TABLE I. Characteristics of the Patients

	CsA500 group (n = 33)	CsA300 group (n = 33)	P-value
Sex			
Male	20	26	0.18
Female	13	7	
Age			
<40	16	17	>0.99
≥40	17	16	
Underlying disease			
AL	24	13	0.017
CML	2	12	
MDS	2	1	
NHL	3	6	
Others	2	1	
Donor			
Related	12	16	0.46
Unrelated	21	17	
HLA			
Match	28	25	0.54
Mismatch	5	8	
Stem cell source			
BM	25	26	>0.99
PB	8	7	
Regimen			
Non-TBI	4	9	0.21
TBI	29	24	
MTX dose			
<31mg/m^2	16	11	0.32
≥31mg/m^2	17	22	

BM, bone marrow; PB, peripheral blood; TBI, total body irradiation; AL, acute leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma.

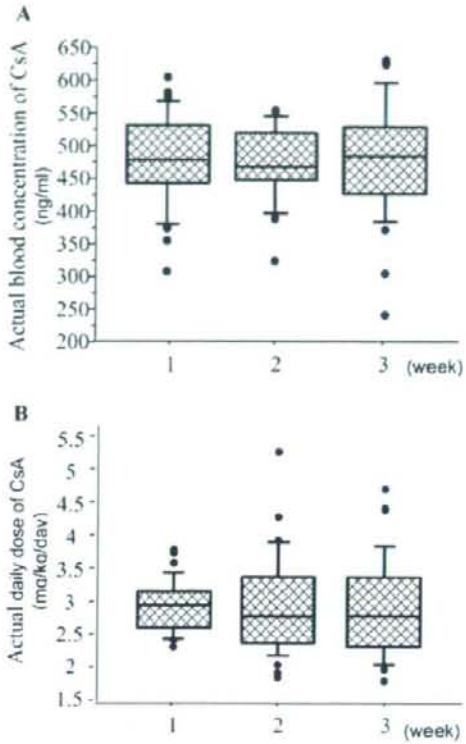

Figure 1. Actual blood concentration (A) and daily dose (B) of cyclosporine. The mean CsA concentration was 488 ± 89, 475 ± 41, and 482 ± 69 ng/ml and the actual dose was 2.9 ± 0.4, 2.8 ± 0.8, and 2.7 ± 0.7 mg/kg at the 1st, 2nd, and 3rd week after HSCT, respectively.

89, 475 ± 41, and 482 ± 69 ng/ml at the 1st, 2nd, and 3rd week after HSCT, respectively (Fig. 1A). The actual dose was 2.9 ± 0.4, 2.8 ± 0.8, and 2.7 ± 0.7 mg/kg at the 1st, 2nd, and 3rd week after HSCT, respectively (Fig. 1B). The median duration of intravenous cyclosporine was 41 days (range 16–74 days) after transplantation.

Toxicity

The incidence of renal dysfunction defined as elevation of the serum creatinine level above ×1.5 and ×2.0 the baseline value was equivalent between the CsA500 group and the CsA300 group (Table II, 24 vs. 24%, P = 0.96 and 15 vs. 13%, P = 0.71, respectively). Liver dysfunction defined as elevation of the total bilirubin level above 2 mg/dl was also similar (30 vs. 24%, P = 0.78). Thrombotic microangiopathy was not observed in any patients. No central nerves system toxicities were observed. In the CsA500 group, we decreased the target level of CsA to 300 ng/ml due to hyperbilirubinemia 9 days after HSCT in one patient and substituted prednisolone for CsA in another patient due to hyperbilirubinemia and renal dysfunction at day 21 after HSCT. The latter patient had already had liver cirrhosis classified to Child-Pugh A due to hepatitis C virus infection before HSCT.

TABLE II. Incidences of Adverse Events Due to Cyclosporine

	(−)	(+)	P-value
Incidence of serum creatinine > 1.5 × baseline value			
CsA500	25	8 (24%)	>0.99
CsA300	25	8 (24%)	
Incidence of serum creatinine > 2.0 × baseline value			
CsA500	28	5 (15%)	0.71
CsA300	30	3 (13%)	
Incidence of bilirubin > 2.0 mg/dl			
CsA500	23	10 (30%)	0.78
CsA300	25	8 (24%)	
Incidence of TMA			
CsA500	33	0 (0%)	>0.99
CsA300	33	0 (0%)	

TMA: thrombotic microangiopathy.

