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Allogeneic Peripheral Blood Stem Cell Rescue of Late Graft Failure after Bone Marrow Transplantation in Patients with Aplastic Anemia

We investigated the effect and outcome of allogeneic peripheral blood stem cell (PBSC) rescue for aplastic anemia (AA) patients with graft failure after allogeneic bone marrow transplantation (BMT). Seven (28%) of 25 AA patients who received BMT from HLA-identical sibling donors developed late graft failure at a median of 7 months (range, 2.0-9.3 months) after transplantation. The patients with graft failure were treated with PBSC collected from the original donor after mobilization with granulocyte-colony stimulating factor (G-CSF). The median boost dose of peripheral blood mononuclear cells was 3.1×10^8/kg (range, 1.4-11.9×10^8/kg). Median times to reach an absolute neutrophil count greater than 0.5×10^9/L and a platelet count greater than 50×10^9/L were 7 days (range, 4-14 days) and 9 days (range, 3-41 days), respectively. There was sustained graft function in 6 of 7 patients, with a median follow-up duration of 3.3 yr (range, 1.0-6.2 yr). Grade-I acute graft-versus-host disease (GVHD) occurred in 2 patients, while extensive chronic GVHD developed in 3 patients. This report shows that G-CSF-mobilized allogeneic PBSC rescue is very effective in achieving complete and sustained engraftment in patients with AA after graft failure. However, more efficacious measures to prevent extensive chronic GVHD remain to be developed.

Key Words : *Anemia, Aplastic; Bone Marrow Transplantation; Peripheral Blood Stem Cells; Graft vs Host Disease*

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INTRODUCTION

Although allogeneic bone marrow transplantation (BMT) from HLA-identical siblings is the treatment of choice in patients with severe aplastic anemia (SAA), graft failure remains one of the important, life-threatening complications following allogeneic BMT in the patients. The graft failure rates after HLA-identical sibling transplantations for SAA range from 5 to 50%, averaging about 10% (1, 2). The therapy for graft failure includes the administration of human recombinant growth factors (3-5) and the reinfusion of donor marrow (6-10). Recently, infusion of allogeneic peripheral blood stem cells (PBSC) mobilized by granulocyte-colony stimulating factor (G-CSF) has been used in the patients (11-15). Allogeneic PBSC transplantation (PBSCT) has some advantages over allogeneic BMT: general anesthesia is not required to collect hematopoietic stem cells and faster hematologic recovery has been reported (16, 17). However, there may be an increased risk of graft-versus-host disease (GVHD), since PBSC products collected by leukapheresis usually contain 10 to 100 times more T lymphocytes than bone marrow grafts (18). Several groups have shown that the incidence and the severity of acute GVHD are similar between PBSCT and BMT (16, 17, 19). However, it is presently unclear whether chronic GVHD occurs more commonly after allogeneic PBSCT compared to BMT. There are a few case reports with a short follow-up on the use of allogeneic PBSCT for the rescue of graft failure after BMT in SAA (12-14).

This paper reports the effect and outcome of allogeneic G-CSF-mobilized PBSC rescue for late graft failure after BMT in 7 patients with SAA, focusing on the sustained graft function and the development of the chronic GVHD.

MATERIALS AND METHODS

Patients

Twenty-five patients with SAA received transplants from HLA-identical sibling donors at Chonnam National University Hospital between May 1991 and May 1999. The patient characteristics are summarized in Table 1. The median age was 16 yr (range, 1 to 43 yr) for recipients and 15 yr (range, 3 to 40 yr) for their HLA-identical sibling donors. The median interval between diagnosis and BMT was 4 months (range, 1 to 61 months). The etiology of the aplastic anemia was idio-

Table 1. Descriptive data of the 25 patients with severe aplastic anemia who received allogeneic bone marrow transplantation (BMT)

