Cytotherapy 24 (2022) 49–58

Contents lists available at ScienceDirect

CYTOTHERAPY

journal homepage: www.isct-cytotherapy.org

FULL-LENGTH ARTICLE
Basic Research

Development of a quantitative prediction model for peripheral blood stem cell collection yield in the plerixafor era

Akira Ishii[1,*], Tomoyasu Jo[1,2,3,*], Yasuyuki Arai[1,2,3,**], Shinichiro Oshima[1], Junya Kanda[1], Toshio Kitawaki[1], Keiko Matsui[3], Norimi Niwa[3], Yoko Nakagawa[3], Akifumi Takaori-Kondo[1,3], Miki Nagao[2,3]

[1] *Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[2] *Department of Clinical Laboratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[3] *Center for Research and Application of Cellular Therapy, Kyoto University Hospital, Kyoto, Japan*

ARTICLE INFO

Article History:
Received 4 April 2021
Accepted 5 September 2021

Key Words:
autologous stem cell transplantation
leukapheresis
peripheral blood stem cell
plerixafor

ABSTRACT

Background aims: Predicting autologous peripheral blood stem cell (PBSC) collection yield before leukapheresis is important for optimizing PBSC mobilization and autologous stem cell transplantation (ASCT) for treating hematological malignancies. Although guidelines for plerixafor usage based on peripheral blood $CD34^+$ ($PB\text{-}CD34^+$) cell count are available, their predictive performance in the real world remains unclear.
Methods: This study retrospectively analyzed 55 mobilization procedures for patients with non-Hodgkin lymphoma or multiple myeloma and developed a novel quantitative prediction model for $CD34^+$ cell collection yield that incorporated four clinical parameters available the day before leukapheresis; namely, $PB\text{-}CD34^+$ cell count the day before apheresis (day −1 $PB\text{-}CD34^+$), number of prior chemotherapy regimens, disease status at apheresis and mobilization protocol.
Results: The effects of $PB\text{-}CD34^+$ cell counts on $CD34^+$ cell collection yield varied widely per patient characteristics, and plerixafor usage was recommended in patients with poorly controlled disease or those with a history of heavy pre-treatments even with abundant day −1 $PB\text{-}CD34^+$ cell count. This model suggested a more proactive use of plerixafor than that recommended by the guidelines for patients with poor pre-collection condition or those with a higher target number of $CD34^+$ cells. Further, the authors analyzed the clinical outcomes of ASCT and found that plerixafor use for stem cell mobilization did not affect short- or long-term outcomes after ASCT.
Conclusions: Although external validations are necessary, the results can be beneficial for establishing more effective and safer mobilization strategies.

Introduction

Autologous stem cell transplantation (ASCT) following high-dose chemotherapy is widely used for the treatment of patients with hematological malignancies, including those with refractory or relapsed non-Hodgkin lymphoma (NHL) and transplant-eligible multiple myeloma (MM) [1]. The optimization of peripheral blood stem cell (PBSC) mobilization regimens as well as conditioning regimens prior to transplantation plays an important role in improving engraftment and the overall outcome after ASCT.

There are two conventional regimens for PBSC mobilization: granulocyte colony-stimulating factor (G-CSF) in combination with chemotherapy and G-CSF alone [2]. The combination of chemotherapy and G-CSF can provide higher $CD34^+$ hematopoietic stem cell (HSC) yields; however, the restricted PBSC mobilization window periods, which are often unpredictable beforehand, can be a burden for both patients and apheresis centers with respect to scheduling. Moreover, the incidence and severity of adverse effects with chemotherapy plus G-CSF are increased compared with G-CSF alone [3,4]. By contrast, the regimen of G-CSF alone can be beneficial with regard to predictable apheresis scheduling (usually 4–5 days after G-CSF initiation) and the rare occurrence of adverse events; however, the existence of

** Correspondence: Yasuyuki Arai, MD, PhD, Center for Research and Application of Cellular Therapy, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: ysykrai@kuhp.kyoto-u.ac.jp (Y. Arai).
* These authors contributed equally to this work.

https://doi.org/10.1016/j.jcyt.2021.09.004

poor mobilizers is a serious problem, particularly for patients with a history of heavy pre-treatment [2].

Plerixafor, a chemokine receptor antagonist, disrupts the interaction between stromal-derived factor 1α and C-X-C chemokine receptor type 4 in the bone marrow niche, thereby facilitating the HSC mobilization effect of G-CSF [5]. Therefore, the regimen of plerixafor plus G-CSF can significantly expand the mobilization of CD34$^+$ HSCs and may be particularly beneficial for patients at high risk of poor mobilization [6,7], thereby enabling nearly all patients to successfully yield a sufficient number of HSCs.

This situation has raised the clinical question of whether plerixafor is indispensable to every patient for HSC mobilization. The current guidelines of the American Society for Blood and Marrow Transplantation (ASBMT) and the position statement of the European Society for Blood and Marrow Transplantation (EBMT) propose the use of plerixafor in a pre-emptive manner based on the peripheral blood CD34$^+$ (PB-CD34$^+$) cell count or as salvage therapy in the case of low apheresis yield [2,8]. However, the predictive performance of the guidelines and position statement has not been fully evaluated in the real world. Furthermore, the effects of several factors other than PB-CD34$^+$, which have been reported to affect CD34$^+$ cell yield [7,9,10], have not been assessed quantitatively in previous studies. Therefore, developing a precise predictive model for HSC yield with PB-CD34$^+$ and other factors is necessary to answer the aforementioned clinical question.

The effects of mobilization agents on ASCT outcomes need to be determined, particularly with respect to the short- and long-term safety of plerixafor, because stem cells mobilized with plerixafor differ from those mobilized by G-CSF alone [2,11–16]. Although an increasing number of patients have undergone PBSC mobilization with plerixafor, few studies have studied its effects on outcomes after ASCT.

The authors therefore performed a retrospective cohort study to evaluate the following: (i) the impacts of pre-collection patient factors on CD34$^+$ collection yield, thereby developing a novel quantitative estimation model with a high predictive performance, and (ii) the effects of plerixafor use on clinical outcomes after ASCT. The authors believe that the present study findings will help develop an integrated approach as well as safe PBSC mobilization and subsequent ASCT for the treatment of NHL and MM.

Methods

Study cohort and inclusion criteria

This study enrolled adult patients with NHL or MM who underwent PBSC collection and transplantation at Kyoto University Hospital from January 2013 to July 2020. Patients with data on PB-CD34$^+$ cell counts a day before apheresis (day −1 PB-CD34$^+$) were included to analyze parameters affecting stem cell mobilization. Moreover, those who subsequently underwent ASCT were subject to outcome analyses. This study was approved by the institutional review board of Kyoto University and was conducted according to the principles of the Declaration of Helsinki.

Definition of disease status

Disease status at leukapheresis and transplantation was assessed using the Revised Response Criteria for Malignant Lymphoma [17] and International Myeloma Working Group Uniform Response Criteria [18]. The disease status was then categorized as follows: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR included CR and unconfirmed CR in NHL as well as CR and stringent CR in MM, whereas PR included PR in NHL as well as PR, very good PR and near CR in MM. The definitions of SD and PD were based on the aforementioned criteria for NHL and MM.

Standardized procedures for stem cell mobilization

Before the approval of plerixafor in Japan in 2016 [19], stem cell mobilization was performed almost exclusively during bone marrow recovery following chemotherapy with G-CSF boost (defined as the CG protocol). After plerixafor approval, stem cell mobilization was performed with either G-CSF alone or plerixafor plus G-CSF without any preceding chemotherapy (defined as the G or PG protocol). For G-CSF administration, either lenograstim or filgrastim was administered at a dose of 10 μg/kg for lenograstim or 400 μg/m^2 for filgrastim when used alone or in combination with plerixafor and 5 μg/kg for lenograstim or 400 μg/m^2 for filgrastim when administered after chemotherapy as per the guidelines for the appropriate use of G-CSF in Japan [20]. Plerixafor was administered at a dose of 240 μg/kg, and its prescription was determined by the physicians in charge based on the position statement of EBMT [8]. For example, plerixafor administration was actively considered in cases with a day −1 PB-CD34$^+$ cell count of $<10/\mu$L but not in cases with a day −1 PB-CD34$^+$ cell count of $>20/\mu$L, and a dynamic approach based on patient characteristics was suggested in those with a day −1 PB-CD34$^+$ cell count of 10–20/μL. Plerixafor was also given at the physicians' discretion despite high CD34 values.

