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Presence of Promyelocytes in Peripheral Blood as a Novel Predictor of Optimal Timing for Single-Step Peripheral Blood Stem Cell Collection

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Background: Because peripheral blood stem cell (PBSC) collection places a burden on the patient and should ideally be completed in a single procedure, a convenient clinical predictive factor is needed.

Methods: This retrospective study included 72 patients who underwent autologous PBSC collection. A median volume of 3.9×10^6 CD34-positive cells/kg (range: $0.3\text{-}47.4 \times 10^6$ cells/kg) was collected on the first day. We defined failure as inability to collect 2.0×10^6 cells/kg on the first day. PBSC collection was classified as failed (n = 25, 34.7%) and successful (n = 47, 65.3%), and patient clinical characteristics were analyzed.

Results: The success group had significantly more cases in which a differential white blood cell count in peripheral blood on the day of PBSC collection detected promyelocytes (n = 34 [72.3%] vs. n = 11 [44.0%] in the failure group; $P = 0.008$). Sixty-two patients underwent autologous PBSC transplantation (median number of transplanted cells, $5.6 \times 10^6/\mu L$; range: $1.60\text{-}47.4 \times 10^6$ cells/μL). Among transplanted patients, the success and failure groups did not significantly differ in relation to the interval until neutrophil, platelet, or red blood cell engraftment.

Conclusion: The presence of promyelocytes in peripheral blood may be a useful indicator of the optimal timing for single-step PBSC collection. (J Nippon Med Sch 2021; 88: 45−53)

Key words: peripheral blood stem cell transplantation, malignant lymphoma, multiple myeloma, stem cell collection

Introduction

Autologous peripheral blood stem cells (PBSCs) are transplanted into patients who have received a maximum dose of anticancer agents, with the aims of amplifying the antitumor effect of treatment and relieving protracted myelosuppression. The efficacy of PBSC transplantation has been confirmed for malignancies such as multiple myeloma, recurrent malignant lymphoma, recurrent acute promyelocytic leukemia, and related diseases[1–3].

To prepare for transplantation, granulocyte colony-stimulating factor (G-CSF) is administered alone or in combination with chemotherapy to mobilize hematopoietic stem cells into the peripheral blood as PBSCs before collection via apheresis. A sufficient PBSC yield is essential, as the collected number correlates with early post-transplantation engraftment[4]. Generally, PBSC transplantation requires a minimum of 1.0×10^6 CD34-positive PBSCs/kg, although 2.0×10^6/kg is preferred.

Previous studies reported that 9.5% to 18.7% of patients are poor mobilizers and cannot produce sufficient PBSCs for collection[5,6]; thus, multiple harvesting procedures are often performed to ensure a sufficient yield. However, these expensive procedures impose a burden on patients, who must remain immobilized for 3–5 hours, as well as on nurses, clinical technicians, and medical resources. Therefore, collection would ideally be completed during a single procedure. Plerixafor was re-

cently approved and has made it possible to efficiently harvest PBSCs. However, it is an expensive drug, so there is a need for clinical considerations such as limiting its use in cases for which peripheral blood stem cell collection proves difficult.

The optimal timing of PBSC collection needs to be determined to ensure success. Currently, several centers use total number of CD34-positive cells in peripheral blood as an indicator of the total number of stem cells that could potentially be collected[7]. However, many centers lack in-house laboratories that can measure CD34-positive cells in peripheral blood. Consequently, a more convenient predictive factor is needed for use in clinical settings. This retrospective study analyzed patients with hematopoietic malignancies who underwent autologous PBSC collection at our hospital. We aimed to identify factors that predict optimal timing for collection of sufficient PBSCs in a single procedure.

Materials and Methods

Patient Selection

This retrospective study analyzed data from 72 patients with malignant lymphoma, multiple myeloma, or acute promyelocytic leukemia who underwent autologous PBSC collection at Nippon Medical School Hospital during the period from 2006 through 2016. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the appropriate institutional ethics committee (30-09-991).

Patients who underwent autologous PBSC transplantation during the treatment of solid tumors were excluded. G-CSF monotherapy or G-CSF subsequent to chemotherapy was used to prepare for autologous PBSC collection in all patients. PBSCs were collected when blood cells had begun to recover, as determined by the attending physician. Patients who received plerixafor for mobilization of hematopoietic stem cells were excluded.