Incidences of acute and chronic GVHD

We performed a univariate analysis to evaluate the impact of potential confounding factors on the incidence of grades II–IV acute GVHD and identified two significant factors; the presence of HLA-mismatch including allele-mismatch and the target level of CsA (Table IIIA). As shown in Fig. 2A, the incidence of grades II–IV acute GVHD in the CsA300 group was significantly higher than that in the CsA500 group (52 vs. 27%, P = 0.033). Corticosteroids therapy for acute GVHD was more frequently required in the CsA300 group (39 vs. 15%, P = 0.051). The percentage of patients who received corticosteroids to treat GVHD was lower than the incidence of grades II–IV acute GVHD, because we did not use systemic corticosteroids for grades II acute GVHD with skin involvement only. The difference in the incidence of

TABLE III. Factors Associated the Incidences of Grades II–IV Acute GVHD and Nonrelapse Mortality

A. Univariate analyses

Factor	Acute GVHD	*P*-value	Nonrelapse mortality	*P*-value
Sex				
Male	20 (44%)	0.31	12 (30%)	0.020
Female	6 (30%)		0 (0%)	
Age				
<40 years	15 (46%)	0.30	4 (14%)	0.21
≥40 years	11 (33%)		8 (30%)	
Underlying disease				
CML	7 (50%)	0.25	2 (14%)	0.49
Non-CML	19 (37%)		10 (25%)	
Donor				
Related	11 (39%)	0.97	8 (36%)	0.052
Unrelated	15 (40%)		4 (13%)	
HLA				
Match	17 (32%)	0.0037	10 (23%)	0.78
Mismatch	9 (69%)		2 (18%)	
Stem cell source				
BM	19 (37%)	0.46	9 (21%)	0.68
PBSC	7 (47%)		3 (24%)	
Regimen				
Non-TBI	4 (31%)	0.56	5 (49%)	0.035
TBI	22 (42%)		7 (15%)	
MTX dose				
<31mg/m^2	12 (44%)	0.32	7 (19%)	0.87
≥31mg/m^2	14 (36%)		5 (24%)	
Target levels of CsA				
CsA500	9 (27%)	0.033	2 (8%)	0.051
CsA300	17 (52%)		10 (27%)	

B. Multivariate analyses

Factor	RR of acute GVHD	*P*-value	RR of nonrelapse mortality	*P*-value
Target levels of CsA				
CsA300	1.00	0.039	1.00	0.064
CsA500	0.43 (0.19–0.96)		0.24 (0.053–1.09)	
HLA				
Match	1.00	0.0062		
Mismatch	3.14 (1.39–7.14)			

grades II–IV acute GVHD between the two groups was more prominent in unrelated HSCT (Fig. 2B, 44 vs. 33% in related HSCT and 59 vs. 24% in unrelated HSCT).

Next, we performed a multivariate analysis to identify independent risk factors for the development of Grades II–IV acute GVHD. Two factors were independently significant with a relative risk (RR) of 3.14 (95% confidence interval [CI] 1.39–7.14, $P = 0.0062$) for the presence of HLA-mismatch and RR of 0.43 (95% CI 0.19–0.96, $P = 0.039$) for the CsA500 group, respectively (Table IIIB). The cumulative incidence of Grades III, IV acute GVHD was only 11%. The target level of cyclosporine (CsA500 vs. CsA300: 3 vs. 18%, $P = 0.045$) was identified as the only significant risk factor for the development of Grades III, IV acute GVHD.

The number of patients who developed limited and extensive chronic GVHD was 5 and 18, respectively, in the CsA300 group and 4 and 11, respectively, in the CsA500 group. The incidence of chronic GVHD was also significantly decreased in the CsA500 group (Table IV and Fig. 3, 47 vs. 73%, $P = 0.016$).

Transplantation outcome

The lower incidence of acute GVHD in the CsA500 group translated into the lower incidence nonrelapse mortality (Table III, 8 vs. 27%, $P = 0.051$). On the other hand, the incidence of relapse tended to be higher in the CsA500 group (Table V, 20 vs. 6%, $P = 0.065$), although this difference became smaller when we excluded patients with CML (19 vs. 10%, $P = 0.29$). Finally, there was no significant difference in disease-free survival between the CsA500 group and the CsA300 group (Fig. 4, 72 vs. 63%, $P = 0.68$).

Discussion

We successfully maintained the blood CsA concentration at around 500 ng/ml and the actual dose at around 3 mg/kg/day by twice a week monitoring for the first 3 weeks after transplantation. The preliminary data in these 33 patients suggested the feasibility and efficacy of the continuous infusion of CsA at this higher target level.

Several studies have reported the relationship between the blood concentration of CsA and the efficacy to prevent GVHD after allogeneic HSCT [2–5]. Especially, the area under the concentration–time curve (AUC) has been believed to be the most important pharmacokinetic parameter for the efficacy of calcineurin inhibitors [8,9]. The monitoring of AUC, however, requires frequent blood sampling and is not suitable for daily practice. Therefore, the trough concentration (C_{TL}) has been measured as a surrogate for AUC in twice-daily infusion of CsA, although recent reports