Patient No.	Age (yr)/ Sex	Etiology	Interval from Dx to BMT (months)	Previous therapy	Preceding transfusion	Infused MNCs ($\times 10^8$/kg)	Conditioning regimen	GF	Outcome (months from BMT)
001	9/F	idiopathic	4.1	no	24	2.3	TNI,CY	no	alive+108.1
002	19/M	idiopathic	17.3	androgen	26	1.3	CY,ATG,Pro	yes	alive+90.3
004	29/M	idiopathic	2.7	no	31	2.3	CY,ATG,Pro	no	died of sepsis+5.0
008	13/M	idiopathic	4.3	no	8	3.2	CY,ATG,Pro	no	alive+74.9
009	24/F	idiopathic	10.2	ALG	8	4.6	CY,ATG,Pro	no	alive+72.6
010	8/M	idiopathic	2.3	no	42	2.3	CY,ATG,Pro	no	alive+64.2
012	6/F	idiopathic	4.0	androgen	17	3.1	CY,ATG,Pro	yes	alive+62.3
023	17/M	idiopathic	3.5	androgen	55	4.3	TNI,CY	no	alive+50.4
024	13/F	idiopathic	2.4	no	6	4.9	CY,ATG,Pro	no	alive+50.0
025	26/F	idiopathic	22.3	ALG	43	3.3	CY,ATG,Pro	yes	alive+48.9
026	10/M	idiopathic	20.6	ALG	15	1.7	CY,ATG,Pro	yes	alive+48.6
028	14/F	idiopathic	1.2	no	12	3.8	CY,ATG,Pro	no	alive+47.4
033	25/F	idiopathic	36.3	ALG $\times 2$	46	3.7	CY,ATG,Pro	yes	alive+44.2
037	16/M	idiopathic	3.6	no	16	3.4	CY,ATG,Pro	no	alive+42.6
038	17/F	idiopathic	10.5	ALG	30	2.5	CY,ATG,Pro	no	alive+40.6
042	1/M	FA	15.2	ATG	42	10.2	CY,ATG,Pro	no	died of GVHD 1.3
049	19/M	idiopathic	8.0	no	96	4.3	TNI,CY	no	alive+36.2
056	30/F	idiopathic	6.3	androgen	11	3.1	CY,ATG,Pro	yes	alive+33.8
061	11/M	FA	61.2	ALG	18	5.9	TNI,CY	no	alive+31.6
065	30/M	idiopathic	1.5	androgen	2	4.9	CY,ATG,Pro	no	alive+29.5
066	27/M	idiopathic	2.5	androgen	6	3.9	CY,ATG,Pro	no	alive+28.3
074	43/M	idiopathic	25.8	androgen	25	2.8	CY,ATG,Pro	no	alive+18.9
083	6/M	idiopathic	2.3	no	26	6.6	CY,ATG,Pro	no	alive+14.8
094	13/F	idiopathic	1.4	no	17	1.8	CY,ATG	yes	alive+10.8
106	11/F	idiopathic	2.3	no	13	3.3	CY,ATG	no	alive+10.7

Dx, diagnosis; MNC, mononuclear cell; GF, graft failure; M, male; F, female; ALG, anti-lymphocyte globulin; CY, cyclophosphamide; ATG, anti-thymocyte globulin; Pro, procarbazine; TNI, total nodal irradiation; FA, Fanconi's anemia.

pathic in 23 (92%) patients and Fanconi anemia in 2 (8%) patients. Nineteen patients received pretransplant immunosuppressive treatment with cyclophosphamide (CY, 50 mg/kg i.v.) for 4 days, ATG (Thymoglobulin, 1.25 mg/kg i.v.; Pasteur Merieux, Lyon, France) for 3 days, and procarbazine (12.5 mg/kg p.o.) for 3 days. Two patients received CY (50 mg/kg i.v.) for 4 days and ATG (Atgam, 30 mg/kg i.v.; Upjohn, Kalamazoo, MI, U.S.A.) for 3 days. Four patients received CY (50 mg/kg i.v.) for 4 days and 6 Gy of total nodal irradiation (TNI). The initial median marrow mononuclear cell (MNC) dose was 3.3×10^8/kg (range, 1.3-10.2 $\times 10^8$/kg). Post-transplant immune suppression to prevent GVHD consisted of methotrexate (MTX) and cyclosporine (CsA) in all 25 patients. MTX was given at a dose of 15 mg/m^2 i.v. on day 1 and 10 mg/m^2 i.v. on day 3, 6 and 11. CsA was given at a dose of 5 mg/kg/day i.v. on day -1 and then 3 mg/kg/day until oral dose was tolerated, continued for 1 yr. Doses were adjusted to maintain a CsA plasma level between 200-400 μg/mL.

Definition of engraftment and graft failure

Marrow engraftment was monitored by hematological criteria. Engraftment was defined as the first day on which the peripheral absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9$/L for 2 consecutive days. Primary graft failure was defined as patients who did not reach an ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days by day 28 after BMT. Late graft failure was defined as patients who demonstrated evidence of initial engraftment followed by development of an ANC $< 0.5 \times 10^9$/L for at least 14 days.