White blood cell (WBC) count, differential WBC, platelet count, and lactate dehydrogenase (LDH) concentration in peripheral blood were determined on the day of collection. Subsequently, we assessed the presence of promyelocytes after technicians evaluated the ratio of these cells in peripheral blood. Three patients for whom a manual blood count could not be performed on the day of collection were excluded from testing for the presence of promyelocytes. The COM.TEC blood cell apheresis system (Fresenius Kabi, Bad Homburg, Germany) was used to collect autologous PBSCs from 10-L samples of peripheral blood (500 mL × 20 times). Patients with an initial CD34-positive cell yield of <2.0 × 10^6/kg on the first day were subjected to collection on the second day and, if necessary, the third day. All 62 patients from whom sufficient stem cells were collected underwent autologous transplantation.

Statistical Analysis

In this study, success was defined as a yield of at least 2.0×10^6 cells/kg during a single procedure; all other cases were defined as failure. Differences in clinical background characteristics between the success and failure groups were analyzed with the t-test and χ-square test. The correlation between number of promyelocytes and number of CD34 cells was analyzed by using Pearson correlation coefficients. Additionally, the 62 patients who underwent autologous transplantation were divided into success and failure groups, and the numbers of days required for neutrophil engraftment, platelet engraftment, and red blood cell (RBC) engraftment were analyzed with the log-rank test. The dates of neutrophil, platelet, and RBC engraftment were defined as the first of 3 successive days when the neutrophil level exceeded 500 /μL, when the platelet level exceeded 20,000 /μL without blood transfusion (or 50,000 /μL with blood transfusion), and when the hemoglobin concentration exceeded 8.0 g/dL without blood transfusion, respectively. The two-sided level of significance was set at a P value <0.05. All statistical analysis was performed with EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan)[8].

Results

Analysis of Background Factors

The median age of patients was 56 years (range: 17-70 years; 42 males, 30 females). Fifty-one patients had malignant lymphoma, while 15, 3, and 3 had multiple myeloma, acute promyelocytic leukemia, and other diseases, respectively. Fifteen patients with malignant lymphoma exhibited bone marrow involvement, and PBSCs collected from 1 patient were contaminated with malignant lymphoma cells. At the time of PBSC collection, the outcomes observed in the lymphoma group were complete response (CR), 27 cases; complete response/unconfirmed (CRu), 3; partial response (PR), 17; stable disease (SD), 2; and progressive disease (PD), 2. In the myeloma group, 2, 6, 5, and 2 cases achieved a CR, very good partial response (VGPR), PR, and SD, respectively. Before collection, patients in the lymphoma and myeloma groups had undergone a median of 9 (range: 2-21) and 4 (3-7) chemotherapy cycles, respectively.

Table 1　Patient characteristics

	Success group (n=47)	Failure group (n=25)
Age, median years (range)	56 (17-70)	57 (26-68)
Sex (Male/Female)	26/21	16/9
BSA, median L/min/m² (range)	1.62 (1.25-2.07)	1.64 (1.22-2.09)
Disease (%)		
DLBCL	17 (36.2)	12 (48.0)
FL	6 (12.8)	0 (0)
MCL	3 (6.4)	1 (4.0)
MALT lymphoma	0 (0)	2 (8.0)
BL	1 (2.1)	1 (4.0)
T cell lymphoma	3 (8.3)	2 (8.0)
HL	3 (6.4)	0 (0)
MM	12 (25.5)	3 (12.0)
Amyloidosis	2 (4.3)	1 (4.0)
APL	0 (0)	3 (12.0)
Chemotherapy cycle (range)	7 (2-18)	7 (3-21)
Mobilization regimen (%)		
ACES	12 (25.5)	8 (32.0)
VP-16	7 (14.9)	3 (12.0)
IVAM	8 (17.0)	2 (8.0)
Hyper CVAD-MA	3 (6.4)	1 (4.0)
ESHAP	3 (6.4)	0 (0)
LMD	0 (0)	1 (4.0)
DEVIC	0 (0)	1 (4.0)
CY+G-CSF	12 (25.5)	1 (4.0)
G-CSF	2 (4.3)	8 (32.0)
PBSC collected, median ×10⁶/kg (range)	7.63 (2.12-47.4)	1.4 (0.05-7.76)

