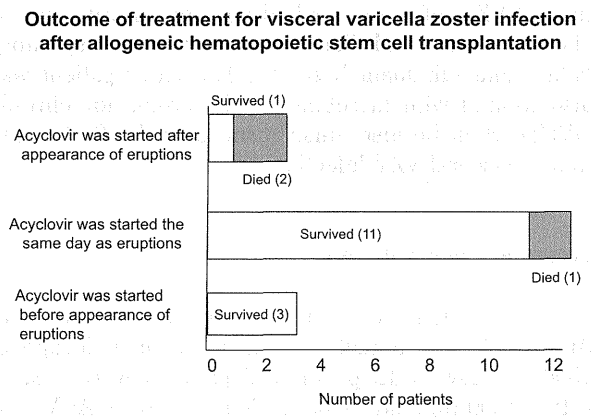

Fig. 1. Outcome of treatment for visceral varicella zoster virus infection after allogeneic hematopoietic stem cell transplant. Treatment with intravenous acyclovir was started before the appearance of eruptions in 3 of the 18 patients who had vesicular eruptions (all 3 survived); the same day in 12 patients (11 survived, 1 died); and after the appearance of eruptions in 3 patients (1 survived, 2 died).

patients with active GVHD had visceral VZV infection even later than 9 months after transplantation.

Most clinical symptoms of visceral VZV infection are associated with abdominal pain in many case reports. David et al. (4) reported that all 10 patients had abdominal pain at the onset. The symptoms of visceral VZV infection in the current series were abdominal pain (80%), unconsciousness (15%), and no symptoms (5%). The pain was located in the epigastric region and dissimilar from the dermatome-limited pain that can characterize the zoster prodrome. This pain was most likely a result of stretching of the Glisson's capsule secondary to hepatitis, VZV-induced pancreatitis, or VZV gastritis (4).

Eighteen patients (90%) had vesicular eruptions, and 2 (10%) had no eruptions. Although many patients present with eruptions, some reports (6–9) reveal patients without eruptions of VZV infection. The occurrence of visceral dissemination in HSCT recipients without any signs of cutaneous disease demonstrates that cell-associated viremia can occur without replication of the virus in skin, presumably by entry of virus into T cells that traffic through sensory ganglia (5, 6).

The current study demonstrates that the mortality rate of visceral VZV infection in recipients of allo-HSCT is 20%. Previous studies (4, 5) showed that the mortality is about 50% among patients with visceral dissemination. David et al. (4) reported that the mean time interval from onset of visceral symptoms to diagnosis was 7 days (range 4–14 days). Antiviral therapy was promptly initiated after the diagnosis of varicella infection. On the other hand, 15 (83%) of the 18 patients with vesicular eruptions in the current study were treated with IV ACV before or on the same day that the eruptions appeared. The interval from onset to diagnosis was shorter than that previously reported (4).

Several studies have shown that long-term prophylactic ACV at 400 mg/day, which is continued until the end of immunosuppressive therapy, successfully decreases the cumulative incidence of VZV disease, even after the discontinuation of ACV (10–12). However, 3 of the patients who developed visceral VZV infection in the current series were on prophylactic ACV at the time of onset. All of these patients were treated with immunosuppressive agents, and the onset of infection was on day 118, day 175, and day 210. Two patients were given 200 mg/day of ACV and 1 patient received 600 mg/day. We did not examine susceptibility to the virus. However, as all 3 patients could respond to the treatment, we assumed that they did not have the resistant virus. These results suggest that patients who are on prophylactic ACV may develop visceral zoster.

Administration of empiric therapy before the appearance of eruptions contributed to patient survival (Fig. 1). Therefore, early IV treatment using an appropriate dosage is effective. Hence, early diagnosis and treatment are important.

In summary, visceral VZV infection after allo-HSCT is a rare complication, but it is associated with high mortality. The possibility of a visceral VZV infection must be considered when patients with chronic GVHD or those being treated with immunosuppressive agents demonstrate abdominal pain or unconsciousness. Therefore, such patients should receive early IV treatment using 30 mg/kg of ACV/day. In conclusion, patients who are on prophylactic ACV are still at risk of developing visceral VZV infection.

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ORIGINAL ARTICLE

PBSC collection from family donors in Japan: a prospective survey

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Severe adverse events (SAE) and late hematological malignancies have been reported after PBSC donation. No prospective data on incidence and risk factors have been available for family donors so far. The Japan Society for Hematopoietic Cell Transplantation (JSHCT) introduced therefore in 2000 a mandatory registration system. It defined standards for donor eligibility and asked harvest centers to report any SAE immediately. All donors were examined at day 30 and were to be contacted once each year for a period of 5 years. Acute SAEs within day 30 were reported from 47/3264 donations (1.44%) with 14 events considered as unexpected and severe (0.58%). No donor died within 30 days. Late SAEs were reported from 39/1708 donors (2.3%). The incidence of acute SAEs was significantly higher among donors not matching the JSHCT standards ($P=0.0023$). Late hematological malignancies in PBSC donors were not different compared with a retrospective cohort of BM donors (N:1/1708 vs N:2/5921; $P=0.53$). In conclusion, acute and late SAEs do occur in PBSC donors at relatively low frequency but risk factors can be defined.

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Keywords: PBSC harvest (PBSCH); family donors; prospective study; acute adverse events; late health problems; predictive factors

INTRODUCTION

Allogeneic PBSC harvest has gained wide acceptance for hematopoietic SCT (HSCT). The stem cell harvest procedure is more convenient for both donors and medical teams,[1–3] the speed of post-transplant, hematological recovery is faster in recipients,[4–7] and outcomes are similar compared to that of BMT.[8–10] However, there have been occasional reports of mortalities[11–15] and severe complications such as splenic rupture.[16,17] Most of these severe adverse events (SAE) occurred with family donors, appeared as anecdotal or were based on retrospective analyses. No standardized or centralized reporting database was available 13 years ago.[18] Therefore, a prospective reporting study was initiated for family donors in Japan in the year 2000 to monitor the types and frequencies of adverse events potentially associated with PBSC donation, and to define factors associated with such events. We present here a comprehensive report summarizing the early adverse events (defined as within 30 days post donation) and late adverse events within 5 years post donation among 3264 consecutively pre-registered PBSC family donors from April 2000 to March 2005. The follow-up was completed in March 2010 and the data were analyzed as of September 2010. Furthermore, these PBSC donor data have been compared with the BM family donor data obtained via retrospective questionnaires shared with EBMT.[19]

MATERIALS AND METHODS

Study design

This was a prospective controlled study on all PBSC donations in Japan for a period of 5 years of recruitment and 5 years of additional follow-up. The prospective study was accompanied by a retrospective survey of an earlier cohort of patients transplanted with BM as stem cell source.

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JSHCT pre-registration mailings to institutes in 2000

JSHCT provided information to all hematology teams that were performing allogeneic PBSC transplants in 2000 or were interested in doing so. The package included: standards for donor eligibility; guidelines for G-CSF mobilization, harvest and storage of PBSC; informed consent form; donor pre-registration instructions including donor name, birth date, gender, relationship to recipient, agreement to annual health check, compliance with JSHCT standards, past/present illness, batch of G-CSF and preliminary information on recipient; donor follow-up procedure and acute SAEs report form. The registration period extended from 1 April 2000 to 31 March 2005 (5 years) and the annual long-term follow-up for 5 years was scheduled for each individual donor from April 2001 to March 2010. A day 30 short-term report had to be submitted in the fourth week after the harvest with the following information: (1) donor profiles, (2) laboratory data pre- and post donation, (3) dose of G-CSF and batch details, (4) harvested PBSC count and (5) any adverse events other than those urgently reported. A long-term report was sent by JSHCT to all donors who did consent to follow-up. It contained the following information: (1) current laboratory data and (2) any adverse events before the day of each health check. The participating transplant/harvest teams were obliged to report any adverse events to the JSHCT registration center via an emergency reporting system. Acute and late SAEs were defined as follows: (1) death, (2) events dangerous to life, (3) prolongation of hospitalization, (4) morbidity, (5) potential morbidity, (6) other events with levels equivalent to (1)–(5), (7) disease or abnormality inherited to offspring and (8) any malignancy ((7) and (8) were designated only for late events).