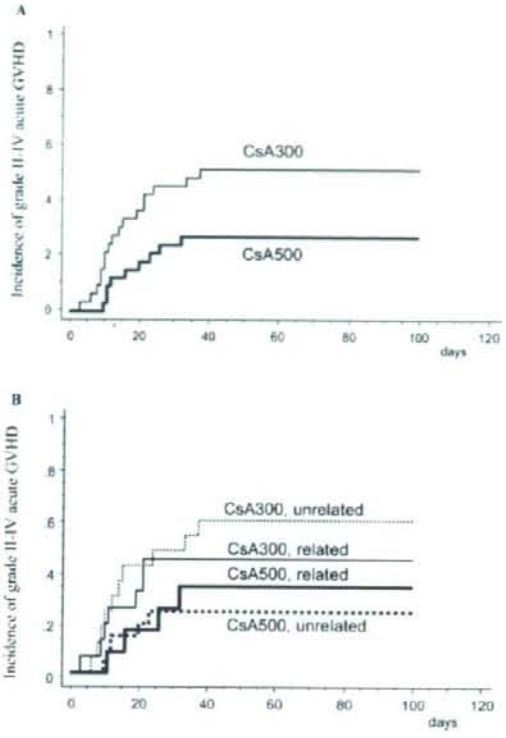

Figure 2. Incidence of Grades II–IV acute GVHD grouped according to the target level of cyclosporine. (A) all patients, (B) stratified by the donor type.

suggested that the measurement of blood concentration at 2–4 hr after infusion may be more appropriate [10]. In continuous infusion, the intradaily variation of the blood concentration of CsA should be minimal and we can evaluate the blood concentration regardless of the timing (steady-state concentration; C_{SS}). However, the relationship between Css in continuous infusion and C_{TL} in twice-daily infusion has not been clarified. Recently, Nakamura et al. reported that the target Css in the continuous infusion of CsA should be 2.55 times the C_{TL} to provide an equal AUC during the twice-daily infusion with a target C_{TL} [11]. Therefore, for example, the target C_{SS} in the continuous infusion of CsA should be 383–638 ng/ml to obtain a similar AUC during the twice-daily infusion with a target C_{TL} at 150–250 ng/ml, that is generally used in daily practice. However, the target blood concentration between 250 and 350 ng/ml is widely used in the continuous infusion of CsA [4]. The expected AUC will be far lower than that during the twice-daily infusion of CsA at the generally used target level. The target C_{SS} in this study at 500 ng/ml (450–550 ng/ml) would be appropriate according to the calculation model. In fact, the actual dose of CsA was maintained at 2.7 and 3.0 mg/kg on average. We had a concern that the incidence of renal dysfunction would be increased, since the relationship between the blood CsA level and drug-induced nephrotoxicity has been shown [12]. The incidence of renal dysfunction, however, was not increased by the dose adjustment and appropriate hydration when CsA levels above the target range were observed.

TABLE IV. Factors Associated the Incidence of Chronic GVHD

A. Univariate analyses

Factor	Chronic GVHD	*P*-value
Sex		
Male	24 (67%)	0.63
Female	10 (56%)	
Age		
<40 years	16 (60%)	0.31
≥40 years	18 (70%)	
Underlying disease		
CML	10 (77%)	0.12
Non-CML	24 (60%)	
Donor		
Related	14 (63%)	0.75
Unrelated	20 (66%)	
HLA		
Match	28 (64%)	0.74
Mismatch	6 (58%)	
Stem cell source		
BM	25 (60%)	0.20
PBSC	9 (81%)	
Regimen		
Non-TBI	27 (64%)	0.75
TBI	7 (65%)	
MTX dose		
<31mg/m^2	15 (64%)	0.81
≥31mg/m^2	19 (68%)	
Target levels of CsA		
CsA500	11 (47%)	0.016
CsA300	23 (73%)	

B. Multivariate analyses

Factor	RR	*P*-value
Target levels of CsA		
CsA300	1.00	0.014
CsA500	0.44 (0.23–0.85)	

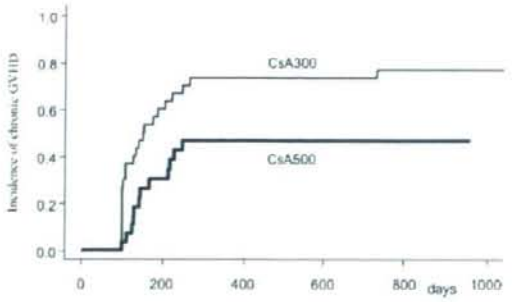

Figure 3. Incidence of chronic GVHD grouped according to the target level of cyclosporine.

Previous randomized control studies that compared continuous infusion of CsA and tacrolimus as GVHD prophylaxis had showed the superiority of tacrolimus to prevent acute GVHD [13–16]. However, these studies employed the lower target level of CsA between 150 and 400 ng/ml. Yanada et al. have also reported that tacrolimus-based regimen was better than cyclosporine-based regimen to prevent GVHD in unrelated bone marrow (BM) transplantation in Japan [17]. However, it was a retrospective analysis

