Safety and efficacy of outpatient-based administration of granulocyte colony-stimulating factor in collection of allogeneic peripheral blood stem cells: 10 years of single-center experience in 86 donors

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Our policy has been to administer granulocyte colony-stimulating factors (G-CSF) for the mobilization of peripheral blood stem cells (PBSC) on an outpatient basis. We evaluated the safety of G-CSF-administered PBSC donation in outpatients and inpatients. Subjects : PBSC donations from 86 healthy donors (78 related, 8 unrelated) between January 2011 and December 2019 were included; 74 donors were administered G-CSF as outpatients, and 12 while under hospitalization. Evaluation of the length of hospital stay (LOHS) : LOHS of the donors who were administered G-CSF as outpatients (median, 2 days; range, 1 to 4 days) was significantly shorter than that of the inpatient donors (median, 4.5; range, 4 to 5) ($P<0.0001$). Adverse events of G-CSF administration : There was no significant difference in the incidence of adverse events related to G-CSF administration between the donors who were administered G-CSF as outpatients and those as inpatients ($P=0.1786$). Efficacy of PBSC mobilization : Most donors donated sufficient PBSC (median $CD34^+ \times 10^6$ cells/kg recipient body weight, 5.65). There was no significant difference in the number of collected $CD34^+$ cells between the two groups ($P=0.6671$). Conclusion : Outpatient-based administration of G-CSF for PBSC mobilization was feasible without compromising donor safety or PBSC donation efficacy.

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Key Points

We retrospectively evaluated the safety of G-CSF-administered PBSC donation in outpatients ($n=74$) and inpatients ($n=12$). There was no significant difference in the incidence of adverse events related to G-CSF administration between outpatients and inpatients.

Outpatient-based administration of G-CSF for PBSC mobilization was feasible without compromising donor safety.

Introduction

The collection of hematopoietic stem cells mobilized from the bone marrow into the bloodstream of healthy donors has

now become a routine procedure throughout the world,¹ with at least comparable or safer toxic profile compared to bone marrow collection.² For the mobilization of peripheral blood stem cells (PBSC), administration of granulocyte colony-

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stimulating factors (G-CSF) for 4 to 6 consecutive days is necessary.³⁻⁶ In Japan, more than 80% of donors have been hospitalized during the period of G-CSF administration.^{7,8}

Our policy has been to administer G-CSF for the mobilization of PBSC on an outpatient basis. Donors are hospitalized the day before PBSC collection, and are discharged the day after the collection is completed. In this study, we evaluated the safety of PBSC donation in related and unrelated donors as outpatients and inpatients in our department who were administered G-CSF during the period from 2011 to 2019.

Methods

Subjects

The PBSC mobilization protocol was in accordance with The Japan Society for Hematopoietic Cell Transplantation (JSHCT) formal standards.^{7,9} PBSC collections in accordance with these procedures between January 2011 and December 2019 from 86 healthy donors were included. All apheresis procedures were performed 4-6 days after start of G-CSF administration. Donors were given recombinant human G-CSF (filgrastim) ($400 \mu\text{g}/\text{m}^2/\text{day}$ filgrastim, Kyowa Kirin Co., Ltd., Tokyo, Japan) subcutaneously, daily until the morning of the last apheresis session.

Complete blood counts (CBCs) were analyzed every day before the administration of G-CSF. Our policy has been to administer G-CSF on an outpatient basis. Twelve donors were hospitalized at the beginning of G-CSF administration, because their places of residence were far from our hospital. Donors were encouraged to contact our hospital immediately if they experienced fever, severe pain, dyspnea, or severe fatigue. All medical staff, including doctors and outpatient and ward nurses in the hematology section, were educated about adverse events during G-CSF administration to healthy donors, and a hospital system was established to provide appropriate initial response.

This study was reviewed and approved by the institutional review board of the Ethics Committee of the Kurume University School of Medicine.

G-CSF administration

CBCs were checked before each administration of filgrastim. The standard dose of filgrastim was $400 \mu\text{g}/\text{m}^2$. The filgrastim dose was reduced to $200 \mu\text{g}/\text{m}^2$ when white blood cell (WBC) count was $\geq 50,000/\text{mm}^3$, and/or platelet count was $\leq 100,000/\text{mm}^3$; and filgrastim administration was dis-

continued when WBC count was $\geq 75,000/\text{mm}^3$, and/or platelet count was $\leq 50,000/\text{mm}^3$.