JSHCT eligibility criteria for PBSC family donors

The JSHCT did define formal standards for the eligibility of PBSC family donors. They were in part derived from blood donation standards, in part out of safety concerns: donor candidates should not have (1) allergy to G-CSF, (2) pregnancy, (3) cardiovascular risk factors defined as history of hypertension, coronary disease, cerebrovascular disease, diabetes mellitus or hyperlipidemia (4) splenomegaly determined by sonography, (5) hematological abnormality, (6) history of of interstitial pneumonitis, (7) history of of any malignancy, (8) ongoing heart, lung or renal disease requiring treatment, (9) ongoing autoimmune disease, (10) ongoing liver disease or (11) history of neurological disorders. Recommended donor age was between 10 and 65 years. Finally, each harvest team was required to have a third-party team to confirm the eligibility of each donor. The harvest team was free to choose a non-JHSCT-standard donor upon request of the family or the patient if no other donor was available; in any case they had to report the donor follow-up as well. No information was obtained on the number of donors rejected during the donor check-up evaluation or on the factors associated with such a decision.

Comparison with adverse events in BM family donors in Japan

To compare the frequency and the SAEs among PBSC donors to those of BM donors, a retrospective survey was conducted in collaboration between JSHCT members and EBMT for all BM donations between 1990 and 2004. The questionnaire items covered (1) any death within 30 days after donation of BM cells, (2) any SAE within 30 days after donation of BM cells and (3) any hematological malignancies (lymphoid/myeloid) at any time post donation of BM in recipients. These items were identical as reported earlier by the European Group for Blood and Marrow Transplantation EBMT.[19]

Statistical analysis

Correlation between groups was examined using the χ^2 test. Incidence of low-frequency events was compared using a Poisson regression analysis. Data were analyzed with STATA statistical software (Stata Cooperation, College Station, TX, USA). Predictive factors on PBSC donation outcomes within 30 days were examined by a logistic regression model. Factors included in the model were (1) donor profiles age (<19, 20–59 and >60 years), gender, body weight (<39, 40–69 and >70 kg), past and current health conditions and previous PBSC donation, (2) pre-and post-donation laboratory data, (3) total dose of G-CSF administered (<2499, 2500–2999, 3000–3499, >3500 μg, converted into dose of Filgrastim), (4) the occurrence of any adverse events such as thrombocytopenia, prolongation of hospitalized period, any clinical symptoms (bone pain, fatigue, headache, insomnia, anorexia, nausea and vomiting), splenomegaly and (5) numbers of mobilized CD34+ cells.

All statistical analyses were performed using the Statistical Analysis System (SAS 9.1, Cary, NC, USA).

RESULTS

Participation in the Japanese family donor PBSC pre-registration system

From 1 January 2000 to 31 March 2005, data on 3264 PBSC donations from 3188 donors (3114 with one, 72 with two and 2 with three donations) were reported to the registration system by 233 harvest teams (see Supplementary Information). This corresponds to the participation of 231 out of the 311 transplant teams that performed allogeneic HSCT during this time period (74.3%). The participating teams performed a total of 11 405 allogeneic HSCT during the same time period; hence, the proportion of PB donation concerned 28% of all allogeneic HSCT. Over the same period, the JSHCT patient registry independently reported 3262 PBSC transplants from family donors (data not shown). This confirms a close correspondence between the donors included in this survey and the actual total PBSC donations performed in Japan during this period. From the 3264 donations, 2873 (88.0%) day 30 check reports were submitted and analyzed. At the close of the projects in March 2010, 6233 reports of annual health checks had been submitted from 1708 donors. Of these 1708, 833 received all five consecutive annual health checks. The numbers of pre-registration, day 30 reports and the annual health-check forms are summarized in Figure 1.

Early SAEs

Out of 3264 PBSC donations, 47 donors (1.44%) were reported by the harvest teams to have experienced one or more SAEs either during the harvest or within the 30-day period as summarized in Table 1. The 47 events were classified by the JSHCT into three subgroups: (1) unexpected and severe (19; 0.58%), (2) transient, probably G-CSF-associated (9; 0.27%) and (3) transient, probably apheresis-associated (19; 0.58%). Some SAEs were potentially life-threatening (subarachnoid hematoma, interstitial pneumonitis), still all donors recovered. All SAEs were reported immediately as requested by the system. A comparison of the urgently reported SAEs with the standard day 30 reports revealed no inconsistencies or additional events.

Factors associated with early outcomes

The factors associated with early outcomes are summarized in Table 2. Risk factors for thrombocytopenia were higher total dose of G-CSF and older age. Risk factors for prolonged hospitalization were older age, low body weight, higher total dose of G-CSF, any past and present illness and previous stem cell donations. Risk

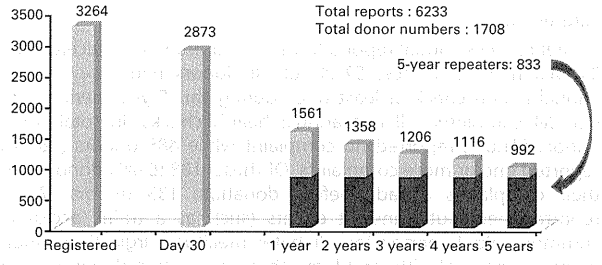

Figure 1. The cumulative numbers of pre-registered donors and Day 30 reports for 5 years, and the status of 5-year follow-up of each donor (April 2000—March 2010) are shown. The numbers of pre-registered donors, the numbers of donors whose day 30 reports were submitted and the numbers of donors who received annual health check at least once for their 5-year follow-up period are 3264, 2873 and 1708, respectively.

Table 1. Forty-seven acute severe[a] adverse events reported as emergencies to the JSHCT donor registration center between April 2000 and March 2005

	Onset	*Resolved*
Unexpected and severe[b]: 19 (/3264 = 0.58%)		
Angina attack with or without hypoxemia (4)	Days 2–4	Days 4–6
Deep vein thrombosis	Day 14	—
Ascites, pericardial effusion and general edema	Day 7	Day 9
Hemosputum	Day 3	Day 5
Subarachnoidal hematoma	Day 23	Day 48 (Ope)
Retroperitoneal hematoma/ Anemia	Day 4	Day 25 (Ope)
Gastric ulcer with bleeding	Day 8	Day 16
Interstitial pneumonitis (2)	Day 3	Day 6
	Day 25	Day 70
Cholangitis and gout attack	Day 2	Day 19 (Ope)
Fever and (or) Infection (5)	Days 2–7	Days 12–32
Disc herniation	Day 7	Day 62 (Ope)
Probably G-CSF-related, transient[b]: 9 (/3264 = 0.27%)		
Liver dysfunction (8)	Days 3–10	Days 11–36
Anorexia, nausea and vomiting	Day 4	Day 19
Probably apheresis-related, transient[b]: 19 (/3264 = 0.58%)		
Thrombocytopenia (1.8–6.6 × 104/mL) (13)	Days 2–6	Days 8–111
Vagovagal reflex (2)	Day 4	Days 4–5
Tetany	Day 4	Day 6
Hypesthesia of extremities	Day 4	Day 6
Hematoma of the leg	Day 7	Day 13
Migraine attack	Day 9	Day 10

Abbreviation: Ope, received surgical operation. ( ): case numbers. [a]Judged by harvest team. [b]Classified by JSHCT donor registration center.

factor for bone pain was any present illness. Female gender was the only risk factor for fatigue, headache, insomnia, anorexia or nausea. Younger age was a risk factor for vomiting. Risk factors for splenomegaly (>150% enlargement from baseline by abdominal sonography) were older age and higher total dose of G-CSF. Risk factors for lower CD34+ cell mobilization/donor body weight ($<2 \times 10^6$ CD34+ cells/kg) were age above 60 years (HR 2.55, $P<0.01$), female gender (HR 1.52, $P<0.01$) and previous stem cell donation (HR 3.10, $P<0.001$). Age below 20 years (HR 2.81, $P<0.001$) was the only parameter associated with higher CD34+ cell mobilization/donor body weight ($>9 \times 10^6$ CD34+ cells/kg).