TABLE V. Factors Associated the Incidence of Relapse and Disease-Free Survival

A. Univariate analyses

Factor	Relapse	*P*-value	Disease-free survival	*P*-value
Sex				
Male	5 (12%)	0.90	29 (58%)	0.054
Female	2 (15%)		18 (85%)	
Age				
<40 years	4 (16%)	0.72	25 (71%)	0.35
≥40 years	3 (10%)		22 (60%)	
Underlying disease				
CML	1 (7%)	0.51	11 (79%)	0.34
Non-CML	6 (15%)		36 (60%)	
Donor				
Related	1 (4%)	0.10	19 (60%)	0.53
Unrelated	6 (20%)		28 (67%)	
HLA				
Match	6 (13%)	0.74	37 (63%)	0.64
Mismatch	1 (10%)		10 (72%)	
Stem cell source				
BM	7 (16%)	0.15	35 (63%)	0.55
PBSC	0 (0%)		12 (76%)	
Regimen				
Non-TBI	0 (0%)	0.14	8 (51%)	0.41
TBI	7 (16%)		39 (69%)	
MTX dose				
<31 g/m^2	1 (4%)	0.071	21 (77%)	0.19
≥31 g/m^2	6 (21%)		26 (55%)	
Target levels of CsA				
CsA500	5 (20%)	0.069	26 (72%)	0.68
CsA300	2 (6%)		21 (63%)	

B. Multivariate analyses

Factor	RR of relapse	*P*-value	RR of disease-free survival	*P*-value
Target levels of CsA				
CsA300	1.00	0.065	1.00	0.68
CsA500	4.08 (0.92–18.1)		0.82 (0.32–2.12)	

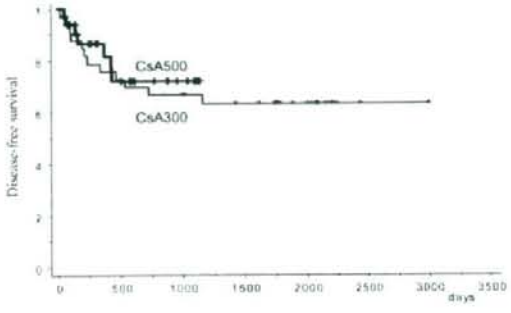

Figure 4. Disease-free survival grouped according to the target level of cyclosporine.

using the database of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and therefore the dose, target blood level, and infusion schedule of both cyclosporine and tacrolimus were various. Especially, the target level of CsA is generally low in the daily practice in Japan. Therefore, the results of these previous studies that compared CsA and tacrolimus as GVHD prophylaxis might have been affected by the target blood concentration [13–17].

The incidence of grades II–IV acute GVHD in the CsA500 group in this study was suppressed to 24% in unrelated HSCT including three HLA allele-mismatched transplants. This incidence was similar to that in the tacrolimus group of patients who underwent HSCT from an alternative donor (30 from an HLA-matched unrelated donor and 4 from the other alternative donor) in a Japanese randomized controlled trial (21%) [13]. Adverse drug reactions were more frequently observed in the tacrolimus group than in the CsA group in this Japanese randomized trial [13], whereas the toxicities in the CsA500 group were equivalent to those in the CsA300 group in the current study. Therefore, the continuous infusion of CsA with a target concentration at 500 ng/ml may provide similar efficacy of GVHD prophylaxis with less frequent toxicities compared to tacrolimus. Wingard et al. have reported that an important relationship between blood concentration of these agents and their efficacy and toxicity using data of a randomized controlled trial [16]. They showed that the efficacy of CsA to prevent GVHD could be improved by elevating the target blood concentration of CsA, whereas the toxicity of tacrolimus could be reduced by lowering the target blood concentration of tacrolimus. Therefore, a randomized controlled trial to compare CsA and tacrolimus with their appropriate target blood concentration is required to draw a definite conclusion.

Another concern about the elevation of the target concentration of CsA was the possible increase in the inci-

dence of relapse [18,19]. We previously showed that the incidence of relapse was significantly lower after the continuous infusion of CsA with the low target CsA concentration at 300 ng/ml compared to twice-daily infusions targeted to 150–300 ng/ml, because the actual dose of CsA was obviously decreased in the continuous infusion group [6]. In this study, the incidence of relapse tended to be higher in the CsA500 group (20 vs. 6%, $P = 0.065$), although there was no significant difference in disease-free survival. A possible explanation of the tendency toward higher relapse rate in the CsA500 group was the impaired graft-versus-leukemia effect due to the higher CsA concentration. Another explanation was the fact that the CsA300 group included significantly more patients with CML in the first chronic phase, the relapse rate of which is expected to be very low. Actually, the difference in the incidence of relapse became smaller when we excluded patients with CML. In addition, relapse in the CsA500 group mainly occurred in patients with relatively poor underlying diseases, including one with chronic neutrophilic leukemia in uncontrollable leukocytosis, one with acute myeloblastic leukemia with monosomy 7, and one with acute lymphoblastic leukemia with minimal residual disease detected by flow cytometry. Therefore, it might be important to make an appropriate definition of standard-risk disease. Currently, we are excluding acute leukemia in first remission with poor cytogenetic abnormalities, such as the presence of Philadelphia chromosome or monosomy 7, from standard-risk disease.

In conclusion, the continuous infusion of CsA with a target level of 450–550 ng/ml appeared to be safe and effective to prevent acute and chronic GVHD. A randomized controlled trial is being planned to confirm the appropriateness of this higher target level of CsA.