Blood cell counts and flow cytometry

Blood cell counts were performed using an electronic cell counter (XE-5000, Sysmex Corporation, Kobe, Japan). The number of CD34^+ cells was determined by flow cytometry (Cytomics FC 500, Beckman Coulter, Fullerton, CA, until August 2018) and FACSCanto II (Becton Dickinson, Franklin Lakes, NJ, from September 2018) with anti-CD34 and anti-CD45 fluorescent markers, using a standard single-platform method. For Cytomics FC500, Stem-Kit (Beckman Coulter, Fullerton, CA) was used, and for FACSCanto II, BD Stem Cell Enumeration Kit (Becton Dickinson, Franklin Lakes, NJ) was used, following standard procedure manuals.

PBSC collection

Apheresis was performed with a COBE Spectra apheresis system between 2011 and 2014, and a Spectra Optia system between 2015 and 2019 (Terumo BCT, Tokyo, Japan). In the COBE Spectra system, Spectra-Auto (Version 6.1) was used,^{5,10} and in the Spectra Optia system, MNC mode (Version 9) was used. In all cases, the manufacturer's protocols were followed. In brief, in both the Spectra-Auto and Spectra Optia MNC modes, mononuclear cells are collected by continuous-flow centrifugation. In each instrument, initial inlet flow rates of 35 and 75 mL/min, and 12 : 1 and 15 : 1 ratios of whole blood to ACD-A solution (Terumo) were used, respectively. The target volume processed was two to three times the total blood volume of the donor.

PBSCs were collected via bilateral (anterior cubital and forearm) peripheral venous access, whenever possible, or otherwise via a central line in the femoral vein.

Statistical analyses

Quantitative variables were described in terms of mean, standard deviation, median, and range. For qualitative variables, absolute and relative frequency distribution were calculated. Comparisons between groups were performed with non-parametric Mann-Whitney U test. Fisher's exact test was used to analyze categorical values. Results were considered significant when p values were not more than 0.05. Statistical analyses were performed using SAS computer software ver. 9.4 (SAS Institute Inc., Cary, NC).

Table 1. Characteristics of the studied groups

	Total	Outpatients	Hospitalized	
No. of donors	86	74	12	
Sex				
Male	52	43	9	
Female	34	31	3	
Age				
Median (range)	38 (19-65)	37.5 (19-65)	39 (21-56)	$P=0.8663$
19-30	20	18	2	
31-40	32	27	5	
41-50	21	18	3	
51-	13	11	2	
Related/Unrelated				
Related	78	71	7	
Unrelated	8	3	5	
Length of Hospital Stay (LOHS) (days)	median, 3; range, 1 to 5	median, 2; range, 1 to 4	median, 4.5; range, 4 to 5	$P<0.0001$
Administration period of G-CSF (days)				
4	37	31	6	
5	49	43	6	

Results

Donor Characteristics

A total 86 consecutive donors were included in this study; baseline characteristics are shown in **Table 1**. The subjects included 78 related and 8 unrelated donors; 52 were male and 34 female; median age 38, range from 19 to 65; 74 donors were administered G-CSF as outpatients, and 12 donors were administered G-CSF as inpatients. The median age of the donors who were administered G-CSF as outpatients was 37.5, ranging from 19 to 65, and those of the donors who were administered G-CSF as inpatients was 39, ranging from 21 to 56; there was no significant difference between the groups ($P=0.8663$).

Evaluation of the length of hospital stay (LOHS)

In total, median LOHS was 3 days, ranging from 1 to 5 days.

For donors with the outpatient-based administration of G-CSF, median LOHS was 2, ranging from 1 to 4 days. For donors hospitalized at the beginning of G-CSF administration, median LOHS was 4.5, ranging from 4 to 5. Hospital stay of the donors who were administered G-CSF as outpatients was significantly shorter than that of the donors who were administered G-CSF as inpatients ($P<0.0001$) (**Table 1**).

Dose modification of G-CSF

Among the 86 donors, reduction of G-CSF dose was required in 36 donors due to high WBC counts. The dose reduction was required on the second day in 2 donors, on the third day in 11, on the fourth day in 16, and on the fifth day in 7 donors. Thus, 41.9% (36 out of 86 donors) required dose reductions of G-CSF (**Figure 1**). No donor required a reduction of G-CSF dose due to thrombocytopenia or other adverse events.

Adverse events of G-CSF administration

Adverse events of the donors during PBSC mobilization are shown in **Table 2**.

