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Effect of Cryopreservation in Unrelated Bone Marrow and Peripheral Blood Stem Cell Transplantation in the Era of the COVID-19 Pandemic: An Update from the Japan Marrow Donor Program

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A B S T R A C T

During the COVID-19 pandemic, donor grafts are frequently cryopreserved to ensure that a graft is available before starting a conditioning regimen. However, there have been conflicting reports on the effect of cryopreservation on transplantation outcomes. Also, the impact of cryopreservation may differ in bone marrow (BM) transplantation (BMT) and peripheral blood stem cell (PBSC) transplantation (PBSCT). In this retrospective study, we analyzed the clinical data of both cryopreserved unrelated BMTs (n = 235) and PBSCTs (n = 118) and compared these with data from a large control cohort without cryopreservation including 4133 BMTs and 720 PBSCTs. Among the patients with cryopreserved grafts, 10 BMT recipients (4.3%) and 3 PBSCT recipients (2.5%) did not achieve neutrophil engraftment after transplantation, including 4 of the former and all 3 of the latter who died early before engraftment. In a multivariate analysis, cryopreservation was not associated with neutrophil engraftment in BMT but significantly delayed neutrophil engraftment in PBSCT (hazard ratio [HR], .82; 95% confidence interval [CI], .69 to .97; $P = .023$). There was an interaction with borderline significance between cryopreservation and the stem cell source ($P = .067$). Platelet engraftment was delayed by cryopreservation after both BMT and PBSCT. Only 2 cryopreserved grafts (<1%) were unused during the study period. The cryopreservation of unrelated donor BM and PBSC grafts is associated with a slight delay in neutrophil and platelet engraftment but an acceptable rate of graft failure. PBSC grafts may be more sensitive to cryopreservation than BM grafts. Cryopreservation

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is a reasonable option during COVID-19 pandemic, provided that the apheresis and transplantation centers are adept at cryopreservation.

INTRODUCTION

During the COVID-19 pandemic, the Japan Marrow Donor Program (JMDP) is allowing the cryopreservation of donor grafts as an exception to ensure that grafts are available before starting a conditioning regimen. Similarly, the National Marrow Donor Program (NMDP) is temporarily requiring that transplantation centers plan cryopreservation of unrelated and related donor products facilitated by the NMDP [1]. Although previous studies have shown that the cryopreservation of allogeneic donor grafts is both safe and effective [2–6], others have raised concerns regarding the deleterious effects of the cryopreservation of donor cells [7–9].

We previously reported that the cryopreservation of unrelated bone marrow (BM) grafts did not affect neutrophil engraftment irrespective of the time from stem cell harvest to cryopreservation [10]. However, the safety of cryopreservation of unrelated peripheral blood stem cell (PBSC) grafts was not analyzed in detail, owing to the small number of patients. Since then, we have accumulated 3 times more clinical data on the cryopreservation of both unrelated BM and PBSC grafts and reanalyzed the results of neutrophil and platelet engraftment, including a comparison with the data in a large control cohort without cryopreservation.

METHODS

Patients

The policy for the cryopreservation of unrelated donor graft has been described previously. In brief, the JMDP Central Office reviewed all requests for cryopreservation of stem cells. After approval, stem cells were harvested and shipped from harvest centers to transplantation centers and then cryopreserved at the transplantation centers. Clinical data on unrelated cryopreserved BMTs and PBSCTs performed between April 2020 and October 2021 were collected by questionnaires sent to the transplantation centers. Control data from a cohort of recipients of noncryopreserved BMTs and PBSCTs performed between January 2016 and December 2018 were provided by the Japanese Data Center for Hematopoietic Cell Transplantation. This study was approved by the Ethics Committee of the JMDP.

