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Infectious Complications after Allogeneic Peripheral Blood Stem Cell Transplantation Compared with Bone Marrow Transplantation

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ABSTRACT

We compared the incidence of bacterial, fungal, and cytomegalovirus (CMV) infections after peripheral blood stem cell transplantation (PBSCT) with that after bone marrow transplantation (BMT). Thirteen patients who received PBSCT and 23 patients who received BMT were analyzed from May 1997 through July 2002. We evaluated the time to neutrophil and platelet engraftment, and the incidence of acute and chronic graft-*versus*-host disease (GvHD). We also monitored CMV infections with the pp65 antigen assay. The time to neutrophil engraftment was significantly less after PBSCT than after BMT ($p=0.01$). However, the time to platelet engraftment and the incidences of acute and chronic GvHD, bacteremia, and fungal infection did not differ between PBSCT and BMT. The incidence of CMV infection during the early-phase was significantly lower after PBSCT than after BMT (33% vs 74%, $p=0.04$). However, the cumulative incidence of CMV infection, including late-phase infection, did not differ significantly between PBSCT and BMT. These results indicate that neutrophil engraftment occurs sooner after PBSCT than after BMT and that early-phase CMV infection is less common after PBSCT. However, late-phase CMV infections are common after PBSCT. Therefore, extended antigenemia surveillance is recommended for patients who receive PBSCT. (Jikeikai Med J 2003 ; 50 : 115-24)

Key words : cytomegalovirus, infectious complication, peripheral blood stem cell transplantation, cytomegalovirus antigenemia surveillance, late-phase cytomegalovirus infection

INTRODUCTION

Advances in the treatment of patients with hematologic malignancies include the use of intensive chemotherapy with hematopoietic stem cell transplantation (HSCT). However, patients undergoing HSCT are at extremely high risk for severe infections. Because of high-dose chemotherapy with or without total body irradiation (TBI), extremely severe myelosuppression induces such changes in the host defense system as neutropenia and disruption of the gastrointestinal mucosa and immune function. The posttransplantation course can be divided into three phases that correspond to immunologic recovery : 1) an aplasia phase (the first 2 to 4 weeks after HSCT until engraftment), 2) an early phase (from engraftment until day 100 after HSCT), and 3) a late phase (from day 101 after HSCT until restoration of the immune system). In all posttransplantation phases, infectious complications remain the major causes of morbidity and mortality.

The two current methods of allogeneic HSCT are

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bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT). Allogeneic PBSCT is increasingly being used instead of BMT. PBSCT is thought to be associated with a reduced risk of transplant-related infections because of early immune reconstitution[1,2] but has a higher risk of chronic graft-*versus*-host disease (GvHD) than does BMT[3]. Despite the development of effective antiviral agents[4–6], conditions caused by cytomegalovirus (CMV), such as interstitial pneumonitis and colitis, are still a major cause of morbidity and mortality after HSCT[7]. Recently, the pp65 antigen assay, which detects a CMV-specific antigen expressed by cells early after infection, has been developed to diagnosis CMV infection[8]. We used the pp65 antigen assay to compare the incidence of CMV infections after PBSCT with that after BMT. In addition, the incidence of other infectious complications, overall survival, and causes of death were analyzed.

Patients and Methods

1. *Patients*

Thirty-six patients with hematologic malignancies and solid tumor admitted to the Jikei University Hospital from May 1997 through July 2002 were analyzed. Hematologic malignancies included acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myeloid leukemia, and non-Hodgkin's lymphoma. The solid tumor was a case of renal cell carcinoma.

2. *Transplantation*

The patients received non-T-cell depleted, HLA-identically related HSCT as either BMT or PBSCT. As conditioning regimens, busulfan/cyclophosphamide/total body irradiation (TBI)[9] or busulfan/cyclophosphamide was used for myeloid leukemia and etoposide/cyclophosphamide/TBI was used for lymphoid leukemia (Table 1). Prophylaxis against GvHD consisted of cyclosporine A[10] or tacrolimus

