Patients: a Report on Behalf of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy

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A B S T R A C T

Prognosis of patients with graft failure is dismal, and retransplantation is the sole option for long-term survival. To address the interest of haploidentical transplantation as a salvage option in this context, we analyzed data from 24 patients with graft failure or loss retransplanted with a haploidentical donor who received post-transplant cyclophosphamide (PTCy) as graft-versus-host disease prophylaxis (GVHD). Fludarabine-based reduced-intensity conditioning was used in 23 patients and the Baltimore regimen in 14 patients. The median delay between previous and salvage transplantation for graft failure was 63 days (range, 39 to 98). In addition to PTCy, all patients received cyclosporine, and 22 patients also received mycophenolate mofetil for GVHD prophylaxis. With a median follow-up of 353 days (range, 16 to 2010), 1-year overall survival (OS) was 56% (95% confidence interval, 38% to 81%). Transplant complications accounted for 80% of deaths. The cumulative incidence of neutrophil engraftment at day +30 was 79%. Cumulative incidence of grades II to IV acute GVHD at day 100 was 14%, and 1-year cumulative incidence of chronic GVHD was 31%. One-year cumulative incidence of relapse was 13%. Stem cell source did not impact on engraftment, GVHD, relapse, or OS. Salvage haploidentical transplant with PTCy for rescuing graft failure patients leads to an acceptable 1-year OS and might be a valid option in this poor situation.

INTRODUCTION

Prognosis of patients with graft failure after hematopoietic stem cell transplantation (HSCT) is dismal, and retransplantation is the sole option for long-term survival [1]. Some classic risk factors for graft failure are well known, such as the disease status

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before transplantation, conditioning regimen, HLA disparity, T cell depletion, and low nucleated cell dose. Graft failure is more frequent in alternative donor transplantations, and its incidence ranges from 4% in matched unrelated donor and to 20% in cord blood transplantations [2]. More recently, donor-specific anti-HLA antibodies were described as a significant liability for graft failure in the setting of haploidentical transplantations, yet there are strategies to detect and treat such cases [3].

Currently, there is no consensus concerning therapeutic options in patients with graft failure, and finding a new donor within an acceptable delay may be challenging. Cord blood, unrelated donors, or haploidentical transplantation are alternatives. However, the literature is scarce on the subject, and the long-term overall survival (OS) of retransplanted patients is estimated to be about 30% [4].

In the past years haploidentical transplantations with post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis have shown promising results in the treatment of many hematologic diseases, including some cases of graft failure [5,6]. Furthermore, most patients have a haploidentical donor that can be promptly identified and harvested. Our group retransplanted a patient who experienced 2 consecutive graft failures and successfully managed her through a third HSCT with PTCy from her haploidentical son [7]. Therefore, we asked what are the outcomes of haploidentical transplantation using PTCy as GVHD prophylaxis for rescuing graft failure patients.

METHODS

To address the interest of haploidentical transplants as a salvage option in this context, we retrospectively collected and analyzed data from the Francophone Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) database. The definitions used for data entry are described elsewhere [8].

First, we included patients with a primary graft failure, defined as non-achievement of a minimum absolute neutrophil count of 500/μL, with no evidence of disease relapse at day +28 after transplantation, or a graft loss, defined as persistent neutropenia or donor chimerism < 5% after neutrophil engraftment with no evidence of disease relapse. Second, we looked for patients treated with an allogeneic HSCT using an HLA-mismatched related donor. Third, we limited the analyses to patients who received PTCy 50 mg/kg at days +3 and +4 as GVHD prophylaxis.

We present continuous variables as medians and range and used the Wilcoxon rank sum to perform comparisons between groups. We present categorical variables as counts and percentages and used the Fisher exact test for comparison.

We used the definitions given in the European Society for Blood and Marrow Transplantation (EBMT) Statistical Guidelines for determining cumulative incidences and survival [9]. OS was estimated using the Kaplan-Meier method and plotted with its 95% confidence interval (95% CI). Cumulative incidences were obtained using Gray's estimator. Death without engraftment was considered as a competing risk for engraftment and acute GVHD. We defined GVHD relapse-free survival as the absence of grades III to IV acute GVHD, severe chronic GVHD, disease relapse, or death from any cause after HSCT [10].

All tests were 2-sided, and $P < .05$ was considered to be significant. We used the R statistical platform (The R Foundation for Statistical Computing, Vienna, Austria, version 3.4.1) to perform the analyses. The SFGM-TC scientific council approved this study.