Patients and Methods

Patients

A continuous infusion of CsA with the target blood level between 450 and 550 ng/ml was started as GVHD prophylaxis for standard-risk patients at our institute in March 2003. We compared the safety and efficacy of this GVHD prophylaxis with those in the historical standard-risk patients in whom the blood CsA level was targeted to 250–350 ng/ml [6]. Standard-risk disease included acute leukemia in complete remission, CML in chronic phase, myelodysplastic syndrome without leukemic transformation, chemosensitive lymphoma, and nonmalignant disorders such as chronic active Epstein-Barr virus infection, while the others were considered high-risk diseases.

Transplantation procedure

Conditioning regimen was mainly a combination of cyclophosphamide (60 mg/kg for 2 days) with either busulfan (4 mg/kg/day for 4 days) or total body irradiation (TBI; 2 Gy twice daily for 3 days). BM was exclusively used as stem cell source in unrelated HSCT, whereas peripheral blood (PB) or BM was chosen in HSCT from a relative. GVHD prophylaxis consisted of CsA and short term methotrexate (MTX). The dose of MTX was 10 mg/m^2 on day 1 and 7 mg/m^2 on days 3 and 6 in HLA-matched related HSCT. MTX at 7 mg/m^2 was added on day 11 in HLA-mismatched related HSCT and HLA-matched unrelated HSCT. In HLA allele-mismatched unrelated HSCT, the doses of MTX were increased to 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11.

CsA was administered as a 24-hr continuous infusion. The concentration of CsA was measured twice a week by fluorescence polarization immunoassay with a specific monoclonal antibody, using whole blood samples [20]. The dose of CsA was adjusted based on the ratio of the measured blood concentration and the target blood concentration of cyclosporine at 500 ng/ml to maintain the blood CsA concentration between 450 and 550 ng/ml. For example, when the measured blood concentration was 400 ng/ml using a daily cyclosporine dose of 200 mg, we multiplied the dose of cyclosporine by the ratio and determined the next cyclosporine dose at 200 mg × 500/400 = 250 mg. The route of CsA administration was converted to oral at a ratio of 1:2 when patients were able to tolerate oral intake after engraftment. Acute GVHD was graded as previously described [21]. Prophylaxis against bacterial, fungal, and *Pneumocystis carinii* infection consisted of fluconazole, tosufloxacin, and sulfamethoxazole/trimethoprim or inhalation of pentamidine. As prophylaxis against herpes simplex virus infection, acyclovir was given from days 7–35. Pre-emptive therapy with ganciclovir for cytomegalovirus infection was performed by monitoring cytomegalovirus antigenemia. The initial dose of ganciclovir was 5 mg/kg once daily and the dose was elevated to 5 mg/kg twice daily, when an increasing antigenemia was observed [22]. Other supportive procedures were not changed.

Statistical considerations

Toxicities were evaluated until the route of CsA was changed to oral. Renal dysfunction was defined as elevation of serum creatinine level above ×1.5 or ×2.0 the baseline value. Liver dysfunction was defined as elevation of the total bilirubin level above 2 mg/dl. Dichotomous variables of the patients' characteristics in the two groups were compared using Fisher's exact test. Overall survival, disease-free survival, and the cumulative incidence of acute GVHD were calculated using the Kaplan–Meier method, whereas the cumulative incidences of relapse and nonrelapse mortality were calculated using Gray's method considering each other event as a competing risk [23]. Potential confounding factors for the analyses included age, sex, donor types (related or unrelated), stem cell sources (BM or PB), conditioning regimens (TBI or non-TBI), HLA-mismatch, total doses of MTX, and the target levels of CsA. To evaluate the influence of the confounding factors on these events, the log-rank test and proportional hazards modeling were used for univariate and multivariate analyses, respectively. Factors that showed at least borderline significance ($P < 0.10$) in univariate analyses were included in the multivariate analyses and stepwisely deleted from the model, although the target level of CsA was persistently stayed in the model. All *P*-values were two-sided and *P*-values of 0.05 or less were considered statistically significant.

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ORIGINAL ARTICLE

Prognostic value of serum surfactant protein D level prior to transplant for the development of bronchiolitis obliterans syndrome and idiopathic pneumonia syndrome following allogeneic hematopoietic stem cell transplantation

T Nakane[1], H Nakamae[1], H Kamoi[2], H Koh[1], Y Takeoka[1], E Sakamoto[3], H Kanashima[3], M Nakamae[1], K Ohta[4], Y Terada[1], K-R Koh[1], T Yamane[1] and M Hino[1]

[1]*Clinical Hematology and Clinical Diagnostics, Graduate School of Medicine, Osaka City University, Osaka, Japan;* [2]*Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan;* [3]*Department of Hematology, Osaka City General Hospital, Osaka, Japan and* [4]*Department of Hematology, Saiseikai Nakatsu Hospital, Osaka, Japan*