Table 1. Patient characteristics

		PBSCT	BMT
Number of patients		13	23
Age (years)	median (range)	35 (23-58)	41 (16-53)
Sex	male/female	9/4	15/8
Disease	chronic myeloid leukemia	2	10
	acute myeloid leukemia	4	5
	acute lymphoblastic leukemia	4	6
	myelodysplastic syndrome	1	1
	non-Hodgkin's lymphoma	1	1
	renal cell carcinoma	1	0
Status	CR/CP	7	16
	non-CR	6	7
Conditioning regimen	BU/CY/TBI	6	13
	ETP/CY/TBI	3	2
	TBI+other combination	1	2
	BU*/CY	0	3
	Others	3	3
Prophylaxis for GvHD	CSP+MTX	11	23
	FK506+MTX	2	0

CR, complete remission; CP, chronic phase; BU, busulfan (4 mg/kg for 2 days); CY, cyclophosphamide (60 mg/kg for 2 days); TBI, total body irradiation (2 Gy×5 times); ETP, etoposide (30 mg/kg for 2 days); BU*, busulfan (4 mg/kg for 4 days); Others, including fludarabine based reduced intensity regimens or non-TBI based regimens; CSP, cyclosporine A; MTX, methotrexate; FK506, tacrolimus hydrate

hydrate[11] combined with methotrexate.

3. *Prophylaxis against infections*

All patients received prophylaxis against bacterial and fungal infection which consisted of polymixin B sulfate (3×10^6 U/day p.o.), fluconazole (200 mg/day p.o.), or itoraconazole (200 mg/day p.o.). Sulfamethoxazole (1,200 mg daily p.o.) and trimethoprim (240 mg daily p.o.) were given for at least 21 consecutive days before transplantation as prophylaxis against *Pneumocystis carinii* pneumonia. Treatment with sulfamethoxazole and trimethoprim was resumed after engraftment using a 2 days/week schedule[12]. Acyclovir was given orally at a dose of 200 mg 5 times a day for herpes virus prophylaxis from 7 days before transplantation to 35 days after transplantation.

4. *Definition of engraftment and GvHD*

The primary measure of hematologic recovery was the time after transplant until neutrophil engraftment, indicated by a neutrophil count of at least 0.5×10^9/L for 2 consecutive days. The time until platelet engraftment, indicated by platelet count of at least 20×10^9/L, was also recorded. In addition, serial monitoring (days 10, 20, 30, 50, 100, 150, 200, and 365 after transplantation) of white blood cell (WBC), neutrophil, and lymphocyte reconstitution was performed. Acute GvHD was graded on the basis of the 1994 Consensus Conference on Acute GvHD Grading[13].

5. *Blood culture, plasma levels of endotoxin, and diagnosis of bacteremia*

Plasma levels of endotoxin were evaluated at least once a week as clinically indicated. On the basis of results of a previous study, plasma endotoxin levels greater than 5 pg/L were considered to indicate endotoxemia[14]. Blood for cultures was drawn twice when body temperature was 38°C or higher and were obtained thereafter as clinically indicated. Bacteremia was diagnosed on the basis of at least 1 positive culture and appropriate clinical findings. Patients received antibiotics intravenously after 1 measurement of a body temperature≥38°C. Empiric antibiotic therapy was performed according to previously published guidelines[15].

6. *Plasma levels of beta-D-glucan and diagnosis of fungal infection*

Plasma levels of beta-D-glucan (βDG) were evaluated at least once a week as indicated clinically, and tests for βDG were considered positive when plasma levels were greater than 10 pg/L[16]. Fungal infections were confirmed by demonstration of fungi with blood culture or biopsy specimen.

7. *CMV pp65 antigen assay*

CMV infections were monitored with the pp65 antigen assay at least once a week as indicated clinically. The CMV pp65 antigenemia assay was performed with peripheral blood leukocytes applied to slides after cytocentrifugation of 1.5×10^5 cells. The cells were stained with a peroxidase-conjugated monoclonal antibody (C7HRP), which specifically binds the pp65 antigen of CMV[8]. The degree of antigenemia was expressed as the number of CMV antigen-positive cells per 5×10^4 leukocytes.

8. *Diagnosis of CMV infection and disease*

CMV infection was indicated by a positive antigenemia assay. CMV diseases were confirmed by the demonstration of CMV in the biopsy specimen or CMV by polymerase chain reaction in bronchoalveolar fluid in presence of pulmonary infiltrates. CMV infection and disease were defined as "early-phase" when occurring from engraftment until days 100 after HSCT and as "late-phase" when occurring after 101 days or more.