RESULTS

Cohort Description

We identified 26 patients who met the inclusion criteria, transplanted between 2011 and 2017. Two patients were excluded from the analyses because of insufficient essential follow-up data. During the same period, among 15,236 allogeneic transplantations performed within the SFGM-TC centers, the frequency of graft failure/loss frequency was 3%.

Transplant series characteristics are presented in Table 1. The male-to-female ratio was 2:1. Twenty patients were initially transplanted because of hematologic malignancies and 4 for nonmalignant disorders. Only 1 patient received a myeloablative conditioning regimen at previous transplantation. One-half of patients received a cord blood graft, whereas peripheral blood was the stem cell source for one-third; 4 patients received a bone marrow graft. Eighteen patients presented a primary graft failure and 6 patients experienced a graft loss after previous engraftment without any signs of relapse. The median interval between previous and salvage transplantations was 63 days (range, 39 to 98) for graft failure and 97 days (range, 39 to 271) for the entire cohort.

Among the haploidentical salvage transplants, the conditioning regimen described by the Baltimore group accounted for 58% of transplantations (n = 14) [11]. Thirteen patients (54%) received a peripheral blood stem cell graft, and the same donor was used in 4 patients at the physician's discretion. As GVHD prophylaxis, all patients received PTCy and cyclosporine, and 22 patients also received mycophenolate mofetil. Median follow-up was 353 days (range, 16 to 2010). Donor and recipient characteristics are presented in Table 2.

Engraftment and Relapse

The cumulative incidence of neutrophil engraftment at day +30 was 79% (Figure 1), and the median time to neutrophil engraftment was 18 days (range, 13 to 34). Four patients (17%) presented another graft failure and died within a median time of 5 weeks [3–8] after salvage transplantation. Of those who engrafted, 17 patients (77%) achieved full donor chimerism (information not available for 4 patients).

The cumulative incidence of platelet engraftment 20,000/μL was 59% at day +50, and the median time to platelet engraftment was 29 days (range, 20 to 49). The cumulative incidence of relapse was 13% at 1 year.

Graft-versus-Host Disease

Cumulative incidence of grades II to IV acute GVHD at day 100 was 14% (Figure 2). One patient presented grade III and another 1 grade IV acute GVHD. Cumulative incidence of chronic GVHD at 1 year was 31%.

Survival and Mortality

The OS is shown in Figure 3. OS and GVHD relapse-free survival were 56% (95% CI, 38 to 81) and 32.4% (95% CI, 9.7 to 58.4), respectively, at 1 year.

HSCT complications accounted for 80% of the causes of deaths (4 from multiorgan failure, 1 GVHD, 1 interstitial pneumonitis, 1 bacterial infection, 1 post-transplant lymphoproliferative disorder). Two patients died of disease relapse (acute myeloid leukemia/myelodysplastic syndrome).

Effect of Transplant Characteristics on Survival

Stem cell source, recipient and donor age, donor sex, disease (malignant versus nonmalignant), and interval between previous and salvage transplantation had no impact on engraftment, GVHD, relapse, mortality, GVHD relapse-free survival, or OS.

DISCUSSION

To the best of our knowledge, this is the largest cohort of patients describing the outcomes of haploidentical transplants with PTCy for rescuing patients with graft failure or loss. In the present study, we showed a 1-year OS of 56% (ie, arguably higher than previous reports); thus, haploidentical transplantation with PTCy might be an acceptable alternative to handle this poor situation.

One important limitation of this study is sample size. A limited number of patients at risk is responsible for the wide 95%