PBSC rescue

Five μg/kg/day of recombinant human GM-CSF was tried for three weeks in four of the seven patients to no avail. The seven patients with late graft failure were treated with G-CSF-mobilized PBSC transfusion from their original donors. Informed consent was obtained from the patients and donors.

Statistics

Statistical significance for variables affecting graft failure, such as infused cell dose, the interval between diagnosis and BMT, and age, was examined using the χ^2 test (Fisher's exact test). The Wilcoxon test was used to compare cell counts before and after PBSC boost.

RESULTS

Graft failure

Graft failure was seen in 7 of 25 patients for an overall rate of 28%. No patients showed primary graft failure after initial BMT. Marrow engraftment was initially documented in all seven patients with a median time to reach an ANC $\geq 0.5 \times 10^9$/L of 18 days (range, 14-20), but later showed signs of late graft failure, with a median interval of 7.0 months (range, 2.0-9.3 months) from the initial transplant.

A contingency table analysis was run for several variables (Table 2). It showed that the infused MNC dose was a significant discriminant factor for developing graft failure. Infusion of MNC $<2.0 \times 10^8$/kg carried an increased risk of graft failure. The mean infused MNC dose was lower in the graft failure group than in the non-graft failure group (2.6 ± 0.9 vs. $4.2 \pm 1.9 \times 10^8$/kg, p=0.048). Other variables, such as interval between diagnosis and BMT, number of previous transfusions, etiology, sex and age of the recipient, sex and age of the donor, sex compatibility, ABO compatibility, and conditioning regimen were not associated with graft failure. Although the reasons for graft failure were not clear, potential risk factors for graft failure were identified in six of these seven patients. Patient 002 received a low dose of marrow cells (1.3×10^8/kg) and transfusions from a family member before BMT. In Patient 012, graft failure was associated with hepatitis C infection (20). In this case, the serum alanine aminotransferase (ALT) level rose abruptly to 821 IU/L on day 144, when the neutrophil and platelet counts began to dwindle. Polymerase chain reaction (PCR) for HCV RNA and anti-HCV by ELISA were positive. Serologic tests for viral hepatitis were negative before BMT. Patients 025 and 033 received transfusions of multiple blood products (43 and 46 units, respectively). Patients 026 and 094 received a low dose of marrow cells (1.7 and 1.8×10^8/kg, respectively).

Table 2. Clinical data of patients with or without graft failure after BMT

	without graft failure	with graft failure	*p* value
Number of patients	18	7	
Sex ratio (Male/Female)	5/13	5/2	0.075
Age (yr)			1.0
<15	9	3	
≥15	9	4	
Etiology			1.0
idiopathic	16	7	
Fanconi's anemia	2	0	
Preceding transfusions			1.0
<20	9	4	
≥20	9	3	
Previous treatment			0.355
no	14	4	
ALG	4	3	
Interval between diagnosis and BMT		0.066	
<12 months	15	3	
≥12 months	3	4	
Sex match			0.656
matched	11	3	
mismatched	7	4	
ABO compatibility			0.181
compatible	14	5	
minor mismatch	3	0	
major mismatch	1	2	
Conditioning regimen			0.294
CY, ATG, ±Procarbazine	14	7	
TNI, CY	4	0	
Infused MNCs			0.015
$<2.0 \times 10^8$/kg	0	3	
$\geq 2.0 \times 10^8$/kg	18	4	

ALG, anti-lymphocyte globulin; CY, cyclophosphamide; ATG, anti-thymocyte globulin; TNI, total nodal irradiation.

PBSC rescue

The median time from the initial transplantation to the booster was 9.2 months (range, 2.9-14.3 months). The donor for Patient 002 was treated with 5 μg/kg G-CSF s.c. daily for seven days and leukapheresis was done on day 8. The other donors were treated with 10 μg/kg G-CSF s.c. daily for 4 or 5 days and leukapheresis was done on one or two consecutive days. The median dose of infused booster MNCs was 3.1×10^8/kg (range, $1.4\text{-}11.9 \times 10^8$/kg). Patient 4 received 3.4×10^6/kg $CD34^+$ cells separated from the pooled PBSC concentrate by the avidin-biotin technique (Ceprate SC, CellPro, Bothell, U.S.A.).