9. *CMV prophylaxis and preemptive therapy*

All blood products were irradiated and filtered, and for CMV prophylaxis all patients were given 5 g immunoglobulin intravenously per week for the first 3

months after transplantation. Patients with antigenemia were given preemptive therapy with gancyclovir (5 to 10 mg/kg body weight/day) for more than 14 days[17,18].

10. Statistical analysis

The time to engraftment, time to CMV infection, and the initial degree and maximal degree of CMV antigenemia were compared using Mann-Whitney U tests for unpaired comparisons. The incidences of acute and chronic GvHD and bacterial, fungal, and CMV infections were compared using the χ^2 test. The serial changes in WBC, neutrophil, and lymphocyte counts were compared by repeated-measures analysis of variance (ANOVA) tests. Overall survival was estimated with the Kaplan-Meier technique, and differences between two groups were compared using the log-rank test.

RESULTS

1. Patient characteristics

Thirteen patients received allogeneic PBSCT, and 23 received allogeneic BMT (Table 1). TBI containing conditioning regimens including TBI were used in 27 patients (10 receiving PBSCT and 17 receiving BMT, Table 1). Reduced-intensity conditioning regimens[19-21] were used in 2 patients who received PBSCT. To prevent GvHD, 34 patients were given cyclophosphamide and methotrexate and 2 patients were given FK506 and methotrexate.

2. Engraftment and GvHD

Thirty-three patients (11 receiving PBSCT and 22 receiving BMT) were followed up for more than 100 days after transplantation and were evaluated for the incidence of chronic GvHD. The time to neutrophil engraftment was significantly less in patients receiving PBSCT (median, 14 days; range, 11 to 51 days) than in patients receiving BMT (median, 19 days; range, 11 to 50 days; $p=0.01$). However, the time to platelet engraftment did not differ significantly between patients receiving PBSCT (median, 16 days; range, 11 to 43 days) and patients receiving BMT (median, 25 days; range, 13 to 55 days; Table 2). The rates of acute and chronic GvHD did not differ significantly between patients receiving PBSCT and patients receiving BMT (Table 3).

3. WBC, neutrophil, and lymphocyte reconstitution

During reconstitution, WBC and neutrophil

Table 2. Time to engraftment

		PBSCT	BMT	P value
Neutrophil ($>0.5\times10^9$/L)	median (range) days	14 (11-51)	19 (11-50)	0.01
Platelet ($>20\times10^9$/L)		16 (11-43)	25 (13-55)	0.13

The time to neutrophil and platelet engraftment were evaluable in all patients. The times to neutrophil and platelet engraftment were analysed with Mann-Whitney U tests.

Table 3. GvHD

		PBSCT	BMT	P value
Acute GvHD				
All grades	number of patients (%)	4 (31)	8 (30)	0.99
Grade II-IV		2 (15)	4 (17)	0.99
Chronic GvHD				
All grades	number of patients (%)	7 (64)	6 (27)	0.1
Extensive		5 (45)	3 (14)	0.11

All patients were evaluable in the incidence of acute GvHD, whereas 11 in PBSCT and 22 in BMT patients were evaluable chronic GvHD.
The incidence of acute and chronic GvHD were compared using the χ^2 test.

counts did not differ significantly between patients receiving BMT and those receiving PBSCT (Fig. 1a, b). However, during lymphocyte reconstitution, early-phase (from engraftment to day 100) lymphocyte numbers were higher in patients receiving PBSCT than in patients receiving BMT, whereas late-phase (day 101 or after) lymphocyte numbers were lower in patients receiving PBSCT (Fig. 1c).

4. *Bacterial infection*

The rate of bacteremia did not differ significantly between patients receiving PBSCT (15%, 2 of 13 evaluable patients) and patients receiving BMT (26%, 6 of 23 evaluable patients, $p=0.75$; Table 4). Four of seven identified pathogens were Gram-negative bacteria. The rates of endotoxemia did not differ significantly between patients receiving PBSCT (0%, 0 of 13 patients) and those receiving BMT (11%, 2 of 19 patient, $p=0.64$).

5. *Fungal infection*

The rates of fungal infection did not differ significantly between patients receiving PBSCT (8%, 1 of 13 evaluable patients) and patients receiving BMT (4%, 1 of 23 evaluable patients, $p=0.99$, Table 4). Furthermore, rates of positivity for βDG did not differ significantly for patient receiving PBSCT (46%, 6 of 13 evaluable patients) and patients receiving BMT (21%, 4 of 19 patients, $p=0.26$). Fungal pneumonia developed on day 68 in 1 patient who received PBSCT, and fungemia developed on day 256 in 1 patient who received BMT.