Abbreviations: BSA, body surface area; DLBCL, diffuse large B-cell lymphoma; FL, Follicular lymphoma; MCL, Mantle cell lymphoma; HL, Hodgkin lymphoma; BL, Burkitt lymphoma; ML, malignant lymphoma; MM, multiple myeloma; APL, Acute promyelocytic leukemia; G-CSF, granulocyte-colony stimulating factor; PBSC, peripheral blood stem cell collection; ACES, cytarabine + carboplatin + etoposide + methylprednisolone; VP-16, etoposide; IVAM, ifosfamide + etoposide + cytarabine + methotrexate; ESHAP, etoposide + methylprednisolone + cytarabine + cisplatin; LMD, L-asparaginase + methotrexate + dexamethasone; DEVIC, dexamethasone + etoposide + ifosfamide; CY, cyclophosphamide.

The preparative regimens for PBSC collection differed somewhat between disease groups. In the lymphoma group, G-CSF was administered in combination with chemotherapy in 49 (96.1%) cases and alone in 2 cases (3.9%). In the multiple myeloma group, G-CSF was administered in combination with cyclophosphamide (CY) in 13 (72.2%) cases and alone in 5 cases (27.8%). All 3 patients in the acute promyelocytic leukemia group received G–CSF alone (100.0%; **Table 1**). The median values recorded on the day of PBSC collection were WBC count, $206 \times 10^2/\mu L$ (range: $96-753 \times 10^2/\mu L$); platelet count, $7 \times 10^3/\mu L$ ($1.6-39.0 \times 10^3/\mu L$); and LDH concentration, 400 IU/L (158-1,737 IU/L). Promyelocytes were observed in 45 (62.5%) cases.

Autologous PBSC transplantation was performed in 62 cases. A PBSC yield of $>2.0 \times 10^6/kg$ was collected in 58 cases, while yields of 1.0 to $<2.0 \times 10^6/kg$ were collected in 4 cases. The median duration until engraftment was 11 days for neutrophils (range: 8-23 days), 10 days for platelets (20,000 /μL; range: 0-56 days), 15 days for platelets (50,000 /μL; range: 0-153 days), and 9 days for RBCs (range: 0-35 days).

Clinical Characteristics of Patients from Whom $\geq 2.0 \times 10^6$ PBSCs/kg Were Successfully Collected in a Single Procedure

The median yield of CD34-positive cells collected on the first day was $3.9 \times 10^6/kg$ (range: $0.3-47.4 \times 10^6/kg$). However, PBSC collection in 25 (34.7%) patients was classified as failed, meaning that $\geq 2.0 \times 10^6$ cells/kg could not be collected on the first day. A comparison of the clinical characteristics of the 2 groups revealed that the success group had a significantly higher LDH level on

Table 2 Factors predicting optimal day for single-day collection of peripheral stem cells necessary for autologous peripheral stem cell transplant

	All (n=72)			Malignant lymphoma (n=51)			Multiple myeloma and amyloidosis (n=18)		
	Success group (n=47)	Failure group (n=25)	P value	Success group (n=34)	Failure group (n=17)	P value	Success group (n=14)	Failure group (n=4)	P value
Age, median ye+C13+B5: K16+B5: K16	56 (17-70)	57 (26-68)	0.263	53 (17-70)	59 (38-68)	0.081	58 (33-68)	55 (50-59)	0.310
Sex (Male/Female)	26/21	16/9	0.649	18/15	11/7	0.77	6/8	2/2	1.000
BSA, median L/min/m² (range)	1.62 (1.25-2.07)	1.64 (1.22-2.09)	0.645	1.62 (1.26-2.07)	1.56 (1.22-2.09)	0.762	1.68 (1.25-1.90)	1.64 (1.59-1.91)	0.505
WBC, median ×10²/μL (range)	259 (98-648)	195 (96-753)	0.462	205 (98-613)	168 (96-753)	0.169	247 (107-648)	354 (195-440)	0.574
Plt, median×10³/μL (range)	6.4 (1.6-37.5)	7.8 (2.4-39)	0.053	6.1 (1.6-15.4)	6.2 (2.4-39)	0.213	7.1 (2.5-37.5)	15.6 (7.5-31.1)	0.056
LDH, median IU/L (range)	400 (158-1,737)	331 (188-821)	0.045	406 (158-1,737)	300 (188-821)	0.054	310 (211-860)	341 (322-424)	0.645
Chemotherapy cycle (range)	7 (2-18)	7 (3-21)	0.603	9 (2-18)	9 (3-21)	0.551	5 (3-7)	4 (3-6)	0.139
BM involvement	22	12	1.000	8	7	0.341	14	3	0.222
Presence of promyelocytes (median: range%)	34 (1: 0-10.5)	11 (0: 0-2.5)	0.008	27 (1: 0-10.5)	7 (0: 0-2.5)	0.007	7 (0.5: 0-1.5)	1 (0: 0-0.5)	0.576
Mobilization regimen (CY+G-CSF)							12	1	0.044
Prior regimen including lenalidomide							0	3	0.007