At the time of PBSC rescue, complete donor chimerisms were documented by fluorescent in situ hybridization (FISH) with X-chromosome minisatellite probes in sex-disparate pairs or PCR of DNA sequences with a variable number of tandem repeats (VNTR). The patients did not receive any additional conditioning for the booster, except Patient 002. He received ALG (Lymphoglobulin, 10 mg/ kg/day i.v.; Pasteur Merieux, Lyon, France) for 5 days. As a GVHD prophylaxis, CsA was reinfused at 3 mg/kg/day in all the seven patients. Patients characteristics at the time of PBSC rescue are summarized in Table 3.

Hematologic recovery

Rescue PBSC were engrafted in all seven patients engrafted with median times of 7 days (range, 4-14) for ANC $>0.5 \times 10^9$/L and 9 days (range, 3-41) for platelets $>50 \times 10^9$/L after infusion. Hematologic recovery in the seven patients is shown in Fig. 1. Platelet counts, ANC, and hemoglobin values were significantly increased one month after the boost. Post-engraftment boost produced sustained graft function in six of the seven patients. Pancytopenia reappeared in only one patient (Patient 026) who received selected $CD34^+$ cells derived from PBSC. At 3 months following rescue, his blood counts grad-

Table 3. Data of 7 patients treated with PBSC boost for late graft failure

Patient No.	Time from BMT to graft failure, booster (months)	Boost cell dose		GVHD prophylaxis	ANC >0.5×10⁹/L (days)	Platelet >20×10⁹/L (days)	GVHD		Current status, months after boost
		MNC (10^8/kg)	$CD34^+$ cell (10^6/kg)				acute	chronic	
002	8.2, 14.3	1.4	4.3	CsA	5	3	no	extensive	alive, 75.5
012	8.3, 11.4	9.0	7.8	CsA	12	9	Gr I	extensive	alive, 50.6
025	7.0, 9.2	3.1	4.7	CsA	14	9	no	extensive	alive, 39.5
026	9.3, 11.0		3.4*	CsA	4	7	no	no	alive, 37.5
033	2.2, 3.4	3.4	3.1	CsA	7	4	Gr I	no	alive, 41.0
056	3.0, 4.1	2.5	0.96	CsA	7	41	no	no	alive, 29.8
094	2.0, 2.9	11.9	4.2	CsA	5	12	no	no	alive, 12.0

PBSC, peripheral blood stem cell; MNC, mononuclear cell; GVHD, graft versus host disease; ANC, absolute neutrophil count; CsA, cyclosporin A. *Indicate number of $CD34^+$ cells separated from the pooled peripheral blood stem cell concentrate with an avidin-biotin column.