6. *CMV infection and CMV disease*

Thirty-five patients (12 receiving PBSCT and 23 receiving BMT) were followed up for longer than 30 days after transplantation. The incidence of early-phase CMV infection was significantly lower in patients receiving PBSCT (33%) than in patients receiving BMT (74%, $p=0.04$). However, the incidence of all cases of CMV infection, including late-phase infection, did not differ significantly between patients receiving PBSCT (50%) and patients receiving BMT (74%, $p=0.29$, Table 4). The median time to the development of CMV infection did not differ significantly between patients receiving PBSCT (46 days; range, 32 to 153) and patients receiving BMT (32 days; range, 14 to 75 days, $p=0.06$). The initial degree of CMV antigenemia (positive cells per 5×10^4 leukocytes) did not differ significantly between patients receiving PBSCT (median, 2.5 cells; range, 1.6 to 6.0 cells) and patients receiving BMT (median, 2.8 cells; range, 1.3-1,866.7 cells; $p=0.48$). How-

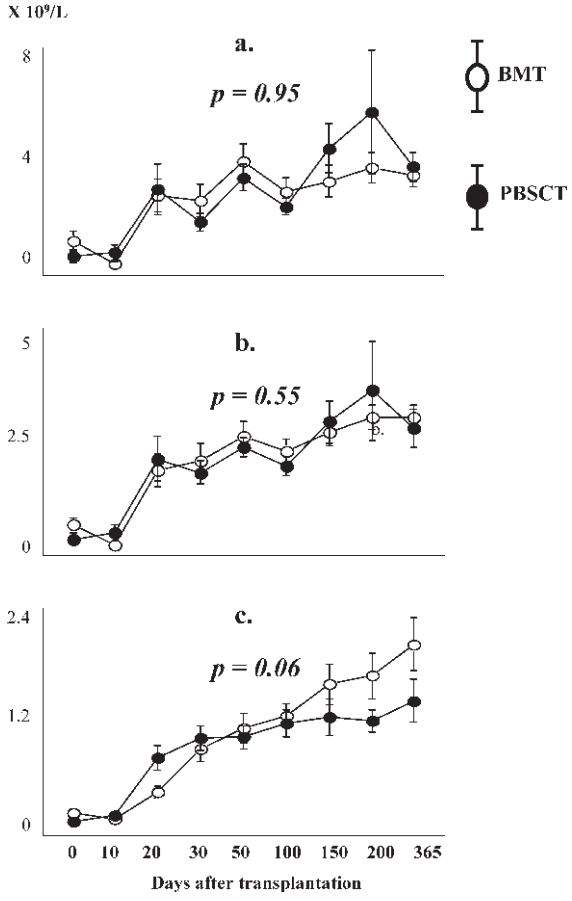

Fig. 1a. WBC reconstitution after PBSCT and BMT.
Fig. 1b. Neutrophil reconstitution after PBSCT and BMT.
Fig. 1c. Lymphocyte reconstitution after PBSCT and BMT. Serial monitoring of WBC, neutrophil, and lymphocyte reconstitution after transplantation was done in all patients. No differences in WBC and neutrophil reconstitution were found between PBSCT and BMT (Fig. 1a, b). Although, early-phase lymphocyte number in PBSCT was higher than that in BMT, late-phase lymphocyte number was lower in PBSCT (Fig. 1c, not significant).

Table 4. Bacterial, fungal, and CMV infections

		PBSCT	BMT	*P* value
Bacterial infection				
Endotoxemia	number of patients (%)	0 (0)	2 (11)	0.64
Bacteremia	number of patients (%)	2 (15)	6 (26)	0.75
Pathogens	Gram-positive bacteria	0	3	
	Gram-negative bacteria	2	2	
Fungal infection				
βDG positivity	number of patients (%)	6 (46)	4 (21)	0.26
Fungal infection	number of patients (%)	1 (8)	1 (4)	0.99
Pathogens	Candida spicies	0	1	
	Aspergillus spicies	1	0	
CMV infection				
Early-phase	number of patients (%)	4 (33)	17 (74)	0.04
Overall		6 (50)	17 (74)	0.29
Time to CMV infection	median (range)	46 (32-153)	32 (14-75)	0.06
CMV disease	number of patients (%)	0 (0)	1 (4)	0.99