Late events

A total of 6233 annual reports from 1708 donors were received by 31 March 2010. Hence, 52.3% of all donors had received the annual health check at least once during this 5-year period; 833 (25.5%) completed all five annual health checks. In total, 1223 donors (71.6%) reported no complaint while 485 donors (28.4%) reported one or more complaints. Of these, 108 (6.4%) donors had their complaints already before donation; 133 donors (7.8%) reported new but transient events (such as a traffic accident, common cold, hypertension, diabetes mellitus, surgical operation or pregnancy). Health problems that arose after donation and could have been related to the donation were reported by 243 (14.2%) donors. They were classified by JSHCT in 204 cases (11.9%) as non-malignant and non-significant diseases, in 26 (1.5%) as non-malignant but significant diseases, in 12 (0.7%) as non-hematological malignancies and in 1 (0.06%) as hematological malignancy.[20] Hence, 39 of 1708 donors (2.3%) were considered to have had severe complications that could have been related to the donation as judged by either the harvest teams or the JSHCT registration center. Classified as non-malignant but significant events were seven donors with thyroid dysfunction (10–34 mo), three with uterine fibroid (14–36 mo), two with rheumatoid arthritis (20, 23 mo), two with cerebral infarction (7, 33 mo) and one each with subarachnoidal hemorrhage, (9 mo), cataract (7 mo), ocular bleeding (33 mo), atopic dermatitis (12 mo), uveitis (20 mo), bronchial asthma (20 mo), ITP (27 mo), endometriosis (20 mo), mole (9 mo), cerebral aneurysm (24 mo), pancreatic cyst (53 mo) and IgA nephritis (44 mo). The 12 cases of non-hematological malignant diseases reported were 6 donors with breast cancer (4~43 mo) and one each with gastric cancer (23 mo), uterus cancer (10 mo), brain tumor (6 mo), pharyngeal cancer (13 mo), lung cancer (54 mo) and prostatic cancer (55 mo). There was one case of hematological malignancy (0.06%) and one donor developed AML. It should be noted that one donor with a chronic myeloproliferative disorder at the time of donation (defined later), who developed acute myelogeneous leukemia 4 years after donation, was not included among the 39 cases.

Donor eligibility and frequency of severe acute and late events

Out of 3264 donors, 133 (4.07%) did not meet the eligibility criteria, 90 because of age (53 older and 37 younger than required by the standards) and 43 because of concurrent health problems. Follow-up with the annual health check was the same, for donors meeting or not meeting the standards at donation (4.3%, 74 donors). As indicated in Table 3, acute and late events tended to increase with age, although neither association was statistically significant. In contrast, early SAEs but not late events were clearly and significantly associated with concurrent health problems at the time of donation.

Comparison of adverse events between PBSC donation (prospective study) and BM donation (retrospective study) of family donors in Japan

To estimate the incidence of acute and late adverse events among BM family donors in Japan, questionnaires corresponding to those used by EBMT[19] were sent to 286 transplant teams belonging to JSHCT. A total of 191 teams (67%) responded with information from 5921 BM harvests from family donors performed between 1991 and 2003. Based on the HSCT Recipient Registry information, ~89.7% of all related BMTs performed in Japan during the reporting period were represented. One of the 5921 donors, who died 1 year after BM donation following anoxia and brain damage during harvest, was counted as a death within 30 days following donation.[21] SAE within 30 days of donation occurred in 25 out of the 5921 (0.42%) donors (for details see Table 4). As for hematological malignancies, 2 donors developed AML after BM donation. The frequencies of adverse events among BM family donors was not significantly different from those following PBSC in terms of either 30-day mortality, frequency of SAE (unexpected SAE being adopted for PBSC donations) within 30 days or frequency of hematological malignancies.

DISCUSSION

PBSC donation is considered by many to be less stressful for a donor than BM donation.[22,23] Nevertheless, it involves other potential stress factors. These include G-CSF administration to healthy individuals, the short- and long-term effects of which remain insufficiently characterized.[24–27] Recent publications have reported that the administration of G-CSF can influence the blood coagulation system of healthy donors.[28–30] Some studies indicated genetic and epigenetic alterations in lymphocytes of healthy donors after G-CSF stimulation[31] while others could not identify such changes.[32,33] The leukapheresis procedure itself may be a

Table 2. Factors associated with adverse events after PBSC donation

Donor basic information	*Thrombo-cytopenia* 985/1074[a]	*Hospitalization >10 days* 208/2605[a]	*Clinical symptoms*							*Splenomegaly* 59/199[a]
			Bone pain 449/2370[a]	*Fatigue* 128/2691[a]	*Headache* 105/2713[a]	*Insomnia* 85/2734[a]	*Anorexia* 38/2781[a]	*Nausea* 29/2790[a]	*Vomiting* 12/2707[a]	
Age										
20–59	1	1	1	1	1	1	1	1	1	1
<19	0.64	0.98	0.75	0.87	0.92	n.o.	0.91	0.19	n.o.	0.78
60>	1.83***	2.16**	0.37	0.44	0.23	1.22	0.33	0.75	0.88	3.23**
Gender										
Female	1.14	1.37	1.02	1.92**	2.08**	2.33**	4.33**	2.89**	2.88	0.7
Body weight										
40–69	1	1	1	1	1	1	1	1	1	1
<39	0.88	2.18*	n.o.	0.64	1.65	1.4	1.86	5.24	9.20*	1.7
70>	0.89	0.68	1.07	0.41*	1.11	1.17	0.5	0.68	1.54	0.27*
Total dose of G-CSF administered										
<2499	1	1	1	1	1	1	1	1	1	1
2500–2999	1.44**	1.17	1.05	1.11	1.07	0.89	1.51	0.75	0.66	1.36
3000–3499	1.63***	1.52*	0.94	1.32	1.38	1.02	1.16	0.76	0.95	2.95*
3500>	1.88***	2.30**	0.89	1.44	1.11	1.7	0.7	1.36	0.44	1.36
Past health problems										
Yes	0.86	1.54**	1.15	1.07	0.92	1.45	1.27	1.1	2.49	1.11
Current health problems										
Yes	0.92	1.78**	1.37*	1.4	1.27	1.44	0.59	2.08	1.06	1.92
Episode of past HSC donation										
Yes	0.8	1.72*	1.11	0.86	1.05	0.68	1.61	0.98	1.4	0.14

*$P<0.5$, **$P<0.01$, ***$P<0.001$. [a]Numbers of present/absent (at clinical symptoms, present means moderate or severe symptoms and absent means none or mild symptoms.)

Table 3. Impact of age and JHSCT standards on acute and late events

	Age (years)				*JSHCT standards fulfilled (age: 10–65)*		
	0–9	*10–65*	*>65*	P-*value*	*Yes*	*No*	P-*value*
Early SAEs							
Yes	0	46	1	–	43	3	–
No	37	3128	52	–	3088	40	–
%	0	1.4	1.9	0.735	1.37	6.98	0.0023
Late SAES							
Yes	0	38	1	–	38	1586	–
No	30	1618	21	–	0	22	–
%	0	2.3	4.5	0.547	0	2.33	0.4693

Abbreviation: SAE, severe adverse event.