Leukapheresis and CD34$^+$ cell measurement

PBSCs were collected using the Spectra Optia (Terumo BCT, Tokyo, Japan) and mononuclear cell collection program with a ratio of anticoagulant (acid citrate dextrose solution A) to blood of 1:12 and maximum blood volume processed (BVP) of 0.3 L/kg body weight, which are within the range recommended by ASBMT [2]. Routine analyses of the peripheral blood or apheresis product samples included complete blood count, CD34$^+$ cell count, viability tests and product volume measurement. CD34$^+$ cells were measured using flow cytometry with single-platform assays on a FACSCanto II (BD Biosciences, Heidelberg, Germany) [21]. Poor mobilization was defined as the failure to collect a minimum of 2.0×10^6 CD34$^+$ cells/kg body weight after completing all apheresis sessions. To adjust variations in BVP among the patients, the authors compared the total CD34$^+$ cell yield collected on the first day of apheresis per 10 L BVP.

Standardized procedures of ASCT and definition of outcomes

Patients received high-dose chemotherapy, including ranimustine, etoposide, cytarabine and melphalan [22], and high-dose thiotepa plus busulfan [23] in NHL and high-dose melphalan [24] in MM followed by autologous CD34$^+$ cell transplantation on day 0. After transplantation, neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of $\geq 0.5 \times 10^9$/L without growth factor support, platelet engraftment was defined as the first of 3 consecutive days with a platelet count of $\geq 20 \times 10^9$/L or 50×10^9/L without transfusion and erythrocyte engraftment was defined as the first of 3 consecutive days with a reticulocyte count $\geq$1%. Non-infectious fever was defined as an axillary body temperature of $\geq$37.5 °C with onset between day 0 and day 30 after transplantation, during which complete infectious workups should be negative.

Statistical analyses

For baseline patient characteristics, categorical variables were assessed using Fisher exact test, whereas continuous variables were compared using two-tailed unpaired Student's *t*-test or one-way analysis of variance with Tukey post-hoc test. The predictive factors of stem cell collection were analyzed using Pearson correlation and univariate regression models. In multivariate analyses for the prediction factors of stem cell collection, all variables with $P < 0.1$ in univariate analyses and known poor collection risk factors were included and a multiple regression model using a backward stepwise elimination method (significance

level = 0.05) was performed. In the regression analyses, all continuous variables were log-transformed to normalize the skewed distribution. The cumulative curves of engraftments or non-infectious fever were described using the Gray method [25], considering death or death and evident infection as competing risks. The survival curves were calculated using the Kaplan–Meier method, and the impacts of plerixafor use on the outcomes of ASCT were analyzed using the Fine and Gray test [26] or log-rank test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata 16 software (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics with regard to CD34⁺ cell mobilization

Patient clinical characteristics for CD34⁺ cell mobilization and collection are presented in Table 1. The authors included 55 patients with a median age of 57 years (range, 26–70) at apheresis. The underlying diseases included NHL (N = 37, 67.3%) and MM (N = 18, 32.7%), and CR was achieved at mobilization attempt in 19 (34.5%) patients. For the chemotherapy regimens before mobilization, nine (16.4%) patients were heavily treated with ≥3 regimens and 12 (21.8%) patients were administered treatments comprising lenalidomide. For the mobilization protocol, 11 (20.0%), nine (16.4%) and 35 (63.6%) patients underwent stem cell mobilization in the chemotherapy plus G-CSF (CG), G-CSF only (G) and plerixafor plus G-CSF (PG) groups, respectively. The baseline patient characteristics were similar, with the exception of the history of lenalidomide administration, which was observed in only the PG group.

During the mobilization protocol, complete blood cell counts, including white blood cell counts, hemoglobin levels and platelet counts on day −1, were lower in the patients of the CG group than in the patients of other mobilization groups. Although day −1 PB-CD34⁺ cell count was significantly higher in the patients of the G group than in the patients of the CG or PG group, PB-CD34⁺ cell count on the first day of apheresis (day 0) was comparable between those in the G and PG groups (Table 1).

With respect to harvest yields, the median number of CD34⁺ cells collected on the first day of leukapheresis was 4.2×10^6 cells/kg (range, 0.3–29.5), with a median value of 10.0 L (range, 4.8–14.5) BVP. Forty-two (76.4%) patients underwent 1-day apheresis to obtain a sufficient number of CD34⁺ cells, whereas the other patients required two or three apheresis sessions. The median number of CD34⁺ cells collected in total leukapheresis was 4.6×10^6 cells/kg (range, 0.3–29.5), and poor mobilization was present in four (7.3%) patients (Table 1).

Predictive performance of PB-CD34⁺ cell count for CD34⁺ cell yield on the first day of apheresis

As the next step, the authors analyzed the correlation between day −1 PB-CD34⁺ cell count and total CD34⁺ cell yields on the first

Table 1
Patient characteristics for CD34⁺ cell harvest according to mobilization strategy.

	Total N = 55	CG N = 11	G N = 9	PG N = 35	*P* value
Basal demographics					
Age at apheresis, years (range)	57 (26–70)	62 (27–66)	53 (33–69)	57 (26–70)	0.58
Male, n (%)	31 (56.4)	5 (45.5)	5 (55.6)	21 (60.0)	0.79
Body weight, kg (range)	61.1 (33.0–96.3)	55.1 (39–67.5)	60.8 (49.8–75.1)	64.0 (33.0–96.3)	0.16
Disease					0.06
NHL, n (%)	37 (67.3)	7 (63.6)	9 (100.0)	21 (60.0)	
MM, n (%)	18 (32.7)	4 (36.4)	0 (0.0)	14 (40.0)	
Disease status at apheresis					0.59
CR, n (%)	19 (34.5)	3 (27.3)	2 (22.2)	14 (40.0)	
PR, n (%)	34 (61.8)	7 (63.6)	7 (77.8)	20 (57.1)	
SD/PD, n (%)	2 (3.6)	1 (9.1)	0 (0.0)	1 (2.9)	
Number of prior chemotherapy regimens					0.83
1, n (%)	19 (34.5)	3 (27.3)	4 (44.4)	12 (34.3)	
2, n (%)	27 (49.1)	5 (45.5)	4 (44.4)	18 (51.4)	
≥3, n (%)	9 (16.4)	3 (27.3)	1 (11.1)	5 (14.3)	
Use of myelotoxic agents					
Lenalidomide, n (%)	12 (21.8)	0 (0.0)	0 (0.0)	12 (34.3)	0.01[a]
Radiation, n (%)	11 (20.0)	3 (27.3)	1 (11.1)	7 (20.0)	0.79
CBC day −1					
WBCs, 10^9/L (range)	34.3 (0.3–68.9)	1.2 (0.3–15.8)	34.3 (14.6–49.2)	42.2 (1.3–68.9)	< 0.01[a]
Neutrophils, 10^9/L (range)	26.6 (0.1–60.0)	0.3 (0.1–13.9)	26.8 (11.8–45.3)	34.4 (0.6–60.0)	< 0.01[a]
Monocytes, 10^9/L (range)	2.0 (0.0–8.6)	0.2 (0.0–1.1)	2.5 (0.5–5.7)	2.6 (0.3–8.6)	< 0.01[a]
Metamyelocytes, 10^9/L (range)	0.0 (0.0–1.8)	0.0 (0.0–0.1)	0.0 (0.0–1.8)	0.0 (0.0–1.1)	0.11
Myelocytes, 10^9/L (range)	0.0 (0.0–3.4)	0.0 (0.0–0.3)	0.4 (0.0–3.4)	0.0 (0.0–3.1)	0.07
Hemoglobin, g/dL (range)	10.8 (7.0–14.1)	9.5 (7.0–10.7)	11.2 (8.7–14.1)	11.5 (7.3–14.1)	0.01[a]
Platelets, $10^4/\mu$L (range)	17.0 (2.4–56.2)	4.4 (2.7–13.4)	22.6 (6.8–56.2)	18.1 (2.4–49.0)	< 0.01[a]
Mobilization outcome					
Day −1 PB-CD34⁺, /μL (range)	6.0 (0.0–244.0)	4.0 (0.0–244.0)	45.7 (15.2–109.8)	5.0 (0.7–170.0)	0.04[a]
Day 0 PB-CD34⁺, /μL (range)	40.3 (4.2–236.0)	12.0 (5.0–64.0)	54.9 (51.5–117.3)	54.5 (4.2–236.0)	0.07
Number of aphereses					0.18
1, n (%)	42 (76.4)	6 (54.5)	8 (88.9)	28 (80.0)	
2, n (%)	12 (21.8)	4 (36.4)	1 (11.1)	7 (20.0)	
3, n (%)	1 (1.8)	1 (9.1)	0 (0.0)	0 (0.0)	
CD34⁺ cell yield, first day, 10^6/kg (range)	4.2 (0.3–29.5)	1.5 (0.3–29.5)	6.2 (1.1–13.4)	3.8 (0.8–13.1)	0.36
CD34⁺ cell yield, total, 10^6/kg (range)	4.6 (0.3–29.5)	4.2 (0.3–29.5)	6.2 (3.0–13.4)	4.5 (1.7–13.1)	0.20
CD34⁺ cell yield $<2.0 \times 10^6$/kg, first day (range)	14 (25.5%)	6 (54.5%)	1 (11.1%)	7 (20.0%)	0.05
CD34⁺ cell yield $<2.0 \times 10^6$/kg, total (range)	4 (7.3%)	3 (27.3%)	0 (0.0%)	1 (2.9%)	0.04[a]
Blood volume processed, first day, L (range)	10.0 (4.8–14.5)	10.0 (10.0–10.4)	10.0 (8.7–10.3)	10.0 (4.8–14.5)	0.92
Total CD34⁺ cell yield/10 L BVP, first day, 10^8	2.5 (0.1–19.9)	0.9 (0.1–19.9)	3.6 (0.8–6.8)	2.4 (0.5–13.2)	0.83