Abbreviations: BSA, body surface area; WBC, white blood cell; Plt, Platelet; LDH, Lactate dehydrogenase; BM, Bone marrow; CY, cyclophosphamide; G-CSF, granulocyte-colony stimulating factor

*The other cases were three cases of APL.

Table 3   Associations of background factors with presence of promyelocytes in patients from whom 2.0×10^6/kg could be collected in a single collection (Success Group)

	Success group (n=47)		
	Promyelocyte positive (n=34)	Promyelocyte negative (n=10)	P value
Age, median years (range)	56 (17-70)	58 (25-66)	0.614
Sex (Male/Female)	19/15	4/6	0.117
BSA, median L/min/m^2 (range)	1.63 (1.26-2.07)	1.51 (1.25-1.87)	0.218
WBC, median ×10^2 /μL (range)	259 (98-613)	199 (107-648)	0.519
Plt, median × 10^3 /μL (range)	7.0 (1.6-15.4)	5.2 (3.5-37.5)	0.845
LDH, median IU/L (range)	449 (158-1,737)	293 (211-912)	0.170
Chemotherapy cycles (range)	7 (2-18)	6 (4-17)	0.662
BM involvement	13	7	0.147

Abbreviations: BSA, body surface area; WBC, white blood cell; Plt, Platelet; LDH, Lactate dehydrogenase; BM, Bone marrow; CY, cyclophosphamide; G-CSF, granulocyte-colony stimulating factor
*Three cases in which a manual blood count could not be performed on the day of collection were excluded from testing for the presence of promyelocytes.

the day of collection (median: 400 IU/L vs. failure group, 331 IU/L, P = 0.045) and a significantly greater number of cases in which promyelocytes were observed in the differential WBC count on the day of PBSC collection [34 (72.3%) vs. failure group, 11 (44.0%), P = 0.008; **Table 2**]. No correlation was observed between total number of promyelocytes and the number of CD34 cells (r=0.245).

Subgroup analyses of patients with malignant lymphoma or multiple myeloma revealed that in the former subgroup, the success group included significantly more cases in which promyelocytes were observed in a differential WBC count on the day of PBSC collection [27 (79.4%) vs. 7 (52.9%) in the failure group, P = 0.007]. In the multiple myeloma subgroup, the success group included significantly more cases that were treated concomitantly with CY+G-CSF [12 (85.7%) vs. 1 (25.0%) in the failure group, P = 0.044] and significantly fewer cases treated with regimens involving lenalidomide [0 (0.00%) vs. 3 (75.0%) in the failure group, P = 0.007; **Table 2**]. Additionally, no background factor significantly differed in relation to promyelocytes in the success group (**Table 3**).

Autologous PBSC transplantation was performed for all 62 cases in which sufficient cells were collected for a feasible procedure. A median of 5.6×10^6 CD34-positive cells/μL (range: 1.60-47.4 $\times 10^6$/kg) were administered during autologous PBSC transplantation. These cases were also classified as successful and failed. However, the numbers of days until neutrophil, platelet, and RBC engraftment did not significantly differ between the groups (**Fig. 1**). Blood cell engraftment was analyzed in groups with and without promyelocytes, but there was no significant difference in the interval to neutrophil en-

graftment, platelet engraftment, or RBC engraftment (**Fig. 2**).

Discussion

This study aimed to identify factors that would predict the optimal timing for collection of a sufficient number of autologous PBSC during a single procedure. To this end, we compared patient clinical characteristics between the success and failure groups and determined that the presence of promyelocytes in a differential WBC count of peripheral blood was associated with a significantly greater likelihood that successful PBSC collection would be achieved in a single procedure.