Bronchiolitis obliterans syndrome (BOS) and idiopathic pneumonia syndrome (IPS) cause high mortality and impaired survival after allogeneic hematopoietic stem-cell transplantation (allo-HSCT). Early recognition of patients at high risk of developing BOS/IPS may lead to improving the outcome of allo-HSCT. We retrospectively analyzed serum surfactant protein A, D (SP-A, -D) and Kerbs von Lungren 6 Ag (KL-6) levels before allo-HSCT in 56 patients who survived more than 90 days after allo-HSCT and compared values of these serum markers and other transplant factors in BOS/IPS patients with those in non-BOS/IPS patients. Five patients developed BOS and two developed IPS at a median interval of 303 and 117 days (range, 100–452 and 95–153) from transplantation. As a result of univariate analysis, pretransplant serum SP-D levels but not SP-A, KL-6 in BOS/IPS patients were significantly lower than those in non-BOS/IPS patients ($P=0.03$). In multivariate analysis, the patients with lower pretransplant serum SP-D level had a trend toward frequent development of BOS/IPS ($P=0.08$). Constitutive serum SP-D level before allo-HSCT may be a useful, noninvasive predictor for the development of BOS/IPS.

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Correspondence: Dr H Nakamae, Clinical Hematology and Clinical Diagnostics, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.
E-mail: hirohisa@msic.med.osaka-cu.ac.jp
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Introduction

Late-onset noninfectious pulmonary complications (LONIPCs) after allogeneic hematopoietic stem-cell transplantation (allo-HSCT) are a critical problem. Many studies have reported that the development of LONIPCs is closely associated with the occurrence of chronic GVHD (cGVHD).[1–3] However, the pathogenesis of LONIPCs is unclear. LONIPCs are classified into bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans with organizing pneumonia and idiopathic pneumonia syndrome (IPS). BOS and IPS are difficult to cure, cause high mortality and decrease survival after allo-HSCT. The incidences of BOS and IPS reportedly vary widely from 1.7 to 26% and from 2.0 to 17% in allo-HSCT, respectively.[4,5] Early identification of patients with high risk for BOS/IPS and early treatment for them may be crucial in improving the outcome of allo-HSCT. Although many other risk factors for BOS/IPS have been reported,[4–8] it remains difficult to detect patients at high risk for BOS/IPS.

Surfactant proteins A (SP-A) and D (SP-D) are collectins mainly synthesized by alveolar type II cells. The best-known function of surfactant (mainly SP-B) is to prevent the collapse of alveoli by decreasing surface tension at the alveolar air-lipid interface. SP-A and -D play an important role as mediators in innate immunity in the lung.[9,10] SP-D has diverse innate immune functions as follows:[9] binding and agglutination of pathogens; enhancement of phagocytosis/killing of pathogens; rapid clearance of bacterial endotoxin; moderation of inflammatory response to infection and in allergy; antioxidant properties, clearance of apoptotic cells and Ag presentation. Furthermore, it has been reported that significant severe lung inflammation frequently occurs in SP-A-deficient mice given allogeneic donor BM plus spleen T cells followed by conditioning with CY and lethal irradiation.[11]

Based on these previously reported studies, we hypothesized that individual constitutive levels of surfactant protein in allo-HSCT recipients might be associated with the development of BOS/IPS. In addition, Kerbs von

Lungren 6 Ag (KL-6), which is a high-molecular-weight glycoprotein (molecular weight >1000K) classified in humans as MUC1 mucin, strongly expressed on type II alveolar pneumocytes and bronchiolar epithelial cells, and is a well-known marker for the activity of interstitial pneumonia, was also reported to increase in BOS after lung transplant.[12] The current study examined whether SP-A, -D or KL-6 in serum before transplant has a prognostic value for noninfectious severe complications, BOS/IPS after allo-HSCT.

Patients and methods

Patients

We retrospectively evaluated 56 patients with hematological malignancies who had undergone allo-HSCT between November 2001 and 2006 at our institute and survived more than 90 days after transplant. Patients who had obstructive lung disease before transplant or active pneumonia at blood sampling were excluded. The median age at transplant was 42 years old (range, 16–69) (Table 1). These patients included 31 with AML, 5 with ALL, 2 with CML, 6 with myelodysplastic syndrome (MDS), 7 with non-Hodgkin's lymphoma and 5 with adult T-cell leukemia (ATL) (Table 1). In total 25 patients (45%) received a transplant in the advanced phase of the disease. Standard disease status included MDS (refractory anemia), acute leukemia or lymphoma in the first or second remission or chronic leukemia in the first chronic phase. Advanced disease status included patients with MDS (refractory anemia with excess blasts), secondary acute leukemia, Ph chromosome-positive ALL, ATL and all patients beyond the second remission or the first chronic phase in acute and chronic leukemia or lymphoma. This study was approved by the Institutional Review Board. The concept, procedure and potential risks of the study were explained and written informed consent was obtained from all enrolled patients.