CBC, complete blood count; WBCs, white blood cells.
[a] $P < 0.05$.

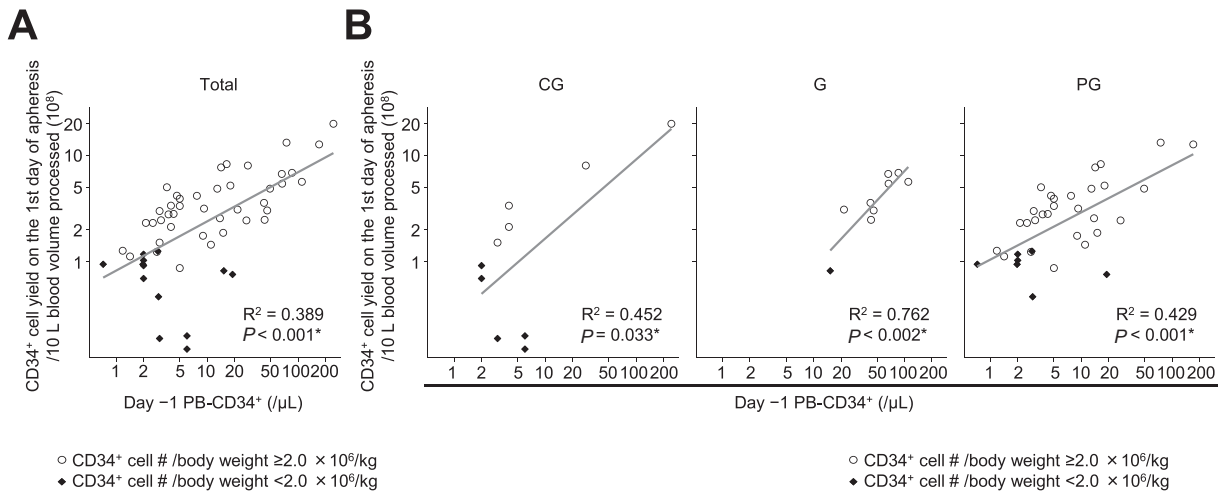


Figure 1. Correlation between CD34$^+$ cell collection yield and PB-CD34$^+$. (A) Correlation between total CD34$^+$ cell yield on first day of apheresis/10 L BVP and peripheral blood CD34$^+$ cell counts on day −1 PB-CD34$^+$ in total patients and (B) in each mobilization group. Axes are displayed in logarithmic scales, and black dots indicate patients in whom CD34$^+$ cell collection yield was $<2.0 \times 10^6$/kg on the first day of apheresis. * indicates P < 0.05.

day of apheresis (per 10 L BVP) to evaluate the predictive performance of the PB-CD34$^+$-based approach that is recommended in the current EBMT position statement. Thus, day −1 PB-CD34$^+$ cell count correlated significantly with CD34$^+$ cell collection yield on the first day of apheresis in the entire cohort (Figure 1A) and in each mobilization group (Figure 1B). However, the coefficient of determination (R^2) was remarkably low, particularly in the CG (0.45) and PG (0.43) groups; this indicated that CD34$^+$ cell collection yield cannot be predicted by day −1 PB-CD34$^+$ cell count alone. Moreover, the simplified model of prediction for the success of apheresis using day −1 PB-CD34$^+$ cell count data was suboptimal (see supplementary Tables 1–4). Sufficient CD34$^+$ cell yield was successfully obtained on the first day of apheresis in all patients with a day −1 PB-CD34$^+$ cell count of $\geq 20/\mu$L. However, among patients with a day −1 PB-CD34$^+$ cell count of $<20/\mu$L, 66% achieved the target yield, whereas the other 34% failed, irrespective of plerixafor use; the difference was not predicted using day −1 PB-CD34$^+$ cell count (see supplementary Table 4). These analyses indicated that prediction models solely dependent on PB-CD34$^+$ cell count can be applicable only in limited clinical situations.

Univariate and multivariate analyses of predictive factors for CD34$^+$ cell yield

Day −1 PB-CD34$^+$ cell count alone was insufficient to predict the harvest yield; thus, the authors investigated other factors that potentially affect CD34$^+$ cell collection yield (Table 2, Figure 2A,B; also see supplementary Figure 1A,B). In the univariate analyses, lower body weight, less controlled disease status (SD or PD), larger number of prior chemotherapy regimens (≥3), use of CG mobilization protocol and lower peripheral blood white blood cell, myelocyte and platelet counts on day −1 as well as lower day −1 PB-CD34$^+$ cells were significantly associated with poorer CD34$^+$ collection yield (Table 2, Figure 2A,B). In the multivariate regression analyses, poorly controlled disease status (SD or PD, P = 0.01), larger number of prior

Table 2
Univariate and multivariate analyses of parameters for CD34$^+$ cell yield in first apheresis.

	Univariate			Multivariate		
	Coefficient	95% CI	*P* value	Coefficient	95% CI	*P* value
Basal demographics						
Age at apheresis, years	−0.902	−2.197–0.392	0.17			
Sex, female versus male[b]	0.704	0.401–1.236	0.22			
Body weight, kg	1.530	0.139–2.921	0.03[a]			
Disease, MM versus NHL[b]	1.630	0.904–2.937	0.10			
Disease status, SD/PD versus CR/PR[b]	0.141	0.034–0.578	0.01[a]	0.243	0.089–0.665	0.01[a]
Number of prior chemotherapy regimens, ≥3 versus ≤2[b]	0.247	0.127–0.478	< 0.01[a]	0.480	0.286–0.804	0.01[a]
Lenalidomide, yes versus no[b]	0.856	0.432–1.699	0.65			
Radiation, yes versus no[b]	0.959	0.472–1.948	0.91			
Harvest regimen[b]						
G versus PG	1.473	0.702–3.091	0.30	0.481	0.278–0.833	0.01[a]
CG versus PG	0.462	0.233–0.916	0.03[a]	0.600	0.384–0.939	0.03[a]
CBC day −1						
WBCs, 10^9/L	0.193	0.013–0.372	0.04[a]			
Neutrophils, 10^9/L	0.115	−0.024–0.255	0.10			
Monocytes, 10^9/L	0.146	0.080–0.371	0.20			
Metamyelocytes, 10^9/L	0.109	−0.152–0.369	0.41			
Myelocytes, 10^9/L	0.316	0.097–0.534	0.01[a]			
Hemoglobin, g/dL	1.424	−0.100–2.948	0.07			
Platelets, $10^4/\mu$L	0.722	0.317–1.128	0.01[a]			
PB-CD34$^+$, /μL	0.463	0.302–0.625	< 0.01[a]	0.525	0.376–0.674	< 0.01[a]

CBC, complete blood count; CI, confidence interval; WBCs, white blood cells.
[a] $P < 0.05$.
[b] Binary variable.