Statistical Analysis

The primary endpoint was neutrophil engraftment, defined as the first of 3 consecutive days with an absolute neutrophil count of at least $.5 \times 10^3/\mu L$, and the secondary endpoint was platelet engraftment, defined as the first day with a platelet count $>20 \times 10^3/\mu L$ without platelet transfusion for at least 7 days. Fisher's exact test was used to compare categorical variables, and the Mann-Whitney *U* test was used to compare continuous variables. Time to engraftment data were analyzed while treating death without engraftment as a competing risk and then compared between the groups using Gray's test. Multivariate analysis was performed using Fine-Gray proportional hazards modeling based on an available case analysis for missing data. Information on the use of granulocyte colony-stimulating factor (G-CSF) was not obtained, and thus background diseases were grouped into myeloid malignancies and others; this was also included as an independent variable as a substitute for the use of G-CSF, because G-CSF was not used for myeloid malignancies in some centers.

All *P* values were 2-sided, and a *P* value $<.05$ was considered to indicate statistical significance. All statistical analyses were performed with EZR version 1.55 (Jichi Medical University Saitama Medical Center, Saitama, Japan) [11].

RESULTS

Patients and Stem Cell Grafts

During the study period, 242 of 1342 (18.0%) unrelated BMTs and 118 of 435 (27.1%) of unrelated PBSCTs facilitated by the JMDP were performed using cryopreserved grafts. Two other BM grafts were cryopreserved but not infused owing to patient death and a freezer problem. Questionnaires were sent to transplantation centers regarding the total 360 unrelated transplantations, and clinical data for 235 recipients of cryopreserved BM grafts and 118 recipients of cryopreserved PBSC grafts were collected. The median age of the BMT recipients was 50.0 years (interquartile range [IQR], 36.0 to 61.0 years), and that of PBSCT recipients was 53.0 years (IQR, 42.25 to 61.75 years) (Table 1). There was an HLA mismatch in approximately 40% of the transplantations.

In the noncryopreservation cohort, 4133 patients received BM grafts and 720 received PBSC grafts, excluding 7 patients without engraftment data. The median age of

Table 1
Patient Characteristics

Characteristic		BMT	PBSCT
No. of patients		235	118
Age, yr, median (IQR)		50.0 (36.0-61.0)	53.0 (42.25-61.75)
Disease, n (%)	ALL	38 (16.2)	20 (16.9)
	AML	75 (31.9)	48 (40.7)
	ATL	10 (4.3)	3 (2.5)
	CML	6 (2.6)	6 (5.1)
	MDS	58 (24.7)	25 (21.2)
	ML-CLL-MM	17 (7.2)	10 (8.5)
	MPN	10 (4.3)	4 (3.4)
	No malignancy	21 (8.9)	2 (1.7)
Disease status, n (%)	CR	120 (51.1)	71 (60.2)
	NR	115 (48.9)	47 (39.8)
Myeloid malignancies, n (%)	Myeloid	149 (63.4)	83 (70.3)
	Others	86 (36.6)	35 (29.7)
HLA mismatch, n (%)	No	131 (55.7)	72 (61.0)
	Yes	104 (44.3)	46 (39.0)

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATL, adult T cell leukemia/lymphoma; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; ML-CLL-MM, malignant lymphoma, chronic lymphocytic leukemia, multiple myeloma; MPN, myeloproliferative neoplasms; CR, complete remission; NR, not in remission.

the patients who underwent BMT was 50.0 years (IQR, 34.0 to 60.0 years) and that of PBSCT recipients was 53.0 years (IQR, 42.0 to 61.0 years).

Outcomes of Cryopreserved Graft Recipients

Ten (4.3%) BMT recipients and 3 (2.5%) PBSCT recipients did not achieve neutrophil engraftment. Of these, 4 of the former and 3 of the latter died early before engraftment. The cause of death was infection in 4 patients and progression of underlying malignancy, diffuse alveolar hemorrhage, and multiorgan failure after early rescue transplantation on day 16 in 1 patient each. The other 6 patients who did not achieve neutrophil engraftment were considered to have graft failure, and none were in remission before transplantation. In 4 of these patients, graft failure was attributed to persistent hematologic malignancy. One patient showed hematologic recovery, but chimerism analysis revealed autologous hematopoiesis. The cause of graft failure in the remaining patient was considered to be hemophagocytic lymphohistiocytosis.