Previous studies of potential predictors of successful PBSC collection have yielded conflicting results. One study of PBSC collection in healthy adults reported more successful collection from young men with a high body mass index (BMI) and high body weight[9]; however, another study reported no associations of BMI, sex, or body weight with number of collected stem cells[10]. In previous studies of lymphoma and myeloma patients, the number of peripheral blood CD34-positive cells obtained on the first day of collection was identified as a useful predictor of the number of autologous PBSCs that could be collected[11]. In lymphoma patients, significantly higher numbers of collected cells were recorded in patients with high platelet counts, a shorter duration from the start of G-CSF administration to the day of PBSC collection, and higher proportions of lymphocytes and monocytes on the first day of collection. In myeloma patients, younger age, a high platelet count before collection, and fewer previous PBSC collection procedures were associated with the
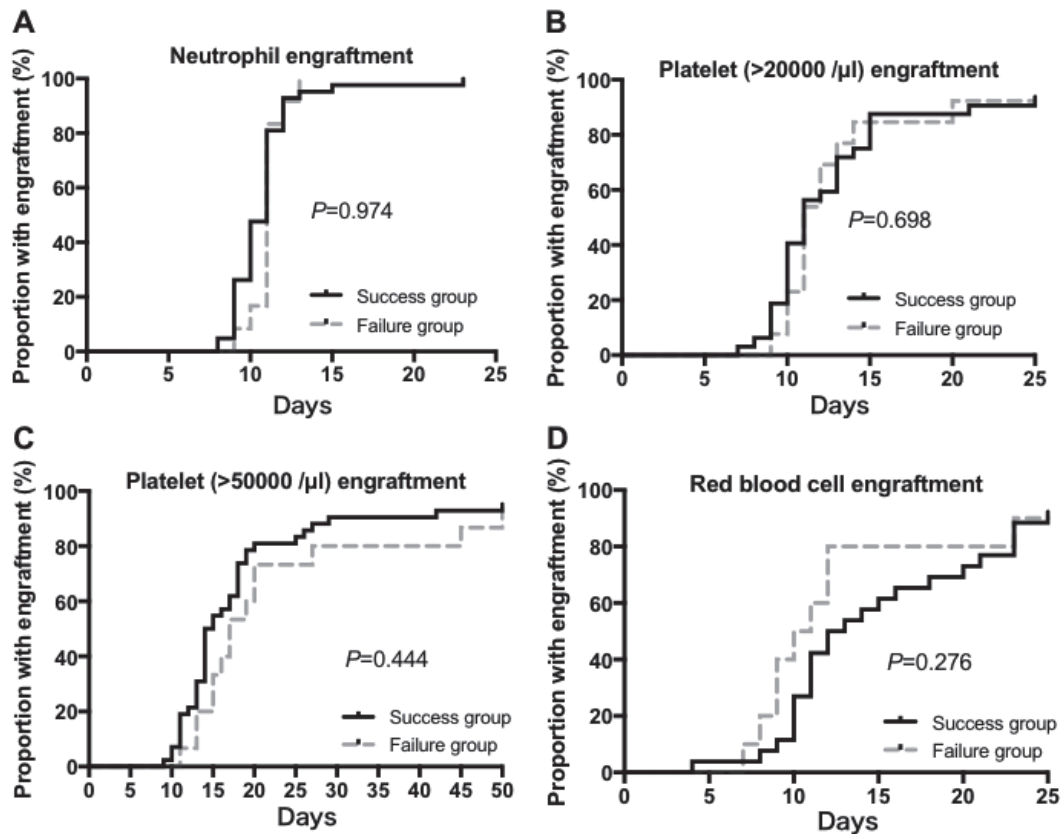
Fig. 1 Comparison of numbers of days until engraftment of various blood cell types in patients who underwent successful peripheral blood stem cell collection—defined as 2.0×10^6 cells/kg in a single procedure (success group) —and those that did not (failure group).
A: Comparison of neutrophil engraftment. Solid line: success group (median = 11 days, range: 8–23 days); dotted line: failure group (median = 11 days, range: 8–12 days).
B: First comparison of platelet engraftment. Solid line: success group (median = 10 days, range: 0–56 days); dotted line: failure group (median = 11 days, range: 0–38 days).
C: Second comparison of platelet engraftment. Solid line: success group (median = 14 days, range: 0–153 days); dotted line: failure group (median = 17 days, range: 0–90 days).
D: Comparison of red blood cell engraftment. Solid line: success group (median = 10 days, range: 0–35 days); dotted line: failure group (median = 8 days, range: 0–33 days).