Thirteen patients in PBSCT and 19 in BMT were evaluable plasma level of endotoxin and βDG. The incidence of positive endotoxin, bacteremia, and plasma level of βDG were compared using χ^2 test. Twelve patients in PBSCT and 23 in BMT were evaluable CMV infection. The incidence of CMV infection and CMV disease were compared using χ^2 test.
The time to develop CMV infection was analysed with Mann-Whitney *U* tests.

ever, the maximum degree of CMV antigenemia was greater in patients receiving PBSCT (median, 4.5 cells ; range, 1.9 to 7.1 cells) than in patients receiving BMT (median, 8.8 cells ; range, 1.3 to 1,866.7 cells, $p=0.05$). CMV gastritis developed in 1 patient who received BMT, but CMV disease did not develop in any patients receiving PBSCT. In this patient, clinical symptoms developed at the same time CMV infection was detected with the pp65 antigenemia assay. The clinical diagnosis was confirmed with endoscopic biopsy. This patient was successfully treated with 10 mg/kg gancyclovir for more than 2 months[22].

7. *Overall survival and cause of death*

As of November 1, 2002, the median duration of follow up was 374 days (range, 27 to 860 days) in patients receiving PBSCT and 517 days (range, 43 to 1960 days) in patients receiving BMT. The overall 2-year survival rate did not differ significantly between patients receiving PBSCT (56%) and patients receiving BMT (58%, $p=0.63$, Fig. 2). At the time of transplantation disease states were considered completely controlled (complete remission [CR] for acute leukemia, myelodysplastic syndrome, and non-Hodgkin's lymphoma and chronic phase [CP] for chronic myeloid leukemia) in 7 patients receiving PBSCT and 16 patients receiving BMT. Two of 7 patients with CR or CP receiving PBSCT died after transplantation (Table 5). One patient died of fungal infection and the other died of acute GvHD. While, 3 of 16 patients with CR or CP receiving BMT died after transplantation. All 3 patients died of progressive disease. The overall 2-year survival rate of patients with CR or CP was 71% after PBSCT and 74% after BMT. Six patients receiving PBSCT and 7 patients receiving BMT were not in CR at the time of transplantation. Two of the 6 non-CR patients receiving PBSCT died after transplantation ; both patients died of progressive disease. While, 5 of 7 non-CR patients receiving BMT died after transplantation : 3 patients died of disease progression and 2 patients died of GvHD. Five hundred days after transplantation, estimated overall survival of non-CR patients was 40% for those receiving PBSCT and 21% for those receiving BMT.

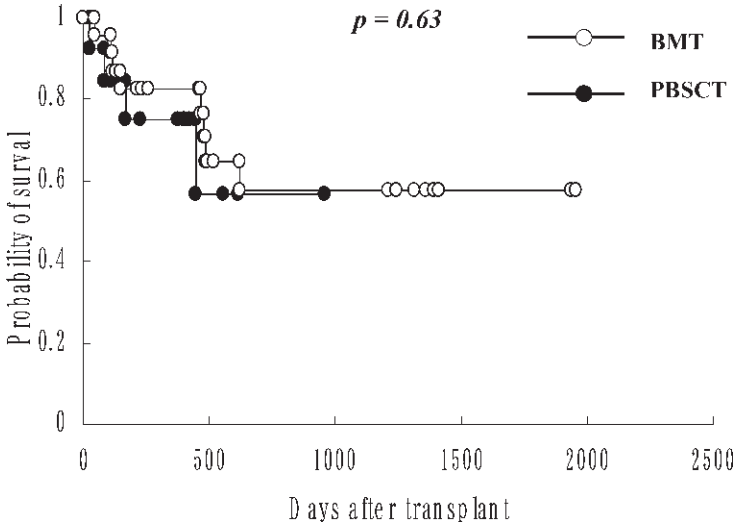

Fig. 2. Overall survival for all patients. Overall survival was estimated using the Kaplan-Meier technique, and differences between two groups were compared using the log-rank test.