The median time to neutrophil engraftment was 18 days (95% confidence interval [CI], 17 to 19 days) after cryopreserved BMT and 16 days (95% CI, 15 to 17 days) after cryopreserved PBSCT. The incidence of neutrophil engraftment at day +28 in the 2 groups was 93.6% and 94.9%, respectively. The median days to platelet engraftment was 34 days (95% CI, 32 to 35 days) after cryopreserved BMT and 26 days (95% CI, 23 to 28 days) after cryopreserved PBSCT. The incidence of platelet engraftment at day +28 was 32.3% and 61.9%, respectively.

Data on the time between graft harvest and graft freezing were available in patients who received cryopreserved grafts. We grouped patients into the longest one-third, shortest one-third, and remaining patients. After cryopreserved BMT, neutrophil engraftment was slightly delayed in the shortest group (median of 19, 18, and 18 days, respectively, in the 3 groups), but the median time to platelet engraftment was equivalent among the 3 groups (32, 33, and 32 days). After cryopreserved PBSCT, the times to neutrophil and platelet engraftment were not different among the 3 groups (median of 15, 15, and 16 days for neutrophil engraftment and 30, 30, and 28 days for platelet engraftment).

Comparison of Cryopreserved and Noncryopreserved Grafts

Characteristics of the patients who received cryopreserved and noncryopreserved grafts are summarized in Table 2. There were significant between-group differences in background diseases and disease status. The numbers of harvested nuclear cells and $CD34^+$ cells did not differ between BM and PBSC grafts. Univariate analysis showed no difference in neutrophil engraftment between recipients of cryopreserved grafts and recipients of noncryopreserved grafts in both BMT and PBSCT, although there was a slight tendency toward delayed engraftment in the cryopreservation group in PBSCT recipients (Figure 1A,B). After adjustment for age, myeloid disease, disease status, and HLA mismatch by a multivariate analysis, cryopreservation was not associated with neutrophil engraftment in BMT (hazard ratio [HR], .98; 95% CI .87 to 1.10; $P = .74$). However, cryopreservation significantly delayed neutrophil engraftment in PBSCT (HR, .82; 95% CI, .69 to .97; $P = .023$) (Table 3). There was an interaction with borderline significance between cryopreservation and the stem cell source (HR, .78; 95% CI, .60 to 1.02; $P = .067$).

Platelet engraftment was delayed by cryopreservation for both BMT and PBSCT (Figure 2A,B). This result was confirmed by multivariate analyses adjusted for age, myeloid disease, disease status, and HLA mismatch (HR, .75; 95% CI, .66 to .87; $P < .0001$ after BMT and HR, .74; 95% CI, .61 to .90; $P = .0029$

Table 2
Patient Characteristics Grouped According to the Use of Cryopreservation in BMT and PBSCT