Table 4. Comparison of adverse events between PBSC harvest (prospective study) and BM harvest (retrospective study) in Japan

	PBSCH	*BMH*
Death within 30 days	0/3264	(1)[a]/5921 $P=0.99$
SAE within 30 days	19[b]/3264	25[c]/5921 $P=0.21$
Hematological malignancy	1[d]/1708	2[e]/5921 $P=0.53$

[a]Respiratory failure during spinal anesthesia for BMH, died after 1 year. [b]Unexpected SAE at PBSCH, see Table 1. [c]Respiratory failure (1), shock (1), malignant hyperthermia (1), lung edema (1), auricular Fibrillation (1), bradycardia (1), hypotension (2), hematoma (1), severe or prolonged pain of aspirated portion (9), chest pain (2), urethral damage (1), fever with infection (2), renal dysfunction (1), ECG abnormality (1). [d]AML. [e]AML × 2.

stress factor; more blood is processed and a longer time for harvest is needed[34] compared with a platelet collection, an apheresis procedure for which donor safety is relatively well established.

To evaluate the safety and risks of PBSC donation, JSHCT initiated a nation-wide pre-registration system followed by an annual health check for family donors. This included consecutive pre-registration for 5 years, emergency reports at any time (for both acute and late events), a formal day 30 report of the laboratory data post donation and an annual health check report for 5 years. Nearly 100% of the collected pre-registration forms and emergency reports were received on time and >80% of day 30 check reports were obtained. The collection rate of the annual health check reports was ~50%. The JSHCT eligibility criteria, specifically lack of donors to fulfill these criteria appeared to be predictive for the occurrence of severe acute adverse events. Still, the 19 donors with unexpected severe events ranged in their age between 10 and 65 years and had no health problems at the time of donation. Of interest, these 19 events were of cardiovascular (angina, thrombosis and so on), hemorrhagic (subarachnoid/retroperitoneal hematoma and so on.) or inflammatory nature (interstitial pneumonitis and so on). Other information and techniques, such as high-sensitivity CRP assay that might predict the presence of active cardiovascular disorders, should be tested to see whether these measures can identify patients at increased risk of severe acute adverse events.[35]

There were no mortality cases within 30 days in our cohort. Our numbers could still be too low. Mortality has been reported in about one death per 10 000–15 000 donations.[19] Still, we consider this absence of mortality to be in part a consequence of pre-registration and setting the eligibility standards for family donors. We cannot identify a single critical factor but pre-registration and nation-wide standards might raise awareness for potential risks in a harvest team. As evidence defines specific factors that define donors at increased risk for SAEs, the harvest team might then refuse harvest of unsuitable family donors despite their request.[36]

To compare the risk of PBSC donation to that of BM donation, the questionnaires shared with EBMT were sent to JSHCT member institutes. The results confirm that the incidence of deaths, unexpected SAEs within 30 days of donation or subsequent hematological malignancies were not different between PBSC and BM donors. There is a note of caution: events were characterized differently in the two cohorts, one was a prospective study (PBSC donation), one a retrospective study (BM harvest) and both were performed in different time periods (PBSC: 2000–2005; BM harvest: 1990–2004). A prospective follow-up system should also be applied for family BM donors.

The donor's safety is an essential part and prerequisite in allogeneic stem cell donation. For BM harvesting, an anesthesiologist usually assesses the suitability of the candidate donor and acts as a life-saving third-party expert for the hematology team. Furthermore, the harvest procedure is performed in a fully equipped operation room. In contrast, PBSC harvest can be performed by a hematology team by its own in an apheresis room; an objective risk assessment and risk management might be compromised. Allogeneic PBSC donation and transplantation are excellent medical procedures; donor safety remains an essential part in order to ascertain the future use of these techniques.[18,37] Our study has shown that the life-threatening SAEs can occur during or immediately after the donation process. These events are not erratic and risk factors can be identified. Tools are required to reduce the complication rate. Strict standards for donor eligibility and an independent third-party evaluation of donor's suitability might eliminate the conflict of interests of transplant physicians and increase donor safety. Both have been a *sine qua non* for unrelated donors in advanced blood and marrow donor bank systems such as NMDP[38]or DKMS,[39] and only a few unexpected SAEs have been reported. The same pre-donation approach and donor follow-up should become the standard-of-care for all HSCTs, from family or unrelated donors as well. It will serve to provide more accurate information about early and late effects of PBSC donation, which is needed now more than ever.[40,41]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

YK, KY and MH designed the study and wrote the paper. YM, HD, SA, MI, KK, SK and MT collected and organized the data. YK, RT, SS, SWK, KN, MH, KM and RS supervised the process of data collection. NH, MF and AK performed the statistical analysis. JH, NS, DN and AG consulted with the study concept and reviewed the results.

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G-CSFの（顆粒球コロニー刺激因子）基礎と臨床

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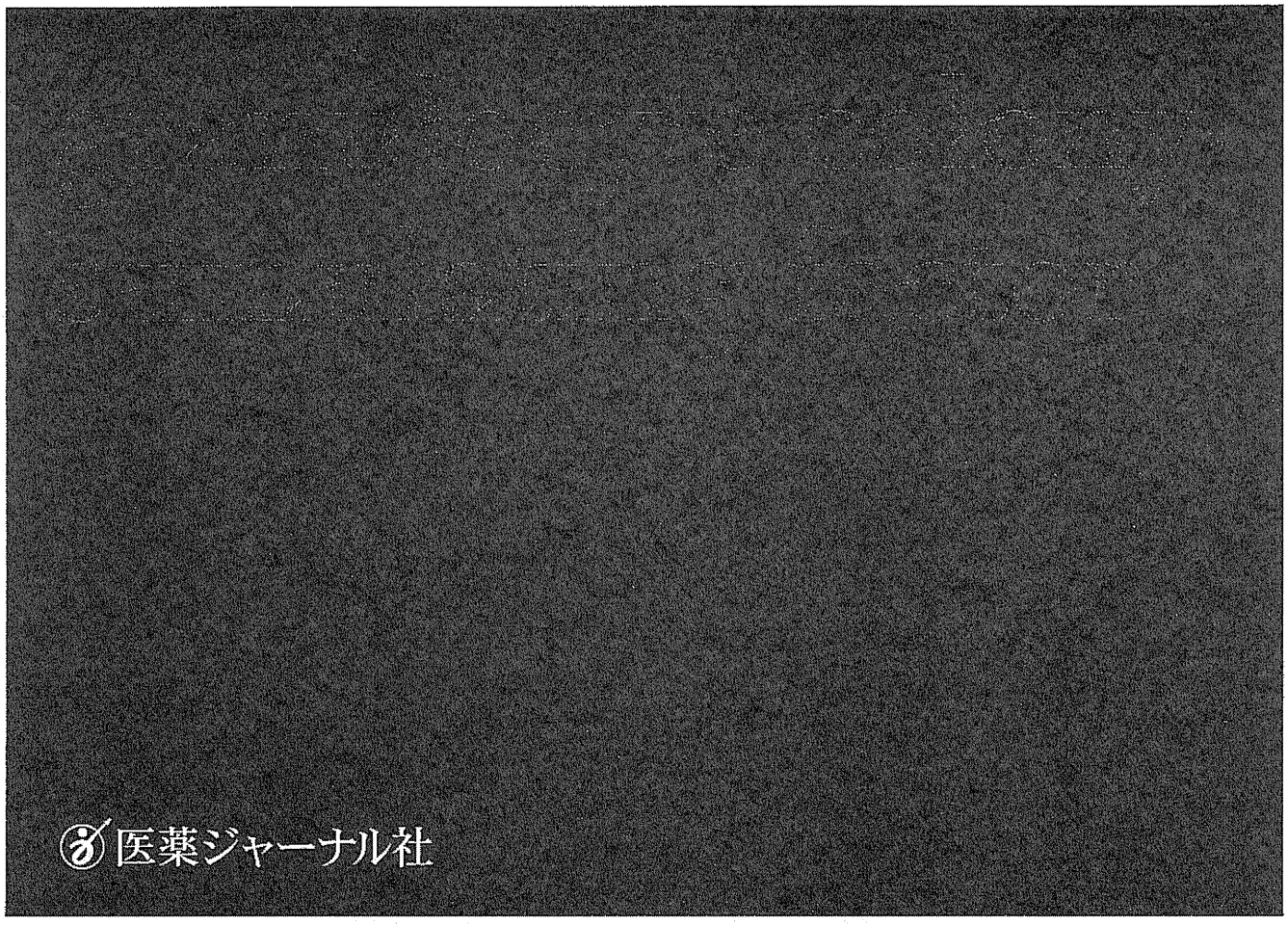