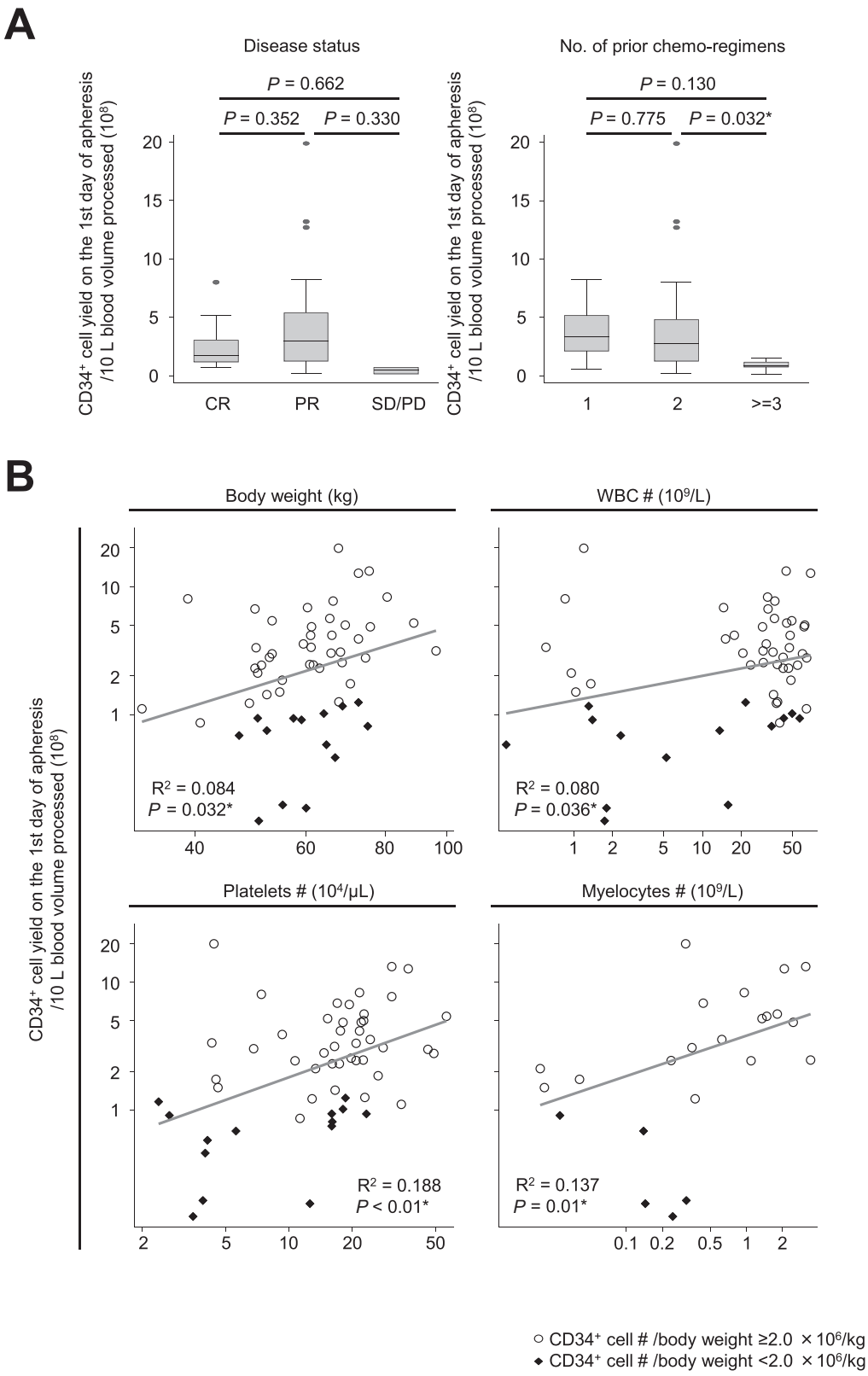
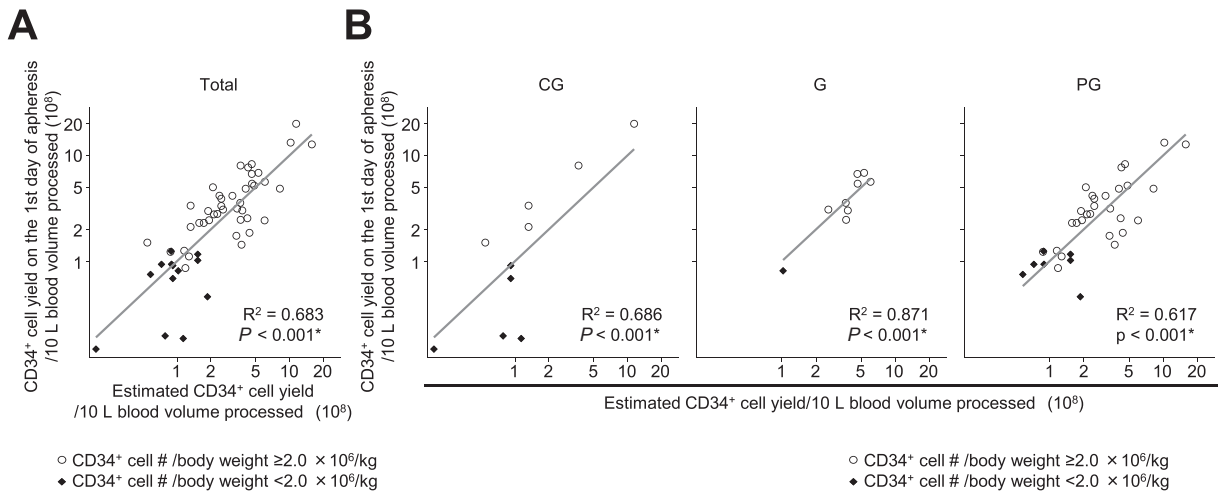


Figure 2. Factors affecting $CD34^+$ cell collection yield. (A) Comparison of total $CD34^+$ cell yield on the first day of apheresis/10 L BVP with respect to indicated categorical variables. (B) Correlation between total $CD34^+$ cell yield on the first day of apheresis/10 L BVP and indicated continuous variables. Axes are displayed in logarithmic scales, and black dots indicate patients in whom $CD34^+$ cell collection yield was $<2.0 \times 10^6$/kg on the first day of apheresis. * indicates $P < 0.05$. WBC, white blood cell.



C

Estimation of CD34+ cell yield on the 1st day of apheresis (10^6/kg) harvested as per the pre-collection parameters.
BW = 60 kg, Blood volume processed = 10 L

	Day −1 PB-CD34+ (/μL)																	
	2		3		5		7		10		15		20		30		50	
	G	PG	G	PG	G	PG	G	PG	G	PG	G	PG	G	PG	G	PG	G	PG
Condition 1	1.22	2.55	1.52	3.15	1.98	4.12	2.37	4.92	2.85	5.93	3.53	7.34	4.11	8.54	5.08	10.56	6.64	13.81
Condition 2	0.59	1.22	0.73	1.51	0.95	1.98	1.14	2.36	1.37	2.85	1.69	3.52	1.97	4.10	2.44	5.07	3.19	6.63
Condition 3	0.30	0.62	0.37	0.77	0.48	1.00	0.57	1.19	0.69	1.44	0.86	1.78	1.00	2.07	1.23	2.57	1.61	3.36
Condition 4	0.14	0.30	0.18	0.37	0.23	0.48	0.28	0.57	0.33	0.69	0.41	0.86	0.48	1.00	0.59	1.23	0.77	1.61