Table 1
Transplant Series Characteristics

Id	Sex	Diagnosis	Age dx (y)	Previous transplantation					Haploidentical transplantation						
				Conditioning	Donor	Source	GvHD prophylaxis	Outcome	# this transplant	Interval (d)	Conditioning	Same donor	Source	GvHD prophylaxis	Engraftment
1	M	PID	0,1	FB2THIO+ATG	Haplo	PB	CsA	failure	2	39	FluCy+ATG	Yes	BM	Cy+CsA+MMF	Yes
2	F	MPN	48,0	FluMel	MRD	BM	CsA+MMF	failure	2	63	FluCyTBI	No	BM	Cy+CsA+MMF	Yes
3	M	AML	59,7	Flamsa+ATG	mMUD	PB	CsA+MMF	failure	2	62	FluCyTBI	No	BM	Cy+CsA+Flu	Yes
4	M	AML	48,3	FB2+ATG	mMUD	PB	CsA+MMF	failure	2	86	FluCyTBI	No	BM	Cy+CsA+MMF	Yes
5	F	AML	57,4	CyFB2	Haplo	PB	Cy+CsA+MMF	failure	3	55	FluTBI	Yes	PB	Cy+CsA+MMF	No
6	M	MDS	44,2	FB2THIO	Haplo	PB	Cy+CsA+MMF	failure	2	78	FluCyTBI+ATG	Yes	PB	Cy+CsA+MMF	Yes
7	M	AML	32,3	FB3THIO+ATG	UCB	CB	CsA+MMF	failure	2	67	FluCyTBI	No	BM	Cy+CsA+MMF	Yes
8	F	ALL	57,7	FB2+ATG	MUD	BM	CsA+MMF	failure	2	59	FluCyTBI	No	BM	Cy+CsA+MMF	Yes
9	M	MPN	22,1	FB3THIO	Haplo	BM	Cy+CsA+MMF	loss	2	124	FluCyTBI	No	BM	Cy+CsA+MMF	No
10	M	MDS	55,4	FB2+ATG	MUD	PB	CsA+MMF	loss	2	147	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
11	F	MDS	49,0	FluCyTBI	UCB	dCB	CsA+MMF	failure	3	59	FB2THIO+ATG	No	PB	Cy+CsA+MMF	Yes
12	F	NHL	35,3	FluCyTBI	UCB	dCB	CsA+MMF	loss	2	164	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
13	M	MDS/MPN	59,7	FB3+ATG	MUD	PB	CsA+MTX	loss	2	211	FluCyTBI	No	BM	Cy+CsA+MMF	Yes
14	M	AML	54,1	FluCyTBI	UCB	CB	CsA+MMF	failure	2	63	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
15	M	AML	21,3	FluCyTBI	UCB	CB	CsA+MMF	loss	2	271	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
16	M	AML	54,8	FB2+ATG	MRD	PB	CsA+MMF	loss	2	211	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
17	M	CML	30,2	FluCyTBI	UCB	dCB	Tacro+MMF	failure	2	59	FB2THIO	No	PB	Cy+CsA+MMF	No
18	M	ALL	41,9	FluCyTBI	UCB	CB	CsA+MMF	failure	2	65	FB2	No	PB	Cy+CsA	Yes
19	M	CML	39,9	BUCy	UCB	dCB	CsA+MTX	failure	2	63	FluTBI	No	BM	Cy+CsA+MMF	No
20	F	AML	48,3	CyFB2VP16THIO+ATG	UCB	CB	CsA+MMF	failure	2	56	FluTBI	No	PB	Cy+CsA+MMF	Yes
21	M	SAA	4,8	FluCyTBI+ATG	UCB	CB	CsA	failure	2	77	FluCyTBI	No	PB	Cy+CsA+MMF	Yes
22	F	IBMF	0,1	FluCyTBI+ATG	UCB	CB	CsA+steroids	failure	2	65	FluTBI+ATG	No	BM	Cy+CsA+MMF	Yes
23	M	MPN	57,8	FluCyTBI	Haplo	BM	Cy+CsA+MMF	failure	2	81	Clofarabine TBI	Yes	PB	Cy+CsA+MMF	Yes
24	F	SAA	1,7	FluCyTBI+ATG	UCB	CB	CsA	failure	2	98	FluCyTBI	No	BM	Cy+CsA+MMF	Yes

Transplant series summarizing features of the previous transplant complicated with graft failure or loss and the salvage haploidentical transplantation. Age is presented in years and the interval between transplantation is shown in days. PID indicates primary immunodeficiency; MPN, myeloproliferative neoplasm; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; CML, chronic myelogenous leukemia; SAA, severe aplastic anemia; IBMF, inherited bone marrow failure syndrome; ATG, antithymocyte globulin; FB, fludarabine and busulfan; THIO, thiotepa; FluCy, fludarabine and cyclophosphamide; TBI, total body irradiation; BUCy, busulfan and cyclophosphamide; MRD, matched related donor; MUD, matched unrelated donor; mMUD, mismatched unrelated donor; UCB, unrelated cord blood; PB, peripheral blood; BM, bone marrow; CB, cord blood; dCB, double cord blood; CsA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate.