5 末梢血幹細胞採取

はじめに

造血幹細胞は通常末梢血中にはほとんどみられない(0.01%程度)が，化学療法後の白血球回復期や顆粒球コロニー刺激因子（granulocyte colony-stimulating factor：G-CSF）投与により，一過性に出現する。この時期に成分採血装置を用いてアフェレーシスを行い，自家または同種造血幹細胞移植に用いることが可能になる。自家末梢血幹細胞移植（peripheral blood stem cell transplantation：PBSCT）は悪性リンパ腫や多発性骨髄腫では標準治療として，広く実施されており，治療成績の向上に寄与している。

一方，同種末梢血幹細胞移植は1990年代後半から臨床応用が行われ，わが国でも2000年4月より（日本造血細胞移植学会の全国調査では1992年より報告がみられる）保険適用となり，血縁者間の幹細胞ソースとして普及し，2011年の日本造血細胞移植学会の全国調査[1]では，血縁ドナーの60%以上が末梢血幹細胞を提供している（図1）。非血縁者間PBSCTに関しては，米国骨髄バンク（National marrow donor program：NMDP）で1999年より開始し，2010年の統計では18歳以上の成人の非血縁ドナーからの移植の76%を占めるに至っており[2]，WMDA(World Marrow Donor Association)のデータでも標準医療として確立されている[3]。

PBSCTは骨髄移植（bone marrow transplantation：BMT）と比較して血球の回復が早く，また，ドナーにとっても全身麻酔や数多くの腸骨穿刺も必要ないが，末梢血幹細胞採取特有の合併症も懸念されたため，わが国ではドナーの安全性の確認を重視し，非血縁ドナーへの適応拡大については慎重な対応がなされてきた。日本造血細胞移植学会における10年にわたる血縁ドナーフォローアップ事業の結果[4]や海外の報告[5]から安全性において，骨髄採取に劣るものではないことが確認され，骨髄移植推進財団（PBSCT委員会），日本造血細胞移植学会，日本輸血・細胞治療学会，厚生労働科学研究班(宮村耕一 班長)が協力し準備を行った結果，2010年10月より非血縁PBSCTが開始され(1例目が2011年3月に実施，2013年2月までに18例

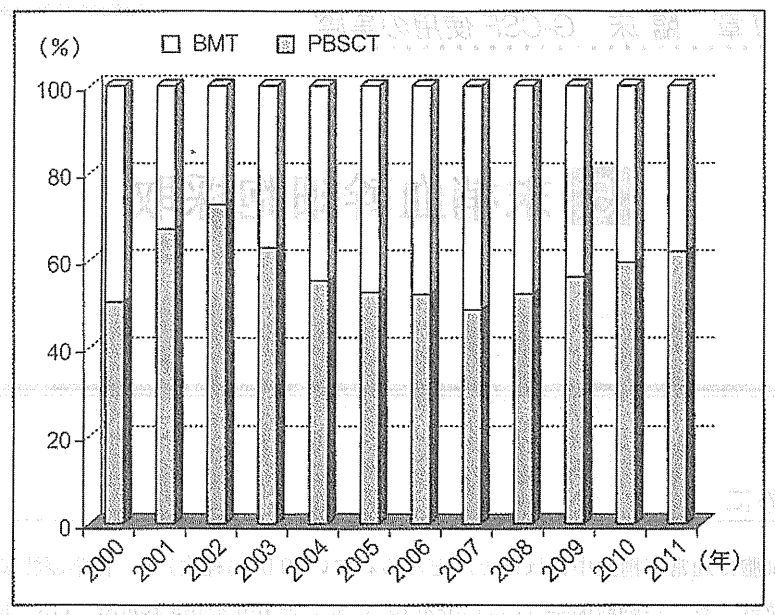

図1　わが国の幹細胞ソース別血縁移植件数の推移
2000年以後の血縁におけるBMTとPBSCTの推移を示す。当初は急速にPBSCTが増加したが，その後徐々に減少し，2007年以後，再び増加傾向にある。
BMT：骨髄移植，PBSCT：自家末梢血幹細胞移植
（文献1より）

が実施），非血縁ドナーにおいても骨髄採取，末梢血幹細胞採取の選択の幅が広がった。

1）同種末梢血幹細胞採取

1）ドナーコーディネート

造血幹細胞の提供には骨髄採取，末梢血幹細胞採取の2つの種類があり，それぞれ方法やドナーへの負担，リスクが異なっている。再生不良性貧血などは移植片対白血病（graft versus Leukemia：GVL）効果を必要としないため，慢性GVHD（graft versus hostdisease；移植片対宿主病）のより少ない骨髄移植の方が適している場合もあることから，患者の病状を考慮しつつ，採取の方法とリスクについてドナーに十分説明し，理解を得た上でドナーの自由意思に基づき，造血幹細胞提供の文書同意を得る必要がある。非血縁ドナーの場合は，適切な研修を受けた骨髄バンクのコーディネーターにより，ドナーの自己決定に十分配慮されたコーディネー

トが行われ，成人であっても本人の同意以外に家族の同意も必要である。ただ，非血縁末梢血幹細胞採取認定施設数が十分ではなく，ドナーが採取認定施設に通院可能であることが条件であるため，現時点では対象となるドナーは限定的であり，骨髄のみのコーディネートとなるドナーが多い。今後，認定施設を増やすことにより，すべてのドナーで骨髄および末梢血両方の提供の機会が与えられる必要がある。

一方，血縁においては，以前は患者主治医がドナーに説明し，同意を得る場合も多かったが，患者優先の意思決定になる可能性もあるため，最近では患者主治医以外のスタッフがHLA(ヒト主要組織適合抗原）検査時から説明することで，ドナーの自由意思による提供に配慮されるようになってきた。また，専任の院内造血幹細胞移植コーディネーターがいる施設も増えてきており，日本造血細胞移植学会では2013年より認定HCTC（Hematopoietic Cell Transplant Coordinator）制度を発足した。

2）適格基準

日本造血細胞移植学会では，同種末梢血幹細胞移植のための健常人ドナーからの末梢血幹細胞動員・採取に関するガイドライン第4版[6]，骨髄バンクでは末梢血幹細胞採取マニュアル暫定版[7]を策定している。

1 年齢

非血縁ドナーの場合は20～55歳，血縁ドナーの場合は18～60歳をドナー適格年齢としている。10～17歳および61～65歳の血縁ドナー候補に関しては，倫理委員会の審議を経るなど，各施設の責任により慎重に判定する必要がある。