There was no significant difference in the incidence of adverse events associated with G-CSF administration between the donors who were administered G-CSF as outpatients and the donors who were administered G-CSF as inpatients ($P=0.1786$). The predominant side effect of G-CSF administration were bone pain and lumbago, either of which was reported in 66 (89.1%) of the 74 outpatient donors and 9 (75.0%) of the 12 inpatient donors. Of these donors, 61 required acetaminophen or other analgesics. Headache occurred in 19 (25.7%) of the 74 outpatient donors and 3

Figure 1. Dose modification of G-CSF. Among 86 donors, reduction of G-CSF dose was required in 36 donors due to high WBC counts. The dose reduction was required on the second day in 2 donors, on the third day in 11, on the fourth day in 16, and on the fifth day in 7 donors. Thus, 41.9% (36 out of 86 donors) required dose reductions of G-CSF.

Table 2. Adverse events of G-CSF and leukapheresis

Treatment	Adverse events	Event names	Total (n=86)	Outpatients (n=74)	Hospitalized (n=12)	P-value
G-CSF						
	No		11	8	3	
	Yes		75	66	9	0.1786
		Bone pain, lumbago	75 (G1: 62/G2: 13)	66 (G1: 61/G2: 4)	9 (G1: 9)	
		Headache	22 (G1: 21/G2: 1)	19 (G1: 18/G2: 1)	3 (G1: 3)	
		General malaise	17 (G1: 16/G2: 1)	16 (G1: 15/G2: 1)	1 (G1: 1)	
		Fever	1 (G1: 1)	1 (G1: 1)	0	
		Others	6	4	2	
		Nausea	4 (G1: 4)	3 (G1: 3)	1 (G1: 1)	
		Sleeplessness	2 (G1: 2)	1 (G1: 1)	1 (G1: 1)	
Analgesics						
	No		25	22	3	
	Yes		61	52	9	1.0000
Leukapheresis						
	No		47	40	7	
	Yes		39	34	5	1.0000
		Paresthesia	37 (G2: 36/G3: 1)	33 (G2: 33)	4 (G2: 3/G3: 1)	
		Muscle cramp	1 (G2: 1)	1 (G2: 1)	0	
		Vasovagal reflex	1 (G3: 1)	0	1 (G3: 1)	

(25.0%) of the 12 inpatient donors. Flu-like symptoms (e.g., general malaise) and other symptoms appeared in a total of 17 donors. There was no case of splenic rupture in the donors investigated. No donor discontinued G-CSF administration because of side effects of G-CSF.

Adverse events of leukapheresis

There was no significant difference in the incidence of adverse events associated with leukapheresis between the

donors who were administered G-CSF as outpatients and the donors who were administered G-CSF as inpatients (**Table 2**) ($P=1.000$). The most frequent symptom during leukapheresis was paresthesia associated with hypocalcemia. Paresthesia occurred in 34 (45.9%) of the 74 outpatient donors and 4 (33.3%) of the 12 inpatient donors. Paresthesia was mild or moderate in 38 donors and quickly disappeared after intravenous calcium substitution. Other problems, such as circulatory disturbances, fatigue, or pain at the site of venipuncture, occurred infrequently. Access via the femoral vein was

Figure 2. Efficacy of PBSC collection: Outpatient versus Hospitalized. For 74 donors with the outpatient-based administration of G-CSF, median $CD34^+ \times 10^6$ cells/kg recipient body weight was 5.65, ranging from 1.4 to 22.7; 4 donors with yield of less than 2×10^6 /kg recipient body of $CD34^+$ cells were included. For 12 donors hospitalized at the beginning of G-CSF administration, median $CD34^+ \times 10^6$ cells/kg recipient body weight was 5.2, ranging from 2.8 to 10.7.

required in 2 female donors, without adverse events associated with vascular access.

Efficacy of PBSC mobilization

Most donors donated sufficient PBSC; median $CD34^+ \times 10^6$ cells/kg recipient body weight was 5.65, ranging from 1.4 to 22.7. In 4 donors, the $CD34^+$ cell yield was less than 2×10^6 /kg recipient body. For 74 donors who received outpatient-based administration of G-CSF, median $CD34^+ \times 10^6$ cells/kg recipient body weight was 5.75, ranging from 1.4 to 22.7; 4 donors with yield of less than 2×10^6 /kg recipient body of $CD34^+$ cells were included. For 12 donors hospitalized at the beginning of G-CSF administration, median $CD34^+ \times 10^6$ cells/kg recipient body weight was 5.2, ranging from 2.8 to 10.7 (**Figure 2**). There was no significant difference in the number of collected $CD34^+$ cells between the two groups ($P = 0.6671$).