Table 2
Donor and Recipient Characteristics

Median donor age (range)	35.4	(23.9 - 63.8)
Median recipient age (range)	47	(2.1 - 63.7)
Female donor	12	50%
ABO matching		
Match	11	46%
Major	5	21%
Minor	7	29%
Missing	1	4%
Median number of $CD34^{+}x10^{6}$/kg (range)		
PB	6	(3.5 - 8.1)
BM	2.5	(1.8 - 6.9)
CMV matching		
R+/D+	7	29%
R+/D-	5	21%
R-/D+	5	21%
R-/D-	6	25%
Missing	1	4%

CMV indicates cytomegalovirus; R, recipient; D, donor.

CI shown on OS and GVHD relapse-free survival. In addition, sample size might also have influenced the analyses on the effect of transplant characteristics on survival. Other limitations are a relatively short follow-up, its retrospective nature, and the heterogeneity of conditioning regimens. In addition, we were not able to retrieve information concerning donor-specific antibodies for most patients, precluding any conclusions regarding its influence in nonengraftment. For this study, we did not evaluate other transplant strategies among SFGM-TC centers for rescuing graft failure or loss. One potential bias for these results is that half of our cohort had failed 1 previous cord blood transplant, and this does not represent the real distribution of transplants in current practice. The day +100

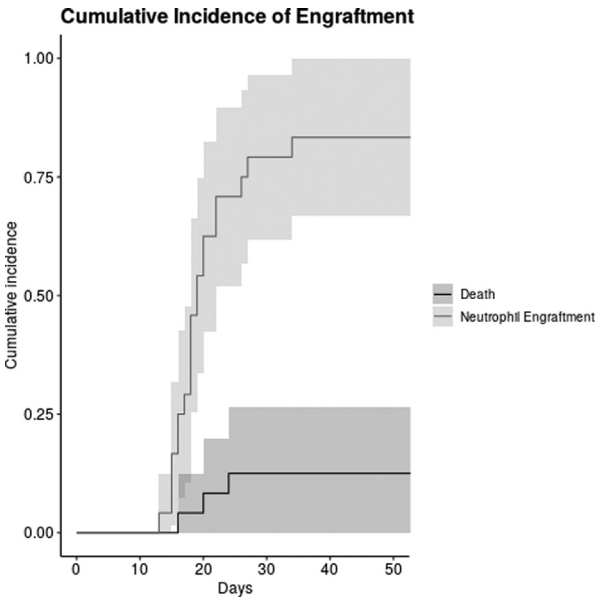

Figure 1. The gray line represents the cumulative incidence of neutrophil engraftment. The black line represent death as a competing event. The shaded areas show the 95% CI.

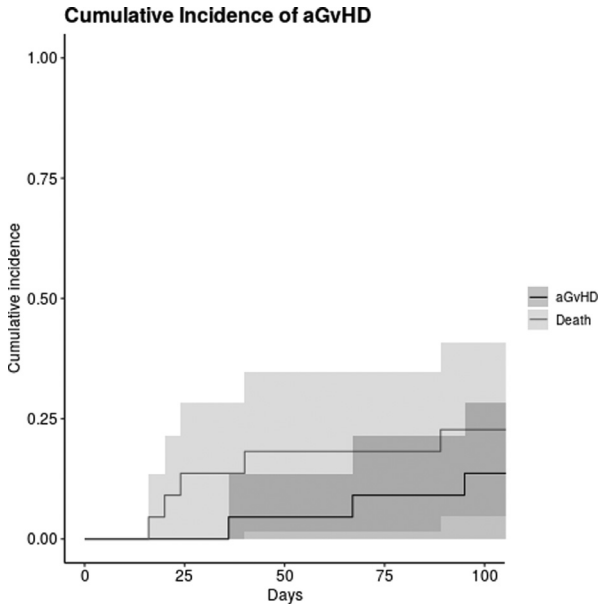

Figure 2. The black line represents the cumulative incidence of acute GVHD grades II to IV. The gray line represent death as a competing event. The shaded areas represent the 95% CI.

cumulative incidence of grades II to IV acute GVHD and chronic GVHD in our study was comparable with current knowledge for patients undergoing haploidentical hematopoietic cell transplantation [12].