2 適格性判定

血算や生化学検査，血液凝固検査，感染症関連などの血液検査，尿検査に加えて胸部X線検査，心電図検査を行い，ドナーの健康上の問題がないかをダブルチェックする。血縁ドナーにおいても，自己免疫疾患，神経疾患，治療が必要な心疾患・肺疾患・腎疾患・肝疾患，コントロール不良な高血圧症・高脂血症，投薬が必要な糖尿病，血栓症・冠動脈疾患・脳血管障害・間質性肺炎・悪性腫瘍の既往，骨髄増殖性疾患，脾腫，精密検査を要する臨床検査値異常がみられた場合や妊娠中は不適格となる。非血縁ドナーの場合は，骨髄バンクによってさらに厳しい適格基準が設けられている[8]。

3）末梢血幹細胞採取の方法

① G-CSF(フィルグラスチム400 μg/m²またはレノグラスチム10 μg/kg)を1日1回または2分割で連日皮下注射する（1回投与と2回投与でCD34陽性細胞の動員効率や有害事象に差があるかどうかに関しては一定の結論は出ていない)。白血球が増加しすぎた場合に

は，減量・休薬も考慮する。白血球数が50,000/μLを超えた場合は50%減量，75,000/μLを超えた場合はいったん中止，血小板数が100,000/μLを切った場合は50%減量，50,000/μLを切った場合はいったん中止する。また，G-CSF投与に伴い多くのドナーでは骨痛（71%）や頭痛（28%）が出現する。原因は，顆粒球の増加による骨髄内圧の増加，ヒスタミン分泌による骨髄内浮腫，ブラディキニンの増加などが考えられているが詳細は不明である。疼痛に対してはアセトアミノフェンなどで対応し，自制不能なgrade 4の骨痛や頭痛が出現した場合はG-CSF投与量を50%減量する。なお，アスピリンは血小板機能を抑制し，出血のリスクを上げるため避けるべきである。嘔気・嘔吐が強い場合も減量・中止を考慮する。

② 造血幹細胞の指標であるCD34陽性細胞は，G-CSF投与4日目から増加し，7日目からは減少するため（図2），血球分離装置を用いて4～6日目にアフェレーシスを実施する[9]。G-CSF投与30分後に，一過性に好中球は減少し，1時間後に回復，その後増加を続け，4～8時間後にピークとなる。CD34陽性細胞についても同様の報告があり，アフェレーシス開始はG-CSF投与後3～4時間以降が望ましい[10]。

③ 抗凝固剤としてACD-A液を用いて血球分離装置の回路をプライミングし，採血および返血のための血管ルート（16～18G針）を確保する。ドナーの穿刺痛を軽減するために，貼付用局所麻酔剤（30分前に貼付）を用いる施設もある。穿刺は両側肘静脈を用いるのが

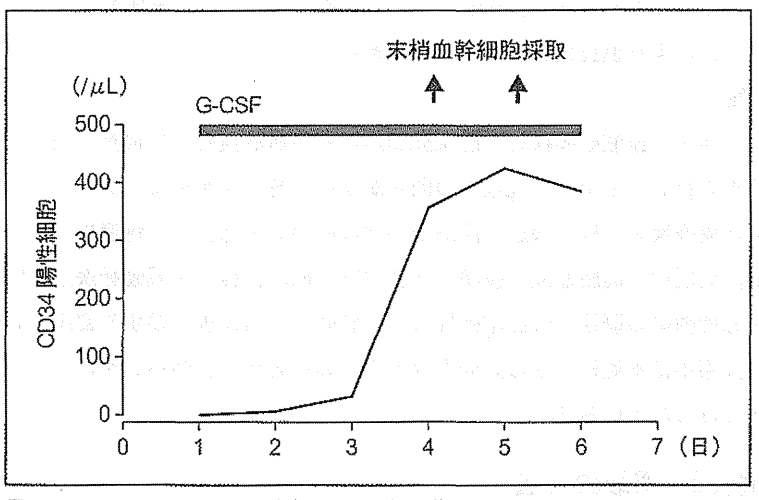

図2　G-CSFを用いた末梢血幹細胞の動員

G-CSF単独投与により，4～6日目までCD34陽性細胞が末梢血に動員され，5日目がピークとなり，その後は減少するため，4～6日目にアフェレーシスを行う。

（大阪市立大学データ；筆者提供）

望ましいが，やむを得ない場合は大腿静脈などにブラッドアクセスを確保する。骨髄バンクでは，肘静脈の確保が難しいドナーは末梢血幹細胞提供不適格としている。なお，数日間留置する場合は，透析用のダブルルーメン・カテーテルを使用する。動脈穿刺をした場合は，直ちに抜針し，30分間圧迫後，1時間程度安静を保ち，止血を確認する。

④採取のための処理血液量は，非血縁ドナーの場合は150～200 mL/kg（最大250 mL/kg），血縁ドナーの場合は150～250 mL/kg（最大300 mL/kg），あるいは循環血液量の2～3倍が一般的で，ACD-A液を加えながら，非血縁ドナーの場合は血流速度50～60 mL/分，血縁ドナーの場合は血流速度50～80 mL/分で体外循環を行い，必要な細胞を濃縮する。アフェレーシスの所要時間は4時間前後となるため，ドナーがリラックスできる環境作りも重要である。

⑤フローサイトメトリーを用いてCD34陽性細胞を測定し，患者体重あたり2.0×10^6個を目標とするが，$1.0 \sim 2.0 \times 10^6$個でも生着は可能である。造血幹細胞の動員が不十分なpoor mobilizerも0.5%程度みられるが（血縁ドナーの場合は骨髄採取を追加することも可能であるが，非血縁ドナーでは認められていない），あらかじめ予測することができないので，十分量が採取できたことを確認してから移植前処置治療を開始するために凍結保存する施設も多い（骨髄移植同様に前処置開後に採取を行い，凍結せずに移植している施設もある）。

凍結保存する場合は，採取された造血幹細胞分画は凍害防止のためDMSO（dimethyl sulfoxide）とHES（hydroxyethyl starch）を調整したCP-1（極東製薬工業 株式会社）[11]を添加し，プログラムフリーザーを用いて緩徐に凍結し液体窒素に保存する方法と，−80℃以下の超低温冷凍庫に直接保存する簡易法がある（1～5年間有効）。骨髄バンクは，原則凍結を認めていないが，必要量以上が採取できた場合は一部を凍結保存し，ドナーリンパ球輸注（DLI）などに使用することは可能である。この際には，日本輸血・細胞治療学会および日本造血細胞移植学会により策定された「院内における血液細胞処理のための指針」を遵守することが適切である[5]。

なお，凍結することは，ドナーにとっては時間的な余裕と提供機会の増加が得られ，患者にとっては病状悪化時の「なだれ込み移植」ではなく，ベストタイミングでの移植が調整できるため，双方にメリットがある。しかし，凍結された骨髄の一部が使用されず，廃棄されていることも事実であり，ドナーの善意を無駄にしない方策について，非血縁ドナーの骨髄を含めた凍結の基準について検討する必要がある。

⑥凍結保存した場合は，移植の際に37～40℃の恒温槽で急速解凍し，輸注する。

4）骨髄採取と末梢血幹細胞採取の比較

骨髄採取と末梢血幹細胞採取はそれぞれ全く異なる手技であり，有害事象も異なっており[12]，ドナーの負担を単純に比較することはできない。肉体的な侵襲は，穿刺回数にも依存するが，骨髄採取の方が強く，採取後から回復までの時間も長い[13, 14]。また，骨髄採取時に尿道カテーテルを挿入する施設では，特に男性ドナーで尿道痛などの不快感も強い。一方，末梢血幹細胞採取では，覚醒状態での 3 ～ 4 時間あまりの採取に対する精神的なストレスや不安を訴えるドナーもいる。また，肘静脈での採取が困難な場合，やむを得ず大腿静脈にブラッドアクセスを挿入する必要があるが，特に若い女性の場合にはストレスになると思われる。非血縁ドナーにおいて骨髄採取と末梢血幹細胞採取に関して SF-36® を用いた身体的，精神的，社会的負担を比較する観察研究が実施中である。