Characteristic		Cryopreservation		*P* Value	SMD
		No	Yes		
BMT					
No. of patients		4140	235		
Age, yr, median (IQR)		50.0 (34.0-60.0)	50.0 (36.0-61.0)	.545	.047
Disease, n (%)	Leukemia	2289 (55.3)	119 (50.6)	.009	.226
	Lymphoma/myeloma	658 (15.9)	27 (11.5)		
	MDS/MPN	830 (20.0)	68 (28.9)		
	No malignancy	363 (8.8)	21 (8.9)		
Disease status, n (%)	CR	1647 (39.8)	120 (51.1)	.001	.228
	NR	2493 (60.2)	115 (48.9)		
Myeloid malignancies, n (%)	Others	1853 (44.8)	86 (36.6)	.015	.167
	Myeloid	2287 (55.2)	149 (63.4)		
HLA mismatch, n (%)	No	2233 (54.0)	131 (55.7)	.638	.034
	Yes	1900 (46.0)	104 (44.3)		
Harvested nuclear cells, $\times 10^{10}$, median (IQR)		13.9 (10.3-17.7)	13.9 (10.0-17.7)	.66	.017
PBSCT					
No. of patients		720	118		
Age, yr, median (IQR)		53.0 (42.0-61.0)	53.0 (42.3-61.8)	.867	.002
Disease, n (%)	Leukemia	426 (59.2)	74 (62.7)	.326	.164
	Lymphoma/myeloma	113 (15.7)	13 (11.0)		
	MDS/MPN	176 (24.4)	29 (24.6)		
	No malignancy	5 (.7)	2 (1.7)		
Disease status, n (%)	CR	274 (38.1)	71 (60.2)	<.001	.454
	NR	446 (61.9)	47 (39.8)		
Myeloid malignancies, n (%)	Others	235 (32.6)	35 (29.7)	.595	.064
	Myeloid	485 (67.4)	83 (70.3)		
HLA mismatch, n (%)	No	430 (59.9)	72 (61.0)	.84	.023
	Yes	288 (40.1)	46 (39.0)		
Harvested $CD34^+$ cells, $\times 10^8$, median (IQR)		2.4 (1.5-3.7)	2.7 (1.8-4.2)	.11	.17

SMD indicates standardized mean difference.

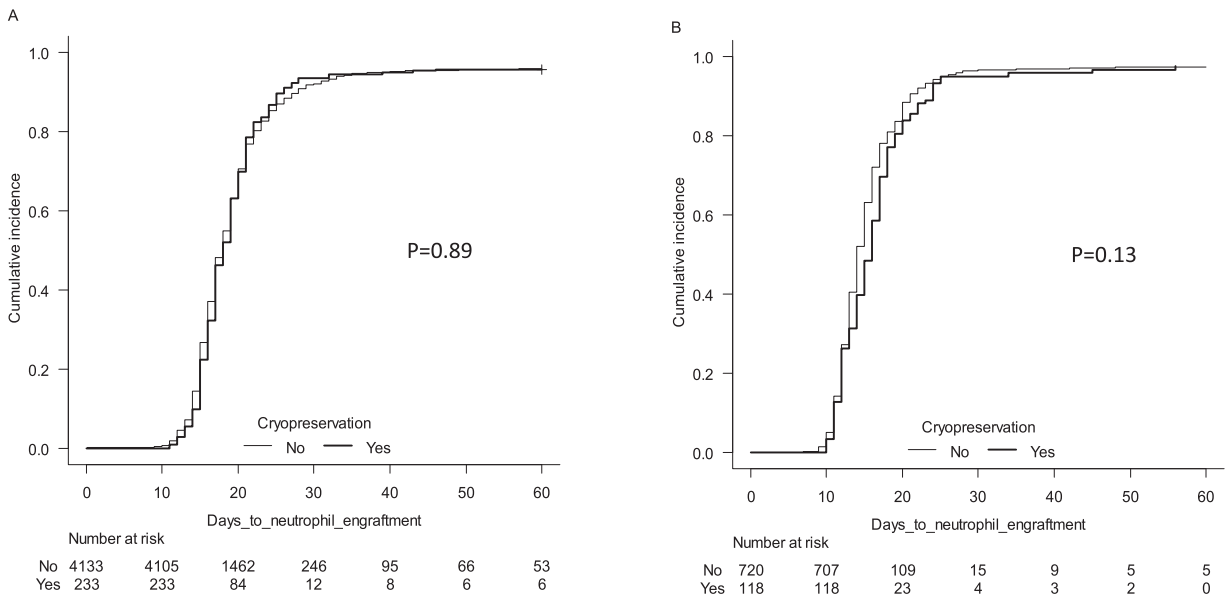

Figure 1. Time to neutrophil engraftment grouped according to the use of cryopreservation after BMT (A) and after PBSCT (B).

after PBSCT) (Table 3). There was no significant interaction between cryopreservation and the stem cell source (HR, .98; 95% CI, .74 to 1.30; $P = .90$).