Discussion

The numbers of related and unrelated donors with allogeneic PBSC in Japan have been increasing steadily. According to the Hematopoietic Cell Transplantation in Japan, Annual Report of Nationwide Survey 2019,¹¹ the number of allogeneic PBSC transplantations in 2018 was 1,081. In Japan, the PBSC mobilization and collection have been conducted in accordance with JSHCT formal standards^{7,9} to ensure donor

safety. According to a mandatory registration system by JSHCT during 2000 to 2005, acute severe adverse events (SAEs) within 30 days were reported from 47/3,264 donations (1.44%), with 14 events considered as unexpected and severe (0.58%). The incidence of acute SAEs was significantly higher among donors not matching the JSHCT standards (6.98%) compared to those matching (1.37%) ($P = 0.00213$). Fortunately, so far there has been no fatal case among PBSC donors in Japan.⁹ Thus, by observing the JSHCT formal standards, PBSC donation can be performed safely in Japan.

In Europe and United States, PBSC mobilization and collection have been performed on an outpatient basis without hospitalization of donors.^{12,13}

On the contrary, in Japan, more than 80% of PBSC mobilizations and collections have been performed with hospitalization of donors. The reason why most donors are hospitalized during G-CSF administration in Japan is multifactorial. These include that the operation system of outpatient departments on weekends is different from weekdays, and the threshold for hospitalization is low, both derived from Japanese health care system. Different from bone marrow collection, PBSC collection requires neither general anesthesia nor preoperative autologous blood storage, which are advantages of PBSC collection compared to bone marrow collection. However, PBSC collection requires G-CSF administration for 4 to 5 consecutive days. If the whole process of G-CSF administration is performed in an inpatient, the donor must stay at hospital for 4 to 5 days, longer than for bone marrow donors, who stay at hospital basically for 4 days in Japan. Hospitalization of healthy related or unrelated donors impair their daily life.

So far, there have been no reports with detailed data on donor safety when G-CSF was administered to outpatients in Japan. In this retrospective analysis of PBSC mobilization and collection in our department, more than 80% of donors were administered with G-CSF as outpatients; 14% of donors were hospitalized for G-CSF administration because their places of residence were far away, and outpatient-based G-CSF administration was rather inconvenient. There was no unplanned hospitalization or SAE during G-CSF administration to outpatients.

The most common adverse events were bone pain and headache, as expected, and those were well-controlled with acetaminophen.^{9,12-14} No SAEs (CTC-AE grade 3 or more) were observed. For 74 donors who received outpatient-based administration of G-CSF, the median LOHS was 2 days, rang-

ing from 1 to 4.

Thus, this analysis clearly demonstrated that G-CSF can be administered safely and effectively to PBSC donors. However, in our practice, donors should come to our clinic daily for evaluation of CBCs. Of the 86 donors, 36 (41.9%) experienced dose modification of G-CSF due to excessive increase of leukocytes (more than 50,000/mm³). There was no dose reduction of G-CSF due to significant thrombocytopenia or other SAE. Because we did not conduct dose modification of G-CSF due to thrombocytopenia, and because G-CSF is administered without measuring CBCs in other countries, we can re-consider the necessity of daily evaluation of CBCs during G-CSF administration. The clinical significance of the excessive increase of leukocytes during G-CSF administration remains to be clarified. If daily CBCs are not necessary, G-CSF could be administered by a nearby practitioner or by self-injection.

G-CSF administration to PBSC donors could result in rare SAEs such as acute respiratory distress,¹⁵⁻¹⁷ splenic rupture,^{18,19} and so on.²⁰ Thus, it is very important to explain to both donors and medical staff the possible adverse events of G-CSF, how the adverse events should be handled, and the means to contact doctors or nurses in case of emergency before the start of G-CSF administration.

In the protocol of our hospital, donors are hospitalized the day before PBSC collection, and are discharged the day after the collection is completed. It might be possible to collect PBSC without hospitalization, as is done in Europe and United States. Because PBSC collections were conducted using a kidney dialysis unit in our hospital, coordination within the hospital was required.

In order to further develop allogeneic PBSC transplantation in the future, it is necessary to give thoughtful attention to donor convenience while giving the highest priority to donor safety.

In conclusion, according to this retrospective analysis in a single institute, G-CSF can be administered safely to Japanese PBSC donors as outpatients. To maximize both donor safety and donor convenience, optimization of the protocol for PBSC mobilization and collection is desired in Japan.

Conflict of Interest disclosure

KN received research funding from Kyowa Kirin Co., Ltd.

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