collection of significantly more PBSCs[12–15]. Regarding pharmaceutical factors, lenalidomide is widely used to treat myeloma. However, it upregulates expression of CXC chemokine receptors on the surfaces of stem cells and thereby blocks mobilization of these cells into peripheral blood. Accordingly, reports have described improved stem cell collection in patients not treated with lenalidomide[16,17]. With the exception of lenalidomide, factors previously reported to be associated with collection of a larger number of PBSCs were not associated with successful collection in a single procedure in the present study.

Although the number of CD34 cells in peripheral blood before collection was reported to be a useful predictive factor, this laboratory test is time-consuming and not readily available on the same day as PBSC collection

at all hospitals. In contrast, detection of promyelocytes in peripheral blood is a rapid, low-cost procedure available on the same day as collection at any center. In addition, previous studies reported that hematopoietic progenitor cells were useful as predictors of the optimal timing of PBSC collection[18,19]. Therefore, promyelocyte detection might be useful for determining the ideal timing of PBSC collection. As was the case in previous reports, this study showed that LDH level could predict single-step peripheral blood stem cell collection[20] (**Table 2**). However, in analysis stratified by disease, LDH did not predict blood stem cell collection; only presence of promyelocytes was extracted. Thus, we believe that promyelocytes are more useful than LDH as a predictor of single-step peripheral blood stem cell collection.

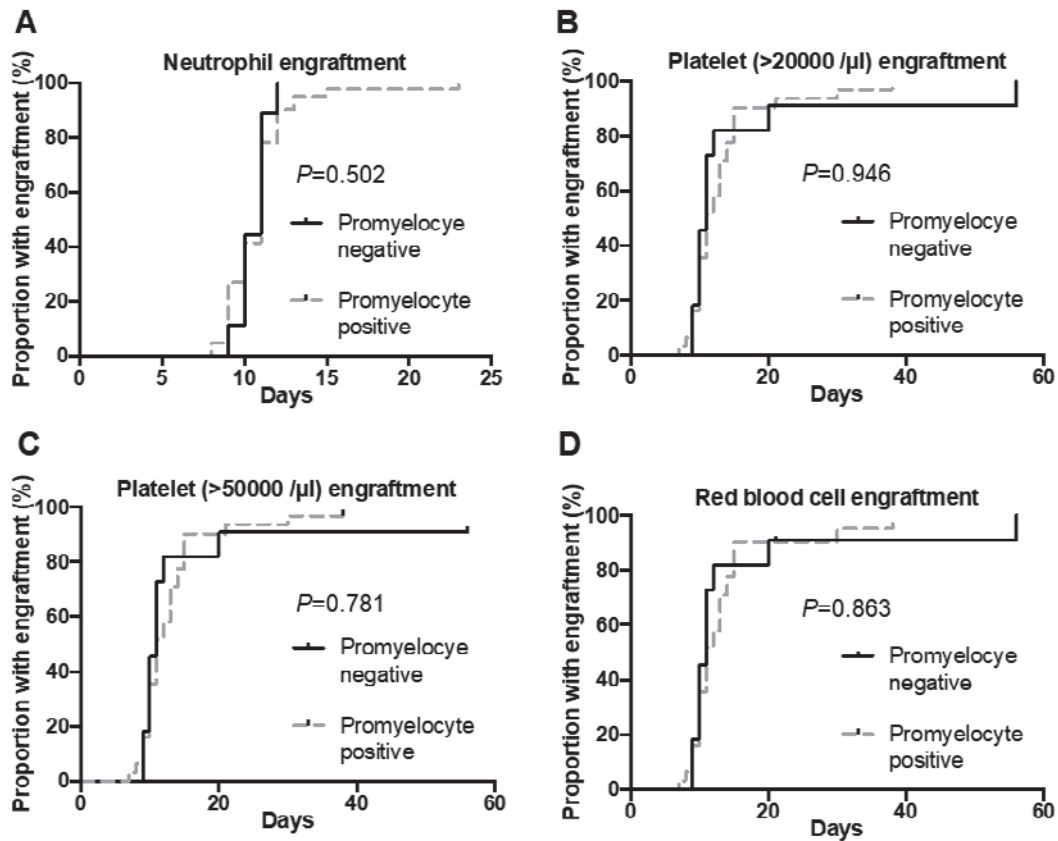Some previous studies reported a correlation of num-

Fig. 2 Comparison of numbers of days until engraftment of various blood cell types in promyelocyte-positive and promyelocyte-negative groups.