DISCUSSION

The cryopreservation of BM and PBSC grafts ensures that they are available before the start of conditioning and has been used frequently during the COVID-19 pandemic. There has been some concern about stem cell damage from the procedure, but several studies have shown no significant delay in hematopoietic recovery after transplantation of cryopreserved stem cells [2–6]. On the other hand, a retrospective study showed delayed neutrophil and platelet engraftment with the use of cryopreserved PBSC grafts with no effect on overall survival [9]. Eapen et al. [7] reported that the use of cryopreserved grafts was associated with increased graft failure and 1-year mortality after transplantation for aplastic anemia, in which two-thirds of the cases involved BM grafts and one-third involved PBSC grafts. In addition, in a recent large-scale retrospective study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the use of cryopreserved graft significantly delayed neutrophil and platelet engraftment in PBSCT but not in BMT [8]. In unrelated PBSCT, overall survival was significantly inferior with cryopreserved grafts; however, more than one-half of the cases involving cryopreservation were due to the patient condition including changes in disease status, reaction to conditioning regimen, and infection. Multivariate analysis revealed significantly shorted survival in patients who received cryopreserved grafts because of their condition; thus, the reasons for cryopreservation are important when comparing cryopreserved and noncryopreserved grafts.

In the era of the COVID-19 pandemic, donor grafts are cryopreserved mainly to ensure their availability before the start of the conditioning regimen. Devine et al. [12] recently compared the outcomes of patients who underwent cryopreserved BMT or PBSCT between March and August 2020 with those of recipients of noncryopreserved BMT or PBSCT in 2019 using the CIBMTR database. Neutrophil and platelet engraftment were delayed after cryopreservation, but there were no significant differences in the incidence of graft failure and overall mortality.

In the current study, cryopreservation was performed exclusively to ensure graft availability. Similar to the recent CIBMTR study, the time to engraftment was longer after cryopreservation, but the effect on neutrophil engraftment was more prominent in PBSCT than in BMT, although the incidence of graft failure was not increased. In previous studies analyzing

Table 3
Multivariate Analyses for Neutrophil and Platelet Engraftment after Unrelated BMT and PBSCT

Factor	Neutrophil Engraftment		Platelet Engraftment	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
BMT				
Age	1.00 (1.00-1.00)	.27	1.00 (.99-1.00)	<.0001
Not in remission	.83 (.78-.88)	<.0001	.76 (.72-.82)	<.0001
Myeloid malignancies	.92 (.87-.98)	.0092	.98 (.91-1.04)	.48
HLA mismatch	.88 (.84-.93)	<.0001	.80 (.75-.86)	<.0001
Cryopreservation	.98 (.87-1.1)	.74	.75 (.66-.87)	<.0001
PBSCT				
Age	1.00 (.99-1.00)	.3	1.00 (.99-1.00)	.11
Not in remission	.90 (.79-1.02)	.11	.72 (.62-.83)	<.0001
Myeloid malignancies	1.01 (.87-1.16)	.92	1.07 (.92-1.24)	.4
HLA mismatch	1.02 (.9-1.16)	.75	.94 (.81-1.08)	.38
Cryopreservation	.82 (.69-.97)	.023	.74 (.61- .9)	.0029