5）ドナーの安全管理

造血幹細胞を提供するドナーは，献血同様，自由意思による健康なボランティアであるため，安全には十分配慮し，また，退院後すぐに社会生活に復帰できるように負担を最小限にする必要がある。末梢血幹細胞採取によるドナーの死亡例は，表 1 に示すように海外で脳血管障害 3 例，心不全，心筋梗塞，硬膜下出血，鎌状赤血球症発作，空気塞栓が各 1 例に加えて，技術的

■ 表 1　末梢血幹細胞提供ドナーにおける死亡症例

患者との関係	年齢	発生時期	死因	併存症
血縁	61	採取 4 日後	心不全	高血圧，冠動脈疾患
血縁	57	帰宅 24 時間以内	脳卒中	
血縁	64	勤員終了後	心筋梗塞	冠動脈疾患
血縁	73	採取数日後	脳血管障害	高血圧，狭心症
血縁	67	採取 2 日後	硬膜下血腫	心筋梗塞，大動脈瘤手術
血縁	47	G-CSF 投与 4 日目	鎌状赤血球症発作	鎌状赤血球症
血縁	未報告	未報告	脳血管障害	
血縁	50	カテーテル抜去後	空気塞栓（技術ミス）	
血縁	43	不明（採取 15 日後死亡）	心停止	高血圧
血縁	52	不明（採取 17 日後死亡）	心停止	喫煙
血縁	27	採取時	心停止（技術ミス）	
非血縁	21	カテーテル挿入時	出血（技術ミス）	

末梢血幹細胞提供ドナーの死亡例は，海外では 12 例報告されているが，わが国での報告例はない。
（骨髄移植推進財団：「骨髄または末梢血幹細胞提供者となられる方へのご説明書」より）

な問題による合併症も含め合計 12 例が報告されており，特に，高齢者や動脈硬化などの合併症を有している例は注意を要する。わが国では日本造血細胞移植学会のガイドラインを遵守し，G-CSF 投与およびアフェレーシスの短期および長期の安全性を確認するため，同学会によるドナーフォローアップ事業が原則全例登録の形で行われてきた。適格基準を逸脱するようなドナーは施設の倫理委員会の承認を受けて実施し，開始当初は学会から確認のための問い合わせがくるほど慎重に進めてきた努力もあり，日本では末梢血幹細胞ドナーの死亡事故は起こっていない。

日本造血細胞移植学会のホームページに 2000 年 4 月～ 2005 年 3 月の同種 PBSCT ドナーフォローアップ事業による有害事象報告（2010 年 9 月 13 日現在），2005 年 4 月以後の血縁造血幹細胞ドナーフォローアップ事業による有害事象報告（2013 年 2 月 4 日現在）が公開されている[4]。なお，採取に伴う合併症に対してドナー傷害保険が用意されており，非血縁ドナーはすべて骨髄バンクで手続きされる（費用負担は患者）が，血縁ドナーの場合は，日本造血細胞移植学会に登録した上で，掛金を患者・ドナー・家族のいずれかが自己負担する必要がある。

なお，今後 G-CSF のバイオシミラーがわが国でも上市される予定であるが，健常人に対する末梢血幹細胞動員の治験が行われていないことから日本造血細胞移植学会では，「健常人からの同種末梢血幹細胞の動員に際しては，まず血縁ドナーにおいて開始し，日本造血細胞移植学会ドナー事前登録・フォローアップ事業に全例登録すること。非血縁ボランティアドナーへの投与は，血縁ドナーにおける短期，中長期安全性が確認されるまでは保留すること。」との見解を表している。

■ 短期的な有害事象

日本造血細胞移植学会には G-CSF やアフェレーシスとの因果関係に関わりなく，採取後 2 カ月以内に起こった重篤有害事象として 102 件が報告されている。最も多いのは血小板減少で，その他，アフェレーシスに伴うものとして，迷走神経反射や低カルシウム血症，血管外漏出，留置針の体内迷入，カテーテル感染，穿刺部の皮下出血なども散見される。アフェレーシス中はドナーの観察を十分に行い，異常がみられた場合には早めに対処することを心がけることが重要であり，熟練した医療スタッフによる常時監視（非血縁ドナーの場合は医師の常時監視）が求められる。また，G-CSF 投与を中止しなければならないような重篤な健康被害は稀であるが，狭心症様発作，発熱，間質性肺炎，急性虹彩炎や痛風性関節炎など，炎症の増悪なども報告されている。

軽度な健康被害としては，腰痛，胸痛，骨痛，背部痛，関節痛，筋肉痛，肝機能異常（GOT，GPT，LDH，ALP 上昇），発疹，紅斑，悪心，嘔吐，発熱，頭痛，倦怠感，動悸，尿酸値上昇，血清クレアチニン値上昇，CRP 値上昇などが報告されているが，いずれも G-CSF 投与終了後 2 ～ 3 日以内で消失する。

（1）血小板減少

アフェレーシス後，血小板数が18,000/μLまで低下した例もある。図3に示すように，非血縁ドナーにおける採取後の血小板数とドナー体重あたりの処理量は逆相関しており[15]，上限量を超えないように注意が必要である。血小板数が80,000/μLよりも減少した場合は，自己多血小板血漿を作製してドナーに輸注することが望ましい。また，このような場合は，2回目のアフェレーシスによるPBSC採取の中止を考慮する必要がある。自己多血小板血漿分離方法（操作は非開放系で実施）を以下に示す。

① 分離用バッグを無菌接合機でPBSCバッグと接続する。

② 遠心条件：遠心（約300～1,100 G）4～5分，20～24℃

③ 多血血小板血漿（PRP）とペレット（血小板以外の細胞成分；幹細胞分画／若干の赤血球）に分離。

④ バッグを分離スタンドにかけ，上清（PRP）を分離バッグに移す。

⑤ PBSCのバッグをよくもみ，血漿中に細胞を浮遊させ経静脈投与する。

（2）血管迷走神経反射

血管迷走神経反射（vaso-vagal reflex：VVR）は，精神的ストレス，緊張，睡眠不足，疼痛等が誘因となって採取の比較的早期で起こり，気分不良，顔面蒼白，冷汗，生あくび，嘔吐，腹痛等が出現し，バイタルサインでは血圧低下，徐脈，呼吸数低下が特徴的である。採取を中

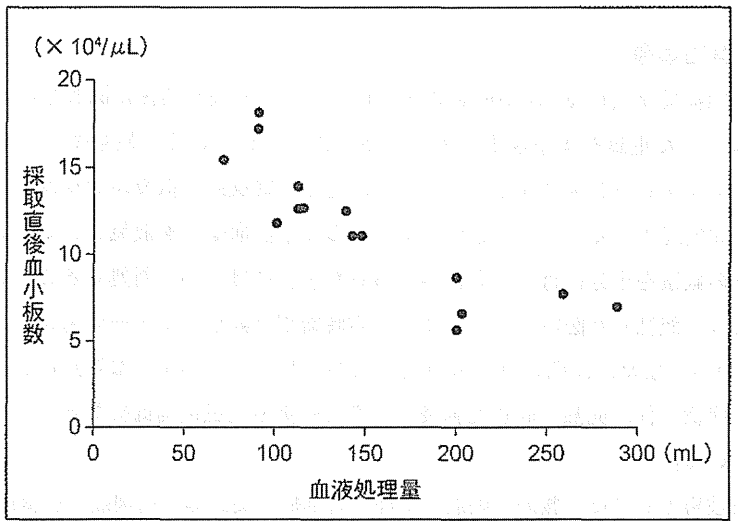

図3　末梢血幹細胞採取時の血液処理量と採取後血小板数
アフェレーシス直後の血小板数は，ドナー体重あたりの血液処理量に逆相関して減少する。

（文献15より）

断し，ほとんどは対症療法で軽快するが，高度の徐脈，意識消失，けいれん，心停止など，重症となる可能性もあるため，治療介入（硫酸アトロピン，エチレフリン，エフェドリン投与など）が遅れないように，採取中は心電図モニターが必須である。精神的ストレスや緊張によって過換気症候群を起こすドナーもいる。