A: Comparison of neutrophil engraftment. Solid line: promyelocyte-negative group (median = 11 days, range: 9–12 days); dotted line: promyelocyte-positive group (median = 11 days, range: 8–23 days).

B: First comparison of platelet engraftment. Solid line: promyelocyte-negative group (median = 9 days, range: 0–56 days); dotted line: promyelocyte-positive group (median = 10 days, range: 0–38 days).

C: Second comparison of platelet engraftment. Solid line: promyelocyte-negative group (median = 14 days, range: 0–45 days); dotted line: promyelocyte-positive group (median = 16 days, range: 0–98 days).

D: Comparison of red blood cell engraftment. Solid line: promyelocyte-negative group (median = 0 days, range: 0–35 days); dotted line: promyelocyte-positive group (median = 9 days, range: 0–34 days).

ber of collected cells with early post-transplantation engraftment, and an association of poor mobilization status with significantly shorter overall survival rate, in patients with lymphoma and myeloma[4,21,22]. These findings highlight the importance of transfusion with a sufficient number of stem cells, even if collection must be performed over ≥3 days. Particularly, transplantation of an increased volume of stem cells does not lead to an increase in the frequency of complications, and collection of PBSCs via multiple procedures may not affect the number of days until engraftment if a minimum of 2.0×10^6 cells/kg is collected[23]. Consistent with those earlier findings, we found no significant differences in the numbers

of days to neutrophil, platelet, or RBC engraftment between the success and failure subgroups of patients who underwent transplantation in our study. However, application of multiple PBSC collection procedures imposes a burden on the patient and requires substantial economic and personnel resources. Therefore, successful collection during a single procedure is desirable when possible.

A difficult stem cell collection can sometimes be predicted. In 2012, Olivieri et al. suggested the following criteria for predicting and defining proven poor mobilizers (PMs)[14]: (1) previous failure of collection; (2) history of radiation therapy or administration of an anticancer agent that affects stem cell mobilization; and (3) at least 2 of

the following criteria-intractable disease, hypocellular bone marrow, and age ≥65 years. Although G-CSF is thought to mobilize stem cells into peripheral blood by reducing expression of vascular cell adhesion molecule-1 (VCAM-1) and other proteins, bortezomib was reported to directly mobilize stem cells by blocking nuclear factor-κB activation, thereby reducing VCAM-1 expression[24–26]. Additionally, the efficacy of plerixafor in cases of poor stem cell mobilization to peripheral blood has been widely reported. Although this drug has been available for use in Japan since 2017, its high cost has limited its use[27,28]. However, concomitant use of bortezomib or plerixafor should be considered for patients that meet the above criteria. In contrast, multiple harvesting of PBSCs negatively affects the patient, increases the burden on medical staff, and wastes medical resources. The present results suggest that it is clinically useful to predict optimal timing for peripheral blood stem cell collection by checking promyelocytes in peripheral blood and that concomitant use of plerixafor and bortezomib should be considered only when single-step collection is difficult.

This study has limitations. First, it was retrospective and analyzed data from only a single center. Second, the sample size was small. Third, the data were limited by the fact that hemograms could not be checked daily. Thus, we could not evaluate the extent of possible collection after the appearance of promyelocytes or the correlation between number of promyelocytes and number of CD34 cells. In the future, we hope to increase the number of cases and check hemograms daily.

In conclusion, collection of PBSCs in a single procedure is desirable, and the timing of collection is therefore important in reducing burdens on patients, medical staff, and medical resources. This study illustrates the need to predict PMs and use drugs such as bortezomib and plerixafor appropriately, to ensure collection of a sufficient number of stem cells. Although the number of CD 34 cells in peripheral blood is presently used as an indicator, the present findings suggest that a simpler marker, presence of promyelocytes, may also be useful for predicting optimal timing for PBSC collection in a single procedure.

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