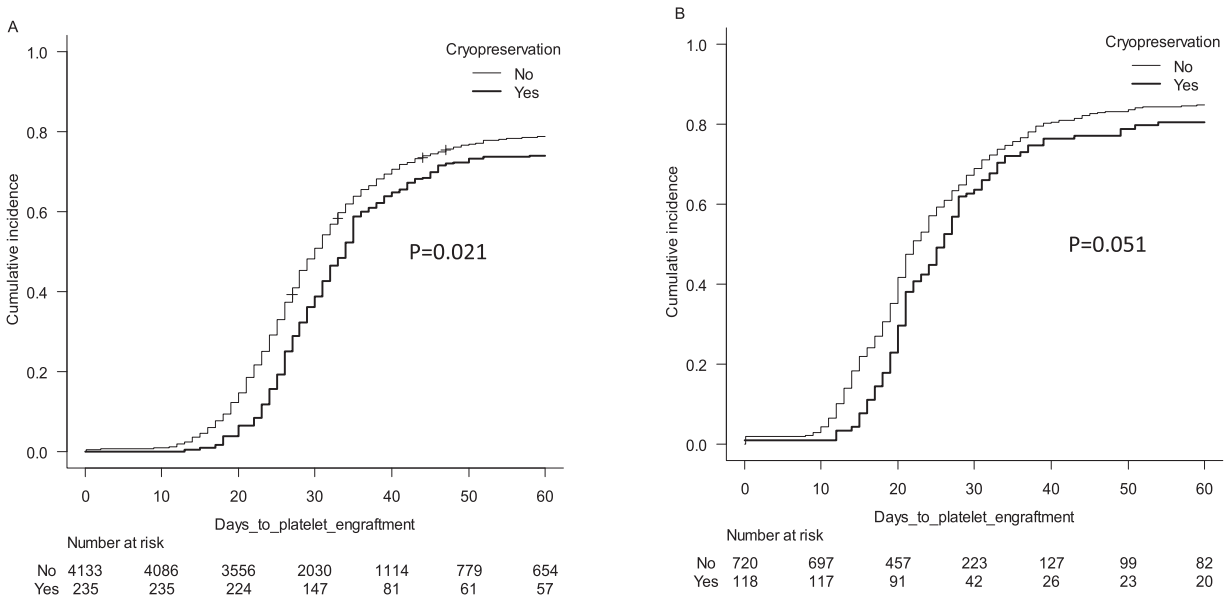

Figure 2. Time to platelet engraftment grouped according to the use of cryopreservation after BMT (A) and after PBSCT (B).

the impact of cryopreservation separately in BMT and PBSCT, a similar tendency toward a stronger effect in PBSCT has been observed (Table 4) [8,13]. Therefore, PBSC grafts may be more sensitive to cryopreservation than BM grafts.

Another concern has been that the cryopreservation of donor grafts may increase the number of unused grafts. The NMDP reported that 222 of 9294 products (2.4%) collected from March 17, 2020, through June 30, 2021, were not infused for a variety of reasons, including patient death, patient choice, poor product quality, clumps in the product, viability, a positive culture, and others [14]. However, the proportion of noninfused grafts decreased over time, likely because transplantation centers and apheresis centers became more adept at cryopreservation during the study period. In fact, in the earlier report during the COVID-19 pandemic, transplantation centers reported problems with 29% of the products, including damage during transit, low cell dose, inadequate labeling, missing representative samples, and missing documentation, which resulted in noninfused products in 22 of 191 (12%) collections [15]. On the other hand, only 2 cryopreserved grafts (<1%) were not infused in Japan during the study period. The policy of the JMDP to strictly restrict cryopreservation of donor grafts before the COVID-19 pandemic might have contributed to the high awareness in transplantation centers of the importance of limiting the number of unused grafts.

A major limitation of this study is the lack of clinical outcomes other than engraftment, such as the incidences of GVHD and nonrelapse mortality. In previous studies, the effect

Table 4
Summary of Studies Comparing Cryopreserved and Noncryopreserved Grafts with Regard to Clinical Outcomes [4-9,12,13,17-24]