Condition 1: Disease status in CR/PR & Number of chemotherapy regimens ≤2
Condition 2: Disease status in CR/PR & Number of chemotherapy regimens ≥3
Condition 3: Disease status in SD/PD & Number of chemotherapy regimens ≤2
Condition 4: Disease status in SD/PD & Number of chemotherapy regimens ≥3

Estimated CD34+ cell yield ≥5 ×10^6/kg)
Estimated CD34+ cell yield ≥2, <5 ×10^6/kg)
Estimated CD34+ cell yield <2 × 10^6/kg)

Figure 3. Development of a prediction model for CD34+ cell collection yield based on patient conditions. Correlation between actual CD34+ cell yield on the first day of apheresis/10 L BVP and predicted CD34+ cell yield/10 L BVP using the mathematical formula of estimated CD34+ cell collection yield on the first day of apheresis/10 L BVP (10^8) = 1.062 × (day −1 PB-CD34+ cell count [/μL])$^{0.525}$ (if disease status in SD or PD × 0.243) (if number of chemotherapy regimens ≥3 × 0.480) (if G group × 0.481, if CG group × 0.600) in (A) total patients and (B) each mobilization group. Axes are displayed in logarithmic scales, and black dots indicate patients in whom CD34+ cell collection yield was <2.0 × 10^6/kg on the first day of apheresis. (C) Predictive heatmap for CD34+ cell yield (showing an example where BVP is 10 L and the patient's body weight is 60 kg). The number in each cell indicates the predicted CD34+ cell yield on the first day of apheresis (10^6/kg) under the designated condition (1–4) and mobilizing protocol (G or PG). Shading indicates that the predicted CD34+ cell collection yield is <2.0 × 10^6/kg or 5.0 × 10^6/kg.* indicates P < 0.05.

chemotherapy regimens (≥3, P = 0.01), mobilization protocols without plerixafor (G group, P = 0.01, CG group, P = 0.03) and lower day −1 PB-CD34+ cell count (P < 0.01) were significantly associated with lower CD34+ cell collection yield (Table 2).

The multivariate model estimated that poor disease control at mobilization and ≥3 chemotherapy lines before mobilization reduced CD34+ cell collection yield on the first day of apheresis by 24% and 48%, respectively. By contrast, plerixafor use in combination with G-CSF increased CD34+ cell collection yields by 208% compared with G-CSF alone (Table 2).

Development of a prediction model for CD34+ collection with various patient conditions

Based on the multivariate model shown in Table 2, the total CD34+ cell yield on the first day of apheresis per 10 L BVP was predicted using the following equation (see supplementary Figure 2): estimated CD34+ cell collection yield on the first day of apheresis/10 L BVP (10^8) = 1.062 × (day −1 PB-CD34+ cell count [/μL])$^{0.525}$ (if disease status in SD or PD × 0.243) (if number of chemotherapy regimens ≥3 × 0.480) (if G group × 0.481, if CG group × 0.600).

The estimated CD34+ cell collection yield significantly correlated with the actual CD34+ cell collection yield in the entire cohort (Figure 3A) and in each mobilization group (Figure 3B); the coefficient of determination (R^2) was remarkably improved compared with the model using PB-CD34+ cell count alone (Figure 1). As per this new model, poor mobilization was predicted with an accuracy of 85.7% (Table 3).

This model can also be applied to determine the need for plerixafor based on both pre-collection parameters and target CD34+ cell number for collection (Figure 3C). For example, in a patient weighing 60 kg and a day −1 PB-CD34+ cell count of 10/μL whose disease was well controlled with a limited number of prior chemotherapy regimens (condition 1), 2.85 × 10^6/kg CD34+ cells were collected on the first day of apheresis with a BVP of 10 L when mobilized with G-CSF alone, whereas 5.93 × 10^6/kg CD34+ cells were collected with plerixafor plus G-CSF. By contrast, even with 20/μL PB-CD34+, plerixafor was required in patients with a history of heavy chemotherapy regimens (condition 2) or those with poorly controlled disease (condition 3) to obtain >2.0 × 10^6/kg CD34+ cells on the first day of apheresis. It is noteworthy to mention that the effects of PB-CD34+ cell count differed widely based on patient characteristics.

Effects of plerixafor use on engraftment and short- and long-term outcomes after ASCT

The authors' model suggests that pre-emptive plerixafor use is beneficial in a wider range of patients than that indicated in the

Table 3
Predictive value of estimation for $CD34^+$ cell yield.

		Estimated yield , 10^6/kg/10 L BVP (%)		
		<2	≥2	Total
Actual yield, 10^6/kg/10 L BVP (%)	<2	12 (85.7)	3 (7.3)	15 (27.3)
	≥2	2 (14.3)	38 (92.7)	40 (72.7)
	Total	14 (100.0)	41 (100.0)	55 (100.0)

$P < 0.01$ based on Fisher exact test.

position statement from EBMT. However, the influence of plerixafor on post-ASCT outcomes, including engraftment and short- and long-term complications, has not been systematically analyzed. Therefore, among all patients who underwent PBSC collection, the authors analyzed 72 patients who subsequently underwent ASCT and compared patient outcomes after ASCT, including hematopoietic recovery, engraftment syndrome, disease relapse and survival between groups treated with and without plerixafor for mobilization. Patient characteristics are shown in supplementary Table 5. No significant differences were observed in the basic characteristics of patients, including transplanted $CD34^+$ cell number, between groups. Thus, the time course and cumulative incidence of engraftment for all lineages were similar between the groups treated with and without plerixafor (PG versus G or CG) (Figure 4A,B; also see supplementary Figure 3A,B). The cumulative incidence and duration of non-infectious fever were comparable between the groups (Figure 4C,D).

With regard to long-term outcomes, the 2-year overall survival after ASCT in patients treated with plerixafor appeared slightly worse compared with those treated without plerixafor (70.1% versus 86.5%); however, the difference was not significant ($P = 0.11$) (Figure 4E). The incidence of progression-free survival, relapse-free survival and relapse was similar between subjects treated with and without plerixafor; no significant difference was detected (Figure 4F; also see supplementary Figure 3C,D).

Discussion

This retrospective cohort study investigated PBSC harvest and subsequent ASCT in patients with NHL and MM in which all diagnostic and therapeutic procedures followed uniform institutional principles, and the authors obtained two major findings. First, the four parameters of disease status at apheresis, previous history of chemotherapy regimens, mobilization protocol and day −1 PB-$CD34^+$ cell count are the predictive factors of $CD34^+$ cell collection yields. A novel quantitative prediction model was established for accurate yield prediction to suggest the necessity of plerixafor administration based on the clinical status of each patient. Second, plerixafor use for mobilization has no harmful impacts on engraftment, non-infectious fever or survival after ASCT. The study findings suggest that a more proactive use of plerixafor than that indicated in the previous guidelines or position statement can be recommended, particularly for patients with heavy pre-treatments or those with poorly controlled disease.

The authors initially developed a clinically applicable predictive model for the yields of $CD34^+$ HSCs. In this model, disease control status and preceding chemotherapy lines were extracted from the wide variety of parameters before PBSC harvest. These factors were first clearly recognized as risk factors for poor mobilization [10,27–30]. Patients with poorly controlled disease (i.e., SD or PD after chemotherapy) often have bone marrow involvement in NHL [31] or a larger number of bone marrow plasma cells in MM [32]. This could partially reduce the number of HSCs owing to the impairment of healthy niches by malignant cells in the bone marrow or because of direct competition between HSCs and malignant cells for a limited number of niches [33,34]. Heavily pre-treated patients, recognized as patients with a history of a large number of prior chemotherapy lines, often have exhausted bone marrow hematopoiesis or clinical/subclinical therapy-related myelodysplasia in addition to impaired marrow stroma to support HSCs [27,35,36]; such a condition poses a high risk of failure in obtaining sufficient HSCs. The authors' analyses indicated that disease status and significant chemotherapy history can suppress HSC yields to a quarter or half; thus, these parameters should be included in the prediction model along with mobilization protocol and day −1 PB-$CD34^+$ cell count.