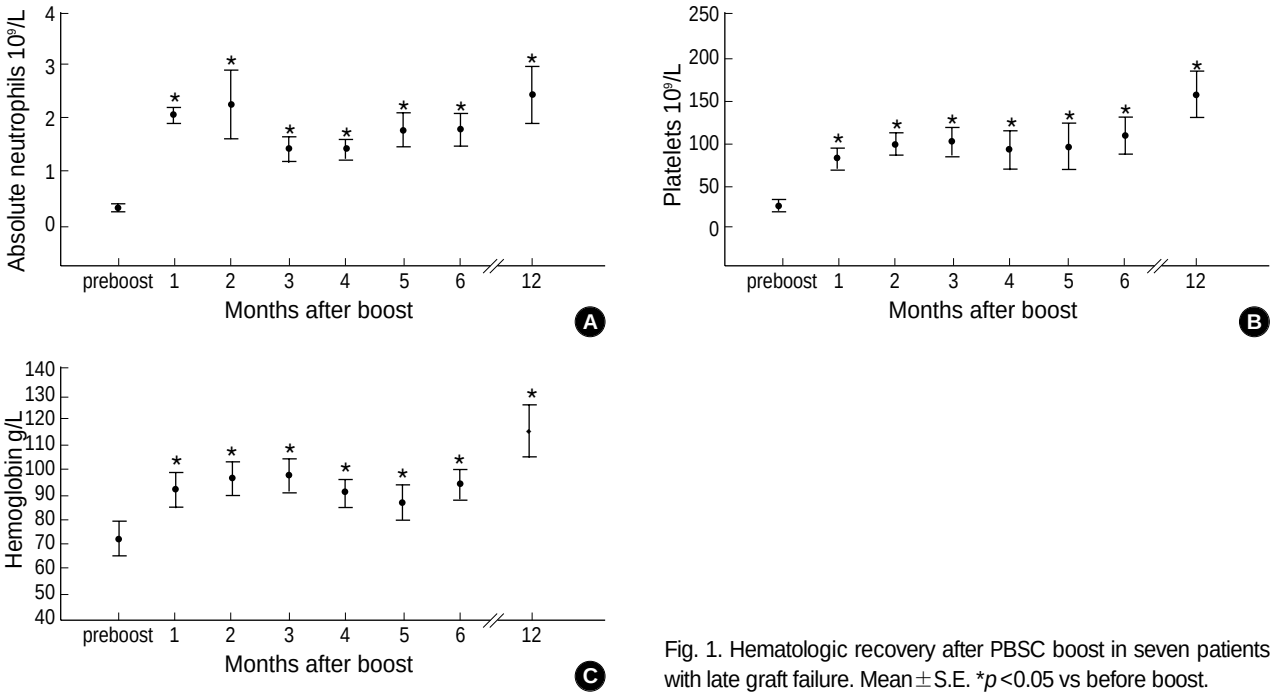

Fig. 1. Hematologic recovery after PBSC boost in seven patients with late graft failure. Mean±S.E. *p<0.05 vs before boost.

ually decreased to 0.2×10^9/L granulocytes and 16×10^9/L platelets. X-chromosome FISH showed 86.3% donor type cells. The patient achieved complete hematologic recovery after a third allogeneic BMT that was done at 417 days after the boost.

GVHD and survival

After the boost, two patients developed grade I acute GVHD, which responded to steroid promptly. Chronic GVHD developed in three patients, all in the extensive form. In Patient 002, involvement of the skin, oral and gastrointestinal mucosa, eye, and liver appeared about 1 yr after the boost, when he was on the oral CsA at 50 mg. Pulse therapy with prednisolone 60 mg/day and CsA 600 mg/day resulted in gradual improvement of the GVHD, and he is now doing well without therapy at 75.5 months after boost. In Patient 012, skin, oral and intestinal mucosa, and lung involvement appeared on day 147, while she was still on CsA. Her GVHD has improved with steroids and hydroxychloroquine added to CsA, and she is now doing well without therapy at 50.6 months after boost. Patient 025 developed chronic GVHD with skin, oral, and hepatic involvement on day 420, when she was off from CsA therapy. With the onset of chronic GVHD, CsA plus steroid therapy was started with a favorable response, and she is now doing well without therapy at 39.5 months after boost. The remaining four patients who did not develop chronic GVHD are alive with good graft function at 41.0, 37.5, 29.8, and 12.0 months after boost, respectively (Table 3).

With a median follow-up time of 3.3 yr (range, 1.0-6.2 yr) from the PBSC rescue, all seven patients, including one who received a third transplant for reappearance of pancytopenia,

are still alive and well.

DISCUSSION

In this study, we evaluated the effect and outcome of reinfusion of allogeneic G-CSF-mobilized PBSC for rescue of late graft failure after BMT in seven patients with SAA. Graft failure remains to be an important obstacle to the successful BMT for patients with SAA. Factors that may contribute to graft failure include prior blood transfusion (21), number of cells infused (22), the type of immunosuppression used (1), T cell depletion (1), and the degree of HLA disparity (23). The infused MNC dose was a significant discriminant factor for developing graft failure in our patients. Although the reasons for graft failure were not clear, potential risk factors for graft failure, such as low dose of marrow cells, multiple prior blood transfusions, transfusion of blood products from family, and hepatitis C virus infection, were identified in six of seven patients. Conditioning regimens including irradiation are less likely to be followed by graft failure (7). In our patients, 7 of 21 patients conditioned without irradiation developed graft failure, while none of 4 patients conditioned with irradiation developed graft failure. However, the conditioning regimen was not a discriminating factor for developing graft failure (Table 2).

Therapeutic options after graft failure include a second marrow infusion, the use of hematopoietic growth factors, and most recently allogeneic G-CSF-mobilized PBSC infusion. Sierra et al. (4) reported their experience of 25 patients with bone marrow failure after BMT who were treated with rhGM-CSF. In that report, 10 of 11 patients with secondary graft failure attained an ANC higher than 0.5×10^9/L, but most became severely neutropenic again at a median of 4 weeks. In addition, no significant changes was observed in the transfusion requirements for red cells or platelets during or after rhGM-CSF. In four of our seven patients, rhGM-CSF at 5 μg/kg/day was tried for three weeks to no avail.

A second marrow transplant from the same donor, or from another HLA-identical sibling if available, is an widely accepted approach. Reinfusion of marrow can be an effective intervention in achieving second engraftment in graft failure patients, but survival is limited because of high mortality from infection (6, 7).