（3）低カルシウム血症

ACD-A液によりカルシウムがキレートされることで，低カルシウム血症を起こし，口唇や手足のしびれ感，倦怠感，悪心，嘔吐などが出現する。ACD-A液の総量だけでなく，単位時間あたりの使用量にも関連し，ひどい場合はけいれんや意識消失に至ることもある。採取後半に発生することが多く，カルシウム液の持続注入（グルコン酸カルシウム5～10 mL/時）によって予防可能である。口唇のしびれなどの症状が出た場合は，適宜，カルシウムの補充を行う。

（4）脾臓破裂

海外ではG-CSF投与により脾臓が腫大し，破裂した報告[16]もあることから，G-CSF投与中は触診やTraube三角の打診，必要に応じて腹部エコーで確認することも重要である。

2 中長期的な有害事象

中長期的な有害事象に関しては，生活習慣によるものや偶発症もあるため，G-CSF投与や末梢血幹細胞採取との因果関係を明らかにすることは困難であるが，因果関係の有無は別として，56件が報告されている。このうち，採取後14カ月目に発症した急性骨髄性白血病（AML）の事例[17]はG-CSFとの因果関係が懸念されたため，日本造血細胞移植学会は「健康被害特別調査委員会」を設置し，詳細な検討が行われた。その結果，この事例におけるG-CSFと白血病発症の因果関係については，「健常者に短期間G-CSFを投与しただけで白血病が発症する可能性は医学的には考えられないが，完全に否定することはできない」という見解が示された。その後のわが国の調査では，骨髄ドナーでの血液腫瘍発生は2/5,921例（白血病2例），末梢血幹細胞ドナーでは1/3,262例（白血病1例）で有意差はないものと考えられた。

米国NMDPの非血縁末梢血幹細胞ドナー2,408例の調査でも，血液腫瘍は慢性リンパ性白血病が1例のみ[12]で骨髄性白血病の事例はなかったが，血縁ドナーの全例調査はわが国以外になかったため，Koderaらの提案により欧州骨髄移植学会（EBMT）を中心に51,024例の後方視的解析が行われた結果，骨髄ドナー27,770人中8例に血液悪性腫瘍（AMLは2例），末梢血幹細胞ドナー23,254人中12例に血液悪性腫瘍（AMLは1例）が発生しており，骨髄ドナーでは0.4/10,000人年，末梢血幹細胞ドナーでは1.2/10,000人年と計算された[13]。年齢および性別によって血液悪性腫瘍発症率は異なる（20～24歳で0.9/10,000，30～39歳で1.3～1.6/10,000人年，55～59歳で6.3/10,000人年）が，一般の発症率よりも低値であった。

以上から，骨髄採取と比較して，末梢血幹細胞採取において特に白血病などの発症が増える

ことはないとの結論に至ったが，リスクがあるとする報告[18]もある。さらに長期の影響に関しては未知数であることから，今後もドナーのフォローアップ体制が重要である。

6）採取後検診

採取終了後，穿刺部位や血液検査に問題がなければ退院可能で，骨髄バンクでは末梢血幹細胞提供ドナーは採取日もしくは翌日（ブラッドアクセスを挿入した場合は翌日）としている。特に問題がなければ1カ月後を目処に採取後検診を行う。

7）ドナーサンクスカード運動

骨髄バンクのドナーは見ず知らずの患者に骨髄や末梢血幹細胞を提供するボランティアである。この「命の贈り物」をもらった患者は，お互いのプライバシーを侵害しないように無記名でお礼の気持ちを手紙に託すことができるが，様々な事情のため，実際にドナーにお礼の手紙が届くのは50%程度しかない。ドナーサンクスカード運動は，移植に携わるチームが移植医療を支えてくださっているドナーへ感謝の意を伝えようと始まった。採取施設のスタッフとして，提供していただいたドナーの方に，採取終了後サンクスカードをお渡しする。また，移植施設のスタッフとして，移植を受ける患者のために骨髄や末梢血幹細胞を提供してくださったドナーの方には，採取施設の主治医に手紙をことづけ，患者・ドナーのプライバシーを侵害しないようにドナーの方に渡してもらう。

2011年9月15日発行の「MONTHLY JMDP」[19]に，「お手紙交換のルール変更について：移植施設の医師・医療スタッフのお立場でドナーの方にお手紙をご準備いただける場合は，当財団を通さずに採取施設のスタッフへ直接お渡しいただいて構いません（お手紙交換の回数にはカウントされません）。ただし，内容については双方の施設にて個人情報と施設情報がないことを必ずご確認くださいますようお願いします。」という新しいルールが公開されており，すべてのドナーの方に感謝の気持ちが伝わることを願っている。

2 自家末梢血幹細胞採取

自家末梢血幹細胞採取は，同種末梢血幹細胞採取と同様，G-CSF投与のみで行う場合もあるが，化学療法後の造血回復期にG-CSFを投与することでより効率よく造血幹細胞を採取することができる。自家末梢血幹細胞を動員する化学療法としては，シクロホスファミド（2 g/m²/日，2日間），シタラビン（2～3 g/m²/回，1日2回，2日間），エトポシド（500 mg/m²/日，3日間）などが用いられる。エトポシドは動員効率が高いが，点滴ルートの材質によっては亀裂が生じることがあるので，特に，希釈せずに原液を使用する場合はルートの材質などに

も注意が必要である。B細胞性腫瘍の場合，抗CD20抗体（リツキシマブ）を併用し，採取した幹細胞分画への腫瘍細胞の混入を防ぐために“*in vivo* purging”を行うこともある。なお，原疾患に対する治療としての化学療法の回復期に採取する場合，メルファランやチオテパは，造血幹細胞に対する毒性が高いため避けた方がよいとされている。

採取のタイミングは，末梢血のCD34陽性細胞をモニターしながら行うと確実であるが，対応が難しい施設もあり，一般的にはnadir（最低値に達した）の時期からG-CSFを投与し，白血球数が5,000～10,000/μLを超えた時期，末梢血に芽球や未熟骨髄球が出現する時期を目安に採取を行っている。また，自動血球分析装置に搭載された未熟白血球検出プログラムを，純化したCD34陽性細胞を用いて補正し[20]，修正されたプログラムを利用して採取時期を推定することも検討されている。採取の合併症は同種末梢血幹細胞採取と同様であるが，血小板減少に対しては濃厚血小板輸血で補充しながら採取を優先することもある。採取後は凍結保存し，自家移植に備える。

おわりに

わが国では，非血縁者間PBSCTの導入に関しては，他の国に比べ大きく遅れたが，その間，学会のガイドラインの下，血縁末梢血幹細胞採取が安全に実施され，また，全ドナーフォローアップ事業により，ドナーの短期および中長期の有害事象の情報が蓄積されてきた。同種造血幹細胞移植は提供していただけるドナーの方がいなければ成り立たない治療であり，採取に関わるスタッフはゼロリスクを目指し，細心の注意を払って採取を行う必要がある。また，医師の負担軽減も重要な問題であり，移植・採取拠点のセンター化など，患者およびドナー，さらに医療スタッフにとってもより良い医療として発展することが望まれる。

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