Allogeneic hematopoietic stem-cell transplantation

In total, 15 patients received allo-HSCT from HLA-identical sibling donors, 6 from HLA-mismatched sibling donors, 20 from HLA-identical unrelated donors and 15 from HLA-mismatched unrelated donors including 10 cord blood transplants (CBT) (Table 1). HLA matching (HLA-A, -B and -DR) was determined by DNA genotyping in siblings and unrelated transplants except CBT, and only serologic typing was performed in CBT. We defined HLA mismatch as the presence of at least one serological or allele mismatch between recipient and donor. As a source of allogeneic stem cell grafts, BM cells were used for 28 patients, mobilized PBSCs for 18 patients and cord blood for 10 patients.

In total, 26 patients (46%) received the following myeloablative conditioning: BU/CY ($n=10$); CY/TBI ($n=7$); Ara-C/CY/TBI ($n=8$) and other ($n=1$) (Table 1). These conditioning regimens were selected individually based on the status of the underlying disease. On the other hand, reduced-intensity conditioning was employed for 30 patients (54%) ineligible for myeloablative conditioning because of advanced age, comorbidity, organ dysfunction or prior intensive chemotherapies. The reduced-intensity conditioning included fludarabine (Flu)/BU ($n=19$); Flu/BU/TBI ($n=3$); other Flu-containing regimens ($n=3$) and total lymphoid irradiation-containing regimens ($n=5$).

Table 1 Characteristics of patients

Characteristics	*Total*
No. of patients	56
Median age at transplant (years)	42 (16–69)
Sex (male/female)	25/31
Disease	
AML	31
ALL	5
MDS	6
CML	2
NHL	7
ATL	5
Disease status	
Standard	31
Advanced	25
Donor HLA	
Matched related	15
Matched unrelated	20
Mismatched related	6
Mismatched unrelated	15 (CB 10)
Stem cell source	
BM	28
PBSC	18
CB	10
Conditioning	
Myeloablative	26
CY + TBI	7
AraC + CY + TBI	8
BU + CY	10
Other	1
Nonmyeloablative	30
Flu + BU	19
Other Flu-based regimen	6
TLI containing regimen	5
GVHD prophylaxis	
CsA + sMTX	44
CsA alone	8
CsA + MMF	1
Tacrolimus + sMTX	2
Tacrolimus alone	1

Abbreviations: ATL = adult T-cell leukemia; CB = cord blood; Flu = fludarabine; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; NHL = non-Hodgkin's lymphoma; sMTX = short-term MTX.

Acute GVHD prophylaxis and diagnosis

As a prophylaxis for acute GVHD (aGVHD), 44 patients received both CsA and short-term MTX; 8, CsA alone; 1, CsA and mycophenolate mofetil (MMF); 1, tacrolimus alone; 2, tacrolimus and short-term MTX (Table 1). The doses of CsA were adjusted to the target of trough level from 150 to 250 ng/ml until Day 100, whereas the doses of tacrolimus were adjusted to the target of trough level from

10 to 15 ng/ml until Day 100 and then these drugs were tapered unless GVHD occurred. Intravenous administration of MTX was performed at 10 mg/m^2 on Day 1, and 7 mg/m^2 on Days 3 and 5. aGVHD was diagnosed clinically, graded according to standard criteria and confirmed by appropriate biopsies. Chronic GVHD (cGVHD) was also defined according to the standard criteria. However, since BOS is generally incorporated as part of the manifestation of extensive cGVHD, there is inevitably a major confounding between BOS and extensive type of cGVHD. Therefore, we classified cGVHD into limited or extensive type except lung manifestation.

Pulmonary function tests

Pulmonary function tests (PFTs) were undergone pre- and post transplant. Pretransplant PFTs were performed within 30 days before transplant and post transplant PFTs were performed at a median time of 355 days (range, 90–1402) after transplant. The following parameters were evaluated: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio.

Definition of BOS and IPS

The criteria used to diagnose BOS were as follows: clinical or radiological signs and symptoms of lung disease and/or abnormalities in PFTs, and a decline in FEV_1 to less than 80% of the predicted value and FEV_1/FVC less than 70% in PFT, without evidence of infectious causes.[2,13] IPS was diagnosed with the following criteria: widespread alveolar injury (multilobular infiltrates on chest radiography or computed tomography, with symptoms and signs of pneumonia and evidence of abnormal pulmonary physiology), absence of clinical or laboratory evidence of active lower respiratory tract infection (bacterial, fungal, viral or parasitic) and absence of malignancy.[7,14]

Collection and analysis of blood samples

Serum samples from peripheral blood were collected from 56 patients before allo-HSCT. Additionally, in five BOS and one IPS patients, we also evaluated post transplant SP-D, -A and KL-6 serum levels. The serum was separated by centrifuging the blood at 3500 r.p.m. for 10 min. The serum samples were then stored at −80 °C until they were used. According to the manufacturer's recommended protocol (SRL Inc.; Tokyo, Japan), levels of SP-D and -A in serum were determined using a commercially available enzyme immunoassay, and levels of KL-6 were measured using a commercially available electro chemiluminescent immunoassay. Since the detection sensitivity limit in the SP-D assay was 17.2 ng/ml, values less than 17.2 ng/ml in SP-D (6 in 49 non-BOS/IPS patients and 2 in 7 BOS/IPS patients) were statistically evaluated as 17.2 ng/ml.