Recent attention has been focused on the use of PBSC for allogeneic transplantation in this setting. Several reports have confirmed the feasibility of allogeneic transplants employing PBSC (16-18). The first report of graft failure treatment by Dreger et al. (11) strongly suggested that a boost with allogeneic PBSC could restore bone marrow function. Other groups successfully reversed graft failure with CD34-selected PBSCT (24, 25). Gurman et al. (13) firstly reported allogeneic PBSCT as a second transplantation for late graft failure in SAA. Rapid, sustained engraftment, along with the presence of mostly donor-type CD3+ lymphocytes in the peripheral blood after G-CSF mobilized PBSCT, implies that a large number of donor T cells can surpass the residual host T cells, even without a prior conditioning regimen (26). Redei et al. (14) reported the first case of allogeneic PBSCT without prior reconditioning for the treatment of primary graft failure following BMT for SAA.

The issue of reconditioning before second marrow or blood cell infusion for graft failure is controversial. Champlin et al. (1) reported that survival in aplastic anemia patients treated with a second bone marrow infusion was not significantly influenced by the use of reconditioning regimen. McCann et al. (7) reported that patients conditioned with irradiation before second BMT had better survival, but it did not reach statistical significance. In a study of patients with primary graft failure who received either no reconditioning or only increased immunosuppression before a second marrow infusion, Davies et al. (6) reported that 8 of 12 (66%) patients achieved engraftment and 4 survived. In contrast, only 4 of 9 (44%) patients who received chemotherapy with or without irradiation as reconditioning experienced engraftment and none of them survived. Therefore, the role of reconditioning remains to be controversial. The potential benefit of potent immunosuppression to counteract immune-mediated graft failure might be offset by the high risk of infection, which may contribute to fatal outcome. Chimeric status at the time of graft failure is of value in considering reconditioning before the second transplantation. Mixed chimerism per se is not always an indicator of impending graft failure, and the degree of mixed chimerism may be the deciding factor for the graft failure (27, 28). In our patients, complete donor chimerism was documented in all the patients at the time of PBSC rescue. All but one were treated with allogeneic PBSCs without immunosuppression, thereby avoiding the risk of reconditioning.

Potential disadvantages of allogeneic PBSCT include the theoretical increased risk of GVHD, due to the presence of approximately 10 to 100 times more T lymphocytes in the leukapheresis products than in bone marrow (18). Unexpectedly, however, the incidence and severity of acute GVHD was not increased in PBSCT (16, 17). In our study, no patients developed grade II-IV acute GVHD after reinfusion of donor cells. The incidence of chronic GVHD after allogeneic PBSCT is still controversial. A tendency toward an increased incidence of chronic GVHD has been reported in some studies (29-31), while other investigators report comparable incidence of chronic GVHD after PBSCT (16, 32, 33). Follow-up duration was too short to accurately assess the incidence of chronic GVHD in most studies (16, 32, 33). In addition, most studies compared retrospective control BMT data with the PBSCT figures. In our study, three of seven (42.9%) patients developed extensive chronic GVHD. This incidence is similar to that reported by Anderlini et al. (30) and less than that reported by Majolino et al. (29) However, it is significantly higher than that observed in 17 SAA patients who survived for at least

100 days and did not show graft failure after BMT in this study (43% vs. 5.9%; p=0.027). The BMT group received CsA and short-course MTX, but the PBSC boost group received only CsA for GVHD prevention. However, this difference in GVHD prophylaxis does not seem to be directly associated with the difference in the incidence of extensive chronic GVHD. Levine et al. (34) reported that there was no statistically significant difference in the probability of developing chronic GVHD between patients who received MTX as part of GVHD prophylaxis and those who did not receive MTX. There is no advantage associated with the development of chronic GVHD in SAA; thus, the development of more effective strategies for the prevention and treatment of chronic GVHD, such as the addition of steroids or partial T cell depletion, is to be considered, although chronic GVHD was not associated with transplant-related mortality in this study.

Hematopoietic recovery after PBSC boost was successful in the majority of patients. Post-engraftment boost showed sustained graft function in six of seven patients. All seven patients, including one who received a third transplant for recurrent pancytopenia after PBSC boost, survived with a median follow-up of 3.3 yr (range, 1.0-6.2 yr).

This report suggests that G-CSF-mobilized allogeneic PBSC rescue is successful in achieving complete, sustained engraftment after graft failure in patients with SAA. But as the incidence of extensive chronic GVHD is higher than that following BMT, more efficacious measures to prevent extensive chronic GVHD should be developed.

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