The authors' quantitative model not only predicts yields precisely using four parameters but also guides the need for plerixafor use based on the clinical status of and target yield in each patient. In the authors' model, for example, plerixafor use is recommended not only for patients with a PB-$CD34^+$ cell count of $<10/\mu L$ to obtain $\geq 2.0 \times 10^6$/kg $CD34^+$ cells, as suggested in the EBMT position statement, but also for patients heavily pre-treated or those with poorly controlled disease; this has not been clearly mentioned in any guidelines or previous studies. For patients with a day −1 PB-$CD34^+$ cell count of $10–20/\mu L$, there are no clear standards regarding plerixafor use. Furthermore, the authors' model can be applied to situations where a larger number of $CD34^+$ HSCs are required to perform ASCT more than once, particularly for patients with MM [37,38]. Thus far, arbitrary decisions have been made by attending physicians for mobilization regimens in such cases; the authors' model can provide quantitative and evidence-based suggestions by considering each parameter. Such a prediction-guided mobilization strategy will mitigate the uncertainness in apheresis, which can be a burden on both patients and the clinical resources involved.

The present study can answer the following frequently asked clinical question: how many PB-$CD34^+$ cells are enough to collect a sufficient number of $CD34^+$ cells in the real world? Of note, the authors found that plerixafor use enabled us to harvest sufficient $CD34^+$ cells in patients with a day −1 PB-$CD34^+$ cell count as low as $1.2/\mu L$ in a single apheresis (Figure 1B) and in patients with a day −1 PB-$CD34^+$ cell count as low as $0.7/\mu L$ in two apheresis sessions. These findings suggest that it is worth performing apheresis after plerixafor administration even if the day −1 PB-$CD34^+$ cell count is extremely low. Moreover, the authors' current model suggests a more expanded indication for plerixafor than that offered by the ASBMT guidelines and EBMT position statement, although the routine use of plerixafor should be avoided from a pharmacoeconomic standpoint [2,8,39].

Since the authors' analyses suggested an expanded indication for plerixafor, the effects on post-ASCT clinical courses and outcomes were systematically analyzed. Previous studies have indicated no significant differences in the time to hematopoietic recovery or in survival between patients treated with and without plerixafor for mobilization [40,41]. However, plerixafor reportedly mobilizes different $CD34^+$ cell subpopulations at different developmental stages as well as non-$CD34^+$ cells, including $CD4^+$ and $CD8^+$ T cells, natural killer cells and dendritic cells [2,11–16]. Therefore, the use of PBSCs mobilized with plerixafor is expected to exert pro-inflammatory effects following ASCT and subsequently increase engraftment syndrome and non-relapse mortality. The results of the current study contradict this hypothesis, and the authors showed that plerixafor use did not increase the incidence or duration of non-infectious fever or alter hematopoietic recovery or survival after ASCT. These results suggest that the mobilization regimen can be determined without considering the effects on ASCT outcomes [42–44]; however, studies

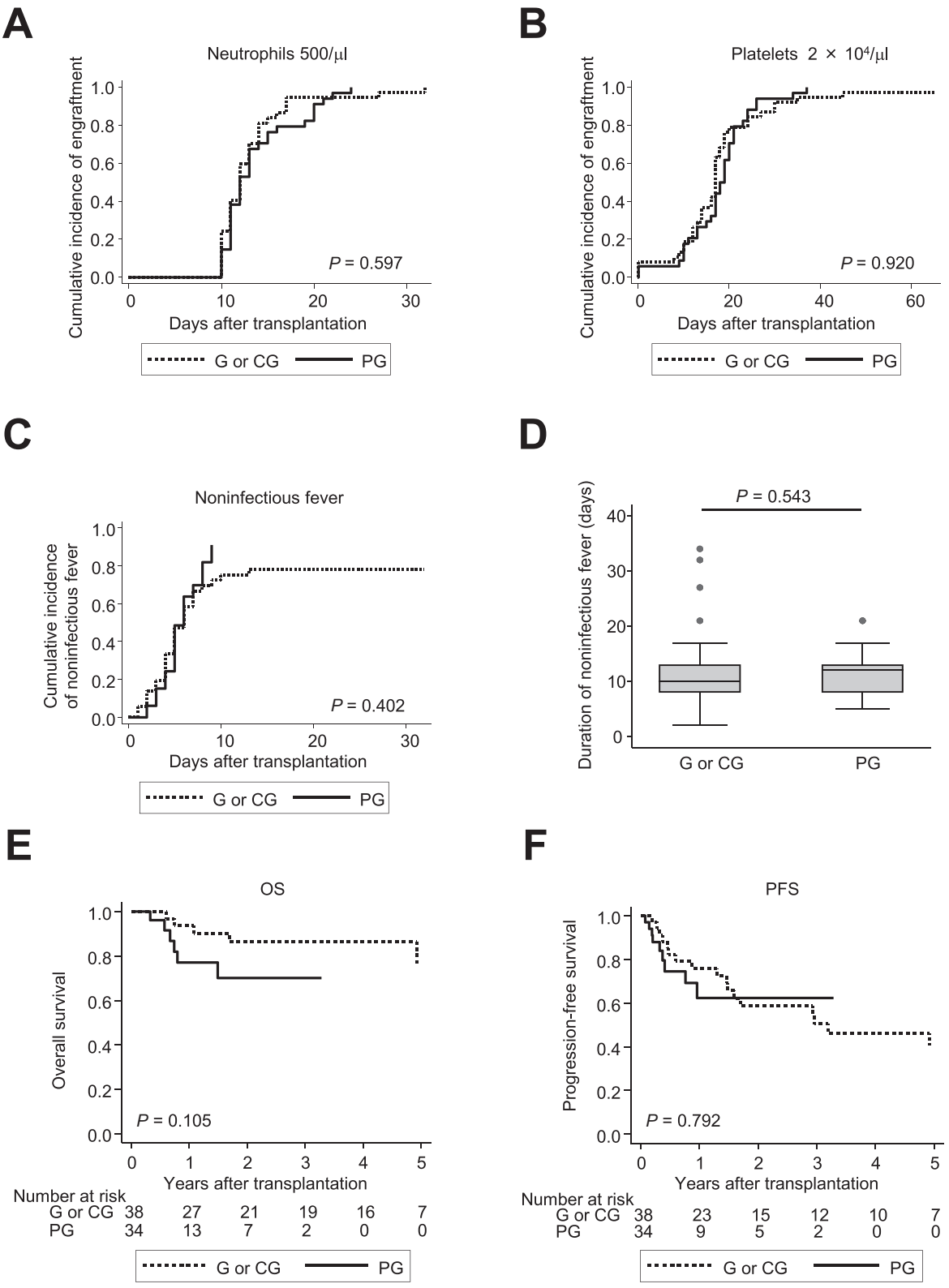


Figure 4. Effects of plerixafor use on clinical outcomes of ASCT. Engraftment of (A) neutrophils and (B) platelets following ASCT. (C) Cumulative incidence and (D) duration of noninfectious fever following ASCT. (E) OS and (F) PFS after ASCT. OS, overall survival; PFS, progression-free survival.

with longer follow-up periods and more patients are necessary to reach a final conclusion.

The present study systematically investigated PBSC harvest and subsequent ASCT for NHL and MM. However, some limitations exist with respect to the retrospective nature of the study and variation in the baseline characteristics of the three mobilization groups. For example, the proportion of patients with a history of lenalidomide-containing regimens was higher in the PG group than in other groups, reflecting the approval of frontline therapy with lenalidomide in Japan in 2015 [45,46]. In the present study,

the effect of plerixafor in combination with chemotherapy plus G-CSF was not evaluated. The trend revealing that plerixafor use was associated with lower overall survival could be related to the potential selection of poor mobilizers for the plerixafor group and should be interpreted cautiously. Moreover, because of the small sample size of this study, the findings should be interpreted with caution. Given that the ethnicity of patients has been reported to be associated with $CD34^+$ cell collection yield [47–49], the authors' model, which is based on a Japanese population, should be evaluated in terms of patients of various ethnicities. To overcome these limitations, the authors' predictive model warrants validation in a larger prospective cohort. Plerixafor use should be determined as per the drug label in a given country.

Conclusions

The present study provides valuable information regarding the prediction of PBSC collection yield and an important suggestion regarding the addition of plerixafor to the mobilization regimen. The use of plerixafor in stem cell collection appeared to have no negative influence on the outcomes of ASCT. Therefore, the authors' results suggest that plerixafor is effective for a wider range of patients than that indicated by the existing guidelines and position statement. The authors believe that the study results and discussion could help establish more efficient and safer PBSC mobilization and ASCT protocols for the treatment of patients with NHL and MM.