Table 5. Causes of death

	PBSCT	BMT
Number of patients	4/13	8/23
Regimen-related death	0	0
Acute GvHD	1	1
Chronic GvHD	0	1
Infectious complications		
Bacterial infection	0	0
Fungal infection	1	0
CMV infection	0	0
Relapse and disease progression	2	6

Thirteen patients received PBSCT and four of them died after transplantation. Twenty-three patients received BMT and eight of them died after transplantation. One patient in PBSCT developed fungal infection together with acute GvHD and died of fungal pneumonia. One patient in BMT died of chronic GvHD. This patient was diagnosed as having fungal pneumonia on the basis of elevated serum level of βDG, but pathogens could not be identified.

Discussion

Results of small randomized studies and studies at single institutions indicate that hematologic recovery is more rapid after allogeneic PBSCT than after BMT[1,2,23-25]. Champlin et al. reported that recoveries of neutrophils and platelets were more rapid in 288 patients who received PBSCT from HLA-identical sibling donors than in 536 patients who received BMT[2]. Although our study had smaller numbers of patients, similar results were obtained. These findings can be used to evaluate possible advantages of PBSCT over BMT. A previous study has reported the risks of bacterial and fungal infections are lower after PBSCT[26]; however, we found no difference in the incidences of bacterial and fungal infections between patients receiving PBSCT and those receiving BMT. The reduced risk of bacterial and fungal infections observed with PBSCT may be due to the more rapid hematologic recovery. Such recovery is likely more important in patients who have been heavily pretreated or have active leukemia. In our study, more patients without CR received PBSCT (46%) than BMT (30%). This difference might have affected the risk of infectious complications.

Differences in immune reconstitution between PBSCT and BMT have also been described[1,27]. PBSC allografts contain 10 times more CD4+ T-cells than do BM allografts[28]. In one study the number of CD4+ T-cells 1 month after engraftment was higher in patients receiving PBSCT than in those receiving BMT, but the difference had disappeared within 3 months after transplant[27]. Additionally, more rapid functional recovery has been observed in PBSCT recipients than in BMT recipients[1]. Although we did not perform immunophenotypical or functional analyses, we did observe more rapid lymphocyte recovery after PBSCT than after BMT. This finding is consistent with previous reports[1,27]. However, an impor-

tant finding in our study was that the late-phase lymphocyte number was lower in PBSCT. This finding may be due to the increased risk of chronic GvHD itself or to the immunosuppressive therapy used for its control.

Acute and chronic GvHD are the most common causes of death after stem cell transplantation. The risk of acute GvHD was once thought to be higher after PBSCT than after BMT because PBSC allografts contain a higher absolute number of lymphocytes. However, many clinical results have shown that the risks of acute GvHD after PBSCT and after BMT are similar[1,2,23-25]. A higher incidence of clinically extensive chronic GvHD after PBSCT than after BMT has been found in some studies[3,27] but not in others[23]. We found that the risk of acute GvHD was similar after PBSCT and after BMT. In Japan, both acute and chronic GvHD after BMT are less frequent than in the United States[29]. However whether the risk of GvHD after PBSCT is lower in Japan than in the United States remains unclear. A prospective randomized trial is warranted in our country to clarify this problem.

CMV infection might occur under the immunodeficient states caused by acute and chronic GvHD or the immunosuppressive therapy used for its control. Chronic GvHD seems to be the most important risk factor for late-phase CMV infection and CMV disease[30]. Therefore, we hypothesize that the incidence of early-phase CMV infection is lower after PBSCT, whereas late-phase CMV infection may be higher after PBSCT associated with chronic GvHD. Because CMV antigenemia usually occurs in the first 100 days after transplantation, in most studies examinations for CMV infection or disease were performed only in the presence of symptoms. Therefore, little surveillance data are available on the incidence of late-phase CMV infection[31]. In our study, the incidence of early-phase CMV infection was significantly lower after PBSCT than after BMT. The cumulative incidence of CMV infection, including late-phase infection, did not differ between PBSCT and BMT. We observed a 17% increase in the probability of antigenemia 100 days after transplantation (from 33% in the early-phase to 50% in the late-phase). Our present data demonstrate that antigenemia is common more than days 100 after PBSCT. The higher rate of late-phase CMV infection in patients who have received PBSCT might be due to the lower number of cytotoxic T lymphocytes with or without functional activity. On the basis of this possibility, we performed preemptive treatments and successfully prevented CMV disease. This result suggests the usefulness of extended antigenemia surveillance and preemptive treatment. Quantification of CMV DNA has recently been introduced and may be useful for monitoring CMV infection and assessing the efficacy of antiviral therapy[32]. Quantitative polymerase chain reaction has several advantages over the antigenemia assay, including an increased sensitivity for CMV reactivation, reliable detection of CMV reactivation during severe neutropenia in the early phase after transplantation, and convenient processing of large numbers of specimens. More recently, direct detection of CMV-specific cytotoxic T lymphocytes using flow-cytometric analysis has been reported[33]. We are planning to perform a prospective study to confirm our hypothesis with these methods.