Authors	Year	Source	Cryopreserved	Noncryopreserved	Neutrophil Engraftment	Platelet Engraftment	Acute GVHD	Chronic GVHD
Eckardt et al. [17]	1993	BM	10	33	No difference	No difference	Decreased	ND
Stockschläder et al. [4]	1997	BM	40	40	No difference	No difference	No difference	No difference
Kim et al. [5]	2007	PB	105	106	No difference	No difference	No difference	No difference
Lioznov et al. [13]	2008	PB	31	493	Increased graft failure	ND	ND	ND
Lioznov et al. [13]	2008	BM	8	14	No difference	ND	No difference	ND
Medd et al. [9]	2013	PB	76	123	Delayed	Delayed	No difference	Increased
Parody et al. [18]	2013	PB	224	107	Faster	No difference	Increased	No difference
Dagdas et al. [19]	2020	PB	30	42	Delayed	No difference	No difference	No difference
Eapen et al. [7],*	2020	BM or PB	52	194	Increased 1-yr graft failure	No difference	No difference	No difference
Alotaibi et al. [20]	2021	PB	310	648	No difference	No difference	No difference	Increased
Hamadani et al. [6]**	2020	BM or PB	274	1080	No difference	No difference	No difference	Decreased
Fernandez-Sojo et al. [21]	2021	PB	32	32	No difference	No difference	No difference	ND
Valentini et al. [22]	2021	PB	32	106	No difference	No difference	No difference	No difference
Maurer et al. [23]	2021	PB	101	203	No difference	Delayed	Increased	ND
Hsu et al. [8]	2021	Related PB	1051	3030	No difference	Delayed	Increased	ND
Hsu et al. [8]	2021	Unrelated PB	678	2028	Delayed	Delayed	No difference	ND
Hsu et al. [8]	2021	BM	154	456	No difference	Delayed	No difference	ND
Novitzky-Basso et al. [24]	2022	PB	135	348	Delayed	No difference	No difference	Decreased
Devine et al. [12]	2021ASH	BM or PB	959	2499	Delayed	Delayed	ND	ND
Current study	2022	PB	118	720	Delayed	Delayed	ND	ND
Current study	2022	BM	235	4133	No difference	Delayed	ND	ND

ND indicates not described.
* Transplantation only for aplastic anemia.†All used post-transplantation cyclophosphamide.

of cryopreservation on the incidences of acute and chronic GVHD has been inconsistent, but several recent studies of cryopreserved PBSCT have reported an increased incidence of acute GVHD compared with noncryopreserved PBSCT (Table 4). In addition, data on the viability of graft cells before and after cryopreservation were not available in this study. In this study, we observed a stronger effect of cryopreservation on PBSC grafts compared with BM grafts. A possible explanation for this difference might be the difference in time between graft collection and cryopreservation. When apheresis for 2 days was required to collect a sufficient number of $CD34^+$ cells, cells collected on the first day may be transferred together with those collected on the second day, leading to a longer time between collection and freezing for the graft collected on the first day. However, the time from collection to freezing was not associated with time to engraftment in the current cohort. The different effects of cryopreservation between BMT and PBSCT were observed only for neutrophil engraftment and not for platelet engraftment; therefore, the difference might be due to the sensitivity of the mobilized myeloid progenitor cells. Viability data for graft cells in each lineage before and after cryopreservation are needed to further clarify the difference in sensitivity between BM and PBSC grafts. Another limitation of this study is the lack of information on infectious events before neutrophil engraftment, which might have affected the time to neutrophil engraftment. However, previous studies including ours have shown an association between high-risk malignant disease and a higher incidence of bloodstream infection before engraftment [16], and in the current study, cryopreserved graft recipients were significantly more frequently in remission before transplantation. Thus, it is unlikely that an infectious event before engraftment was the major reason for the delayed engraftment after transplantation of cryopreserved grafts.

In conclusion, the cryopreservation of unrelated donor BM and PBSC grafts is associated with slight delays in neutrophil and platelet engraftment but with an acceptable rate of graft failure. Cryopreservation is a reasonable option in the era of the COVID-19 pandemic, provided that the apheresis and transplantation centers are adept at cryopreservation. Further analyses are warranted when the data on clinical outcomes, including the incidence of GVHD and nonrelapse mortality, become available.

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