This work was supported in part by the Cell Science Research Foundation, Ono Medical Research Foundation, SGH Foundation, MSD Life Science Foundation, GlaxoSmithKline Research Grant, L-INSIGHT (Kyoto University), and Fujiwara Memorial Foundation (YA).

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: AI, TJ, SO, JK and YA. Acquisition of data: KM, NN and YN. Analysis and interpretation of data: AI, TJ, SO, JK, YA, TK, AT-K and MN. Drafting or revising the manuscript: AI, TJ, YA, SO, JK, TK, KM, NN, YN, AT-K, and MN. All authors have approved the final article.

Acknowledgments

The authors thank the clinical medical engineers and nurses of the artificial kidney unit, transplant coordinators and all clinicians at the Kyoto University Hospital as well as patients who contributed to this research.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcyt.2021.09.004.

References

[1] Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354(17):1813–26.
[2] Giralt S, Costa L, Schriber J, Dipersio J, Maziarz R, McCarty J, Shaughnessy P, Snyder E, Bensinger W, Copelan E, Hosing C, Negrin R, Petersen FB, Rondelli D, Soiffer R, Leather H, Pazzalia A, Devine S. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014;20(3):295–308.
[3] Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, Westervelt P, Vij R, Abboud CN, Stockerl-Goldstein KE, Sempek DS, Smith AL, DiPersio JF. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant 2008;14(9):1045–56.
[4] Gertz MA, Kumar SK, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, Dingli D, Gastineau DA, Winters JL, Litzow MR. Comparison of high-dose CY and growth factor with growth factor alone for mobilization of stem cells for transplantation in patients with multiple myeloma. Bone Marrow Transplant 2009;43(8):619–25.
[5] Jantunen E. Novel strategies for blood stem cell mobilization: special focus on plerixafor. Expert Opin Biol Ther 2011;11(9):1241–8.
[6] D'Addio A, Curti A, Worel N, Douglas K, Motta MR, Rizzi S, Dan E, Taioli S, Giudice V, Agis H, Kopetzky G, Soutar R, Casadei B, Baccarani M, Lemoli RM. The addition of plerixafor is safe and allows adequate PBSC collection in multiple myeloma and lymphoma patients poor mobilizers after chemotherapy and G-CSF. Bone Marrow Transplant 2011;46(3):356–63.
[7] Lanza F, Lemoli RM, Olivieri A, Laszlo D, Martino M, Specchia G, Pavone V, Imola M, Pasini A, Milone G, Scortechini I, Todisco E, Guggiari E, Cascavilla N, Martinelli G, Rambaldi A, Bosi A. Factors affecting successful mobilization with plerixafor: an Italian prospective survey in 215 patients with multiple myeloma and lymphoma. Transfusion 2014;54(2):331–9.
[8] Mohty M, Hubel K, Kroger N, Aljurf M, Apperley J, Basak GW, Bazarbachi A, Douglas K, Gabriel I, Garderet L, Geraldes C, Jaksic O, Kattan MW, Koristek Z, Lanza F, Lemoli RM, Mendeleeva L, Mikala G, Mikhailova N, Nagler A, Schouten HC, Selleslag D, Suciu S, Sureda A, Worel N, Wuchter P, Chabannon C, Duarte RF. Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2014;49(7):865–72.
[9] Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Gastineau DA, Litzow MR, Fonseca R, Roy V, Rajkumar SV, Gertz MA. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia 2007;21(9):2035–42.
[10] Mendrone Jr. A, Arrais CA, Saboya R, Chamone Dde A, Dulley FL. Factors affecting hematopoietic progenitor cell mobilization: an analysis of 307 patients. Transfus Apher Sci 2008;39(3):187–92.
[11] Larochelle A, Krouse A, Metzger M, Orlic D, Donahue RE, Fricker S, Bridger G, Dunbar CE, Hematti P. AMD3100 mobilizes hematopoietic stem cells with long-term repopulating capacity in nonhuman primates. Blood 2006;107(9):3772–8.
[12] Gazitt Y, Freytes CO, Akay C, Badel K, Calandra G. Improved mobilization of peripheral blood CD34+ cells and dendritic cells by AMD3100 plus granulocyte-colony-stimulating factor in non-Hodgkin's lymphoma patients. Stem Cells Dev 2007;16(4):657–66.
[13] Devine SM, Vij R, Rettig M, Todt L, McGlauchlen K, Fisher N, Devine H, Link DC, Calandra G, Bridger G, Westervelt P, Dipersio JF. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. Blood 2008;112(4):990–8.
[14] Varmavuo V, Mantymaa P, Kuittinen T, Nousiainen T, Jantunen E. Blood graft lymphocyte subsets after plerixafor injection in non-Hodgkin's lymphoma patients mobilizing poorly with chemotherapy plus granulocyte-colony-stimulating factor. Transfusion 2012;52(8):1785–91.
[15] Worel N, Frank N, Frech C, Fritsch G. Influence of plerixafor on the mobilization of CD34+ cell subpopulations and lymphocyte subtypes. Transfusion 2017;57(9):2206–15.
[16] Worel N, Fritsch G, Agis H, Bohm A, Engelich G, Leitner GC, Geissler K, Gleixner K, Kalhs P, Buxhofer-Ausch V, Keil F, Kopetzky G, Mayr V, Rabitsch W, Reisner R, Rosskopf K, Ruckser R, Zoghlami C, Zojer N, Greinix HT. Plerixafor as preemptive strategy results in high success rates in autologous stem cell mobilization failure. J Clin Apher 2017;32(4):224–34.
[17] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. L. International Harmonization Project on, Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579–86.
[18] Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Blade J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS, Avet-Loiseau H. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17(8):e328–46.
[19] Matsue K, Kumagai K, Sugiura I, Ishikawa T, Igarashi T, Sato T, Uchiyama M, Miyamoto T, Ono T, Ueda Y, Kiguchi T, Sunaga Y, Sasaki T, Suzuki K. Plerixafor for mobilization and collection of haematopoietic stem cells for autologous transplantation in Japanese patients with non-Hodgkin lymphoma: a randomized phase 2 study. Int J Hematol 2018;108(5):524–34.
[20] Usui N. [Appropriate use of granulocyte-colony stimulating factor in treating hematologic malignancies]. Rinsho Ketsueki 2015;56(10):2267–76.
[21] Keeney M, Chin-Yee I, Weir K, Popma J, Nayar R, Sutherland DR. Single platform flow cytometric absolute CD34+ cell counts based on the ISHAGE guidelines. International Society of Hematotherapy and Graft Engineering, Cytometry 1998;34(2):61–70.
[22] Sugimoto M, Ito S, Mashima K, Umino K, Minakata D, Nakano H, Yamasaki R, Kawasaki Y, Ashizawa M, Yamamoto C, Fujiwara S, Okazuka K, Hatano K, Sato K, Oh I, Ohmine K, Suzuki T, Muroi K, Kako S, Kanda Y. Retrospective evaluation of the MEAM regimen as a conditioning regimen before autologous peripheral blood stem cell transplantation for lymphoma in two centers with different dosing schedules of melphalan. Ann Hematol 2016;95(9):1513–9.