Another poorly understood problem is the graft-versus-leukemia (GVL) effect after PBSCT. We found no significant difference in overall survival between non-CR patients after PBSCT and BMT. Longer follow-up is necessary to evaluate whether the risk of relapse is affected by the type of graft. The higher rate of chronic GvHD with PBSCT might also be associated with greater GVL effects.

In summary, we conclude that the time to neutrophil engraftment is less and the incidence of early-phase CMV infection is lower after PBSCT than after BMT. However, episodes of late-phase CMV infection, as indicated by antigenemia, are common after PBSCT. Therefore, extended antigenemia surveillance is recommended for patients who have received PBSCT.

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References

1. Ottinger HD, Beelen DW, Scheulen B, Schaefer UW, Grosse-Wilde H. Improved immune reconstitution after allotransplantation of peripheral blood stem cells instead of bone marrow. Blood 1996 ; 88 : 2775-9.
2. Champlin RE, Schmitz N, Horowitz MM, Chapuis B, Chopra R, Cornelissen JJ, et al. Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. Blood 2000 ; 95 : 3702-9.
3. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH. Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation : a meta-analysis. J Clin Oncol 2001 ; 19 : 3685-91.
4. Winston DJ, Ho WG, Bartoni K, Du Mond C, Ebeling DF, Buhles WC, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients : results of a placebo-controlled, double-blind trial. Ann Intern Med 1993 ; 118 : 179-84.
5. Reusser P, Einsele H, Lee J, Volin L, Rovira M, Engelhard D, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood 2002 ; 99 : 1159-64.
6. Vusirikala M, Wolff SN, Stein RS, Brandt SJ, Morgan DS, Greer JP, et al. Valacyclovir for the prevention of cytomegalovirus infection after allogeneic stem cell transplantation : a single institution retrospective cohort analysis. Bone Marrow Transplant 2001 ; 28 : 265-70.
7. Wingard JR. Infections in allogeneic bone marrow transplant recipients. Semin Oncol 1993 ; 20 : 80-7.
8. van der Bij W, Torensma R, van Son WJ, Anema J, Schirm J, Tegzess AM, et al. Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leukocytes. J Med Virol 1988 ; 25 : 179-88.
9. Asai O, Yano S, Sugiyama K, Saito T, Okawa Y, Sekiguchi N, et al. Adding busulfan with cyclophosphamide-total body irradiation as preparative regimen for allogeneic transplantation reduced relapse rate in advanced myeloid leukemia. Blood 2002 ; 100(suppl) : 634a.
10. Storb R, Pepe M, Deeg HJ, Anasetti C, Appelbaum FR, Bensinger W, et al. Long-term follow-up of a controlled trial comparing a combination of methotrexate plus cyclosporine with cyclosporine alone for prophylaxis of graft-versus-host disease in patients administered HLA-identical marrow grafts for leukemia. Blood 1992 ; 80 : 560-1.
11. Nash RA, Antin JH, Karanes C, Fay JW, Avalos BR, Yeager AM, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood 2000 ; 96 : 2062-8.
12. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1987 ; 316 : 1627-32.
13. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant 1995 ; 15 : 825-8.
14. van Deventer SJ, Buller HR, ten Cate JW, Sturk A, Pauw W. Endotoxaemia : an early predictor of septicaemia in febrile patients. Lancet 1988 ; 8586 : 605-8.
15. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002 ; 36 : 730-51.
16. Kohno S, Mitsutake K, Maesaki S, Yasuoka A, Miyazaki T, Kaku M, et al. An evaluation of serodiagnostic tests in patients with candidemia : beta-glucan, mannan, candida antigen by Cand-Tec and D-arabinitol. Microbial Immunol 1993 ; 37 : 207-12.
17. Mori T, Okamoto S, Matsuoka S, Yajima T, Wakui M, Watanabe R, et al. Risk-adapted pre-emptive therapy for cytomegalovirus disease in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant 2000 ; 25 : 765-9.
18. Kanda Y, Mineishi S, Saito T, Saito A, Ohnishi M, Niiya H, et al. Response-oriented preemptive therapy against cytomegalovirus disease with low-dose ganciclovir : a prospective evaluation. Transplantation 2002 ; 27 : 568-72.
19. Champlin R, Khouri I, Shimoni A, Gajewski J, Kornblau S, Molldrem J, et al. Harnessing graft-versus-malignancy : non myeloablative preparative regimens for allogeneic haematopoietic transplantation, and an evolving strategy for adoptive immunotherapy. Br J Haematol 2000 ; 111 : 18-29.
20. Childs R, Chernoff A, Contentin N, Bahceci E, Schrump D, Leitman S, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. N Engl J Med 2000 ; 343 : 750-8.
21. Saito T, Kanda Y, Kami M, Kato K, Shoji N, Kanai S, et al. Therapeutic potential of a reduced-intensity preparative regimen for allogeneic transplantation with cladribine, busulfan and antithymocyte globulin against advanced/refractory acute leukemia/lymphoma. Clin Cancer Res 2002 ; 8 : 1014-20.
22. Yano S, Usui N, Asai O, Dobashi N, Sugiyama K, Saito T, et al. Early cytomegalovirus (CMV) gastrointestinal disease that developed within 19 days after bone marrow transplantation with a high-level of CMV antigenemia up to 1120 cell/slide. Submitting.
23. Bensinger WI, Martin PJ, Storer B, Clift R, Forman SJ, Negrin R, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J