Retransplantation with an alternative donor is a possible option for treating these cases, but outcomes demonstrate this is still an unmet need. A study conducted by the Center for International Blood and Marrow Transplant Research reporting the outcomes of a second transplant with unrelated donors for patients with graft failure found day +28 engraftment of 66% and a 1-year OS of 11% [13]. A Spanish retrospective cohort with different strategies of salvage transplants for graft failure found a 5-year OS of 31% [4]. Bojic et al. [14] reported 7 patients transplanted with umbilical cord blood for primary graft failure, all achieving full donor engraftment, but 4 patients were alive after 29 months. Tang et al. [15] reported 17 cord blood graft failure patients who were treated with unmanipulated haploidentical transplant showing a 1-year OS of 64.7%. However, the median age of this cohort was 11 years, whereas in ours it was 47 years.

Finding a new donor in this desperate situation may be challenging. In 2017 in France, the median time elapsed between searching the unrelated registry and harvesting was at least 98 days (range, 12 to 1203) for acute myeloid leukemia and at most 167 days (range, 54 to 348) for Hodgkin lymphoma [16]. This delay was longer than the 63 days we found in this cohort previously to salvage transplantation for graft failure, and the faster the hematologic recovery, the lower the probability of complications. Also, ethnicity is a concern because the availability of matched unrelated donors ranges from about 19% for African Americans to near 80% for European whites [17].

These first encouraging results presented here suggest it is safe to use haploidentical transplantation with PTCy for rescuing graft failure patients. We plan to conduct a prospective phase II study to confirm the safety and efficacy of this strategy.

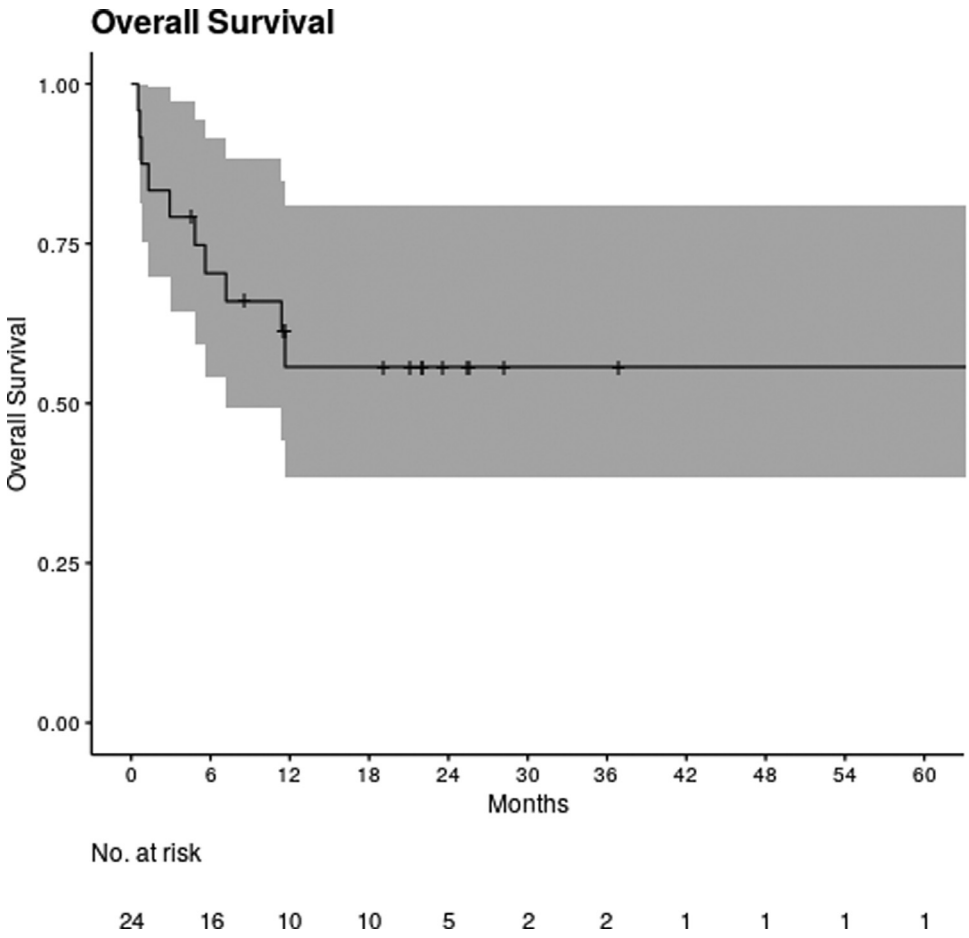

Figure 3. Kaplan-Meier analysis representing the probability of survival for patients with graft failure/loss rescued with a haploidentical transplantation with PTCy. The black line shows the OS; the shaded area shows the 95% CI.

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