[23] Wada F, Nishikori M, Hishizawa M, Watanabe M, Aiba A, Kitano T, Shimazu Y, Shindo T, Kondo T, Takaori-Kondo A. Secondary failure of platelet recovery in patients treated with high-dose thiotepa and busulfan followed by autologous stem cell transplantation. Int J Hematol 2020;112(5):609–13.
[24] Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT, Selby PJ. Medical Research Council Adult Leukaemia Working, High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348(19):1875–83.
[25] Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18(6):695–706.
[26] Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999;94(446):496–509.
[27] Ford CD, Green W, Warenski S, Petersen FB. Effect of prior chemotherapy on hematopoietic stem cell mobilization. Bone Marrow Transplant 2004;33(9):901–5.
[28] Perseghin P, Terruzzi E, Dassi M, Baldini V, Parma M, Coluccia P, Accorsi P, Confalonieri G, Tavecchia L, Verga L, Ravagnani F, Iacone A, Pogliani EM, Pioltelli P. Management of poor peripheral blood stem cell mobilization: incidence, predictive factors, alternative strategies and outcome. A retrospective analysis on 2177 patients from three major Italian institutions. Transfus Apher Sci 2009;41(1):33–7.
[29] Han X, Ma L, Zhao L, He X, Liu P, Zhou S, Yang J, Qin Y, Yang S, Yao J, Shi Y. Predictive factors for inadequate stem cell mobilization in Chinese patients with NHL and HL: 14-year experience of a single-center study. J Clin Apher 2012;27(2):64–74.
[30] Sancho JM, Morgades M, Grifols JR, Junca J, Guardia R, Vives S, Ferra C, Batlle M, Ester A, Gallardo D, Milla F, Feliu E, Ribera JM. Predictive factors for poor peripheral blood stem cell mobilization and peak CD34(+) cell count to guide pre-emptive or immediate rescue mobilization. Cytotherapy 2012;14(7):823–9.
[31] Campbell J, Seymour JF, Matthews J, Wolf M, Stone J, Juneja S. The prognostic impact of bone marrow involvement in patients with diffuse large cell lymphoma varies according to the degree of infiltration and presence of discordant marrow involvement. Eur J Haematol 2006;76(6):473–80.
[32] Olivieri A, Marchetti M, Lemoli R, Tarella C, Iacone A, Lanza F, Rambaldi A, Bosi A. T. Italian Group for Stem Cell, Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by ad hoc working group Gruppo ItalianoTrapianto di Midollo Osseo. Bone Marrow Transplant 2012;47(3):342–51.
[33] Colmone A, Amorim M, Pontier AL, Wang S, Jablonski E, Sipkins DA. Leukemic cells create bone marrow niches that disrupt the behavior of normal hematopoietic progenitor cells. Science 2008;322(5909):1861–5.
[34] Shiozawa Y, Pedersen EA, Havens AM, Jung Y, Mishra A, Joseph J, Kim JK, Patel LR, Ying C, Ziegler AM, Pienta MJ, Song J, Wang J, Loberg RD, Krebsbach PH, Pienta KJ, Taichman RS. Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow. J Clin Invest 2011;121(4):1298–312.
[35] To LB, Levesque JP, Herbert KE. How I treat patients who mobilize hematopoietic stem cells poorly. Blood 2011;118(17):4530–40.
[36] Papanikolaou X, Szymonifka J, Rosenthal A, Heuck CJ, Mitchell A, Johann Jr. D, Keller J, Waheed S, Usmani SZ, Van Rhee F, Bailey C, Petty N, Hoering A, Crowley J, Barlogie B. Metronomic therapy is an effective salvage treatment for heavily pre-treated relapsed/refractory multiple myeloma. Haematologica 2013;98(7):1147–53.
[37] Jimenez-Zepeda VH, Mikhael J, Winter A, Franke N, Masih-Khan E, Trudel S, Chen C, Kukreti V, Reece DE. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biol Blood Marrow Transplant 2012;18(5):773–9.
[38] Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, Chng WJ, Moreau P, Attal M, Kyle RA, Caers J, Hillengass J, San Miguel J, van de Donk NW, Einsele H, Blade J, Durie BG, Goldschmidt H, Mateos MV, Palumbo A, Orlowski R. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 2016;127(24):2955–62.
[39] Douglas KW, Gilleece M, Hayden P, Hunter H, Johnson PRE, Kallmeyer C, Malladi RK, Paneesha S, Pawson R, Quinn M, Raj K, Richardson D, Robinson S, Russell N, Snowden J, Sureda A, Tholouli E, Thomson K, Watts M, Wilson KM. UK consensus statement on the use of plerixafor to facilitate autologous peripheral blood stem cell collection to support high-dose chemoradiotherapy for patients with malignancy. J Clin Apher 2018;33(1):46–59.
[40] Maziarz RT, Nademanee AP, Micallef IN, Stiff PJ, Calandra G, Angell J, Dipersio JF, Bolwell BJ. Plerixafor plus granulocyte colony-stimulating factor improves the mobilization of hematopoietic stem cells in patients with non-Hodgkin lymphoma and low circulating peripheral blood CD34+ cells. Biol Blood Marrow Transplant 2013;19(4):670–5.
[41] Varmavuo V, Rimpilainen J, Kuitunen H, Nihtinen A, Vasala K, Mikkola M, Kutila A, Lehtonen P, Kuittinen T, Mantymaa P, Nousiainen T, Kuittinen O, Jantunen E. Engraftment and outcome after autologous stem cell transplantation in plerixafor-mobilized non-Hodgkin's lymphoma patients. Transfusion 2014;54(5):1243–50.
[42] Micallef IN, Stiff PJ, Nademanee AP, Maziarz RT, Horwitz ME, Stadtmauer EA, Kaufman JL, McCarty JM, Vargo R, Cheverton PD, Struijs M, Bolwell B, DiPersio JF. Plerixafor Plus Granulocyte Colony-Stimulating Factor for Patients with Non-Hodgkin Lymphoma and Multiple Myeloma: Long-Term Follow-Up Report. Biol Blood Marrow Transplant 2018;24(6):1187–95.
[43] Chen J, Pan J, Zhan T, Tuazon S, Saini N, O'Hara W, Filicko-O'Hara J, Klumpp T, Kasner M, Carabasi M, Porcu P, Wagner JL. Autologous Stem Cell Transplantation for Multiple Myeloma: Growth Factor Matters. Biol Blood Marrow Transplant 2019;25(9):e293–7.
[44] Shah H, Kim S, Singh P, Alavi A, Ratanatharathorn V, Ayash L, Uberti J, Deol A. Clinical outcomes of multiple myeloma patients who undergo autologous hematopoietic stem cell transplant with G-CSF or G-CSF and plerixafor mobilized grafts. Am J Hematol 2020;95(2):198–204.
[45] Ando K, Chou T, Suzuki K, Shinagawa A, Uchida T, Taniwaki M, Hirata H, Ishizawa K, Matsue K, Okamoto S, Otsuka M, Matsumoto M, Iida S, Matsumura I, Ikeda T, Takezako N, Ogaki Y, Midorikawa S, Houck V, Ervin-Haynes A, Terui Y. [Lenalidomide and low-dose dexamethasone therapy for Japanese patients with newly diagnosed multiple myeloma: updated results of the MM-025 study]. Rinsho Ketsueki 2017;58(11):2219–26.
[46] Suzuki K, Shinagawa A, Uchida T, Taniwaki M, Hirata H, Ishizawa K, Matsue K, Ogawa Y, Shimizu T, Otsuka M, Matsumoto M, Iida S, Terui Y, Matsumura I, Ikeda T, Takezako N, Ogaki Y, Midorikawa S, Houck V, Ervin-Haynes A, Chou T. Lenalidomide and low-dose dexamethasone in Japanese patients with newly diagnosed multiple myeloma: A phase II study. Cancer Sci 2016;107(5):653–8.
[47] Vasu S, Leitman SF, Tisdale JF, Hsieh MM, Childs RW, Barrett AJ, Fowler DH, Bishop MR, Kang EM, Malech HL, Dunbar CE, Khuu HM, Wesley R, Yau YY, Bolan CD. Donor demographic and laboratory predictors of allogeneic peripheral blood stem cell mobilization in an ethnically diverse population. Blood 2008;112(5):2092–100.
[48] Hsu JW, Wingard JR, Logan BR, Chitphakdithai P, Akpek G, Anderlini P, Artz AS, Bredeson C, Goldstein S, Hale G, Hematti P, Joshi S, Kamble RT, Lazarus HM, O'Donnell PV, Pulsipher MA, Savani BN, Schears RM, Shaw BE, Confer DL. Race and ethnicity influences collection of granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells from unrelated donors, a Center for International Blood and Marrow Transplant Research analysis. Biol Blood Marrow Transplant 2015;21(1):165–71.
[49] Uzoka C, Liu LC, Park Y, Lin Y, Patel P, Campbell-Lee S, Sweiss K, Wang X, Tepak E, Peace D, Saraf S, Rondelli D, Mahmud N. Race/ethnicity and underlying disease influences hematopoietic stem/progenitor cell mobilization response: A single center experience. J Clin Apher 2021;36(4):634–44.