Med 2001 ; 344 : 175–81.
24. Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, et al. Allogeneic bone marrow transplantation vs filgrastim-mobillized peripheral blood progenitor cell transplantation in patients with early leukemia : first results of a randomized multicenter trial of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1998 ; 21 : 995–1003.
25. Beelen DW, Ottinger HD, Elmaagacli A, Scheulen B, Basu O, Kremens B, et al. Transplantation of filgrastim-mobilized peripheral blood stem cells from HLA-identical sibling or alternative family donors in patients with hematologic malignancies : a prospective comparison on clinical outcome, immune reconstitution, and hematopoietic chimerism. Blood 1997 ; 90 : 4725–35.
26. Elmaagacli AH, Basoglu S, Peceny R, Trenschel R, Ottinger H, Lollert A, et al. Improved disease-free-survival after transplantation of peripheral blood stem cells as compared with bone marrow from HLA-identical unrelated donors in patients with first chronic phase chronic myeloid leukemia. Blood 2002 ; 99 : 1130–5.
27. Storek J, Gooley T, Siadak M, Bensinger WI, Maloney DG, Chauncey TR, et al. Allogeneic peripheral blood stem cell transplantation may be associated with a high risk of chronic graft-versus-host disease. Blood 1997 ; 90 : 4705–9.
28. Bensinger WI, Weaver CH, Appelbaum FR, Rowley S, Demirer T, Sanders J, et al. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. Blood 1995 ; 85 : 1655–8.
29. Morishima Y, Morishita Y, Tanimoto M, Ohno R, Saito H, Horibe K, et al. Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings ; possible role of genetic homogeneity. Blood 1989 ; 74 : 2252–6.
30. Krause H, Hebart H, Janh G, Muller CA, Einsele H. Screening for CMV-specific T cell proliferation to identify patients at risk of developing late onset CMV disease. Bone Marrow Transplant 1997 ; 19 : 1111–6.
31. Machado CM, Menezes RX, Macedo MCA, Mendes AVA, Vilas Boas LS, Castelli JB, et al. Extended antigenemia surveillance and late cytomegalovirus infection after allogeneic BMT. Bone Marrow Transplant 2001 ; 28 : 1053–9.
32. Caliendo AM, St George K, Kao SY, Allega J, Tan BH, LaFontaine R, et al. Comparison of quantitative cytomegalovirus (CMV) PCR in plasma and CMV antigenemia assay : clinical utility of the prototype AMPLICOR CMV MONITOR test in transplant recipients. J Clin Microbiol 2000 ; 38 : 2122–7.
33. Cwynarski K, Ainsworth J, Cobbold M, Wagner S, Mahendra P, Apperley J, et al. Direct visualization of cytomegalovirus-specific T-cell reconstitution after allogeneic stem cell transplantation. Blood 2001 ; 97 : 1232–40.