Statistics

Univariate analysis was performed by the Mann–Whitney *U*-test for metric variables and χ^2-test for categorical variables. The Mann–Whitney *U*-test was used to compare values of SP-D, -A, KL-6 levels and age between the BOS/IPS and the non-BOS/IPS groups. χ^2-test was used to compare disease status (high vs standard), donor type (HLA mismatched vs others), conditioning regimen (myeloablative vs reduced-intensity conditioning), TBI (high-dose TBI (12 Gy) vs others), BU (BU vs no BU), aGVHD (grades II–IV vs 0–I) and cGVHD (extensive type vs none and limited) in the BOS/IPS group with those in the non-BOS/IPS group. Multivariate analysis was performed with logistic analysis. Multivariate logistic analysis was conducted with covariates with *P*-values <0.10 on univariate analysis. All *P*-values were two-sided and a significance level of 0.05 was used.

Results

The median follow-up time of 56 patients was 615 days (range, 91–2040). Of 56 patients, 40 patients (71%) had aGVHD including 27 patients with grades II–IV (48%) and 12 patients with grades III–IV (21%), and 39 patients (70%) had cGVHD including 28 patients with extensive type (50%). In all patients, 2-year overall survival (OS) and event-free survival (EFS) were 70 and 66%. In total, 2-year OS and EFS in the BOS/IPS and the non-BOS/IPS patients were similar (2-year OS: 71 vs 69% and 2-year EFS: 71 vs 64%, respectively).

Characteristics of BOS/IPS patients

Of 56 patients, 5 (9%) developed BOS and 2 (4%) developed IPS (Table 2). Respiratory failure progressed rapidly in the two IPS patients, leading to death despite undergoing mechanical ventilation. Thus, it was difficult to perform transbronchial lung biopsy in these patients. However, in one of these patients, the autopsy was performed and the results of autopsy showed pulmonary congestion, fibrosis and diffuse alveolar damage, and did not show any evidence of viral, bacterial or fungal pulmonary infections. In the other patient, the results of bronchoalveolar lavage (BAL) examination showed no evidence of viral, bacterial and fungal pulmonary infections. Therefore, we diagnosed these patients as having IPS. The median time between the diagnosis of BOS/IPS and allo-HSCT was 303 days (range, 100–452) and 135 days (117 and 153), respectively. The median age of the BOS/IPS patients was 32 years (range, 18–67). Of seven BOS/IPS patients, there were no patients receiving allo-HSCT from matched related donors (3 matched unrelated donors, 2 one Ag-mismatched related donors, 1 one allele-mismatched unrelated donor and 1 one Ag and one allele-mismatched unrelated donor). All of the seven BOS/IPS patients had extensive type of cGVHD classified except lung manifestation. All patients received steroid-based therapies, but two IPS patients died. Among five BOS patients, BOS was stable in three patients and improved in two patients and all of the five BOS patients are still alive.

Serum SP-A, -D and KL-6 levels pre- and post transplant

In all patients, median pretransplant SP-A, -D and KL-6 levels in serum were 27.2 ng/ml (range, 6.7–83.7), 45.3 ng/ml (range, 17.2–159) and 232 U/ml (range, 104–725), respectively (Figure 1). The median pretransplant

Table 2 Characteristics of patients with BOS/IPS

No.	*Sex*	*Age*	*Disease*	*Donor*	*HLA mismatch*	*aGVHD*	*cGVHD*[a]	*Event*	*Onset*[b]	*Therapy*	*Response*	*Pretransplant serum markers*			*Outcome (cause of death)*
												SP-D (ng/ml)	*SP-A (ng/ml)*	*KL-6 (U/ml)*	
1	F	29	AML	Unrelated	Match	0	Extensive	BOS	307	mPSL	No change	27.6	31.9	164	1621+
2	M	57	MDS	Related	1 Ag	2	Extensive	BOS	452	mPSL	No change	26.2	26.4	246	1972+
3	M	18	NHL	Related	1 Ag	1	Extensive	BOS	303	HD-miPSL	Improved	41.2	13.8	106	897+
4	F	48	AML	Unrelated	Match	1	Extensive	BOS	100	mPSL	Improved	17.2	32.3	310	770+
5	F	32	AML	Unrelated	1 allele	2	Extensive	BOS	146	mPSL	No change	45.5	14.1	165	1944+
6	F	67	ALL	Unrelated	Match	1	Extensive	IPS	153	HD-miPSL	Progression	17.2	24.9	223	155 (IPS)
7	M	28	MDS	Unrelated	1 Ag+1 allele	2	Extensive	IPS	117	HD-miPSL + sivelestat	Progression	43.4	26.3	135	136 (IPS)

Abbreviations: aGVHD = acute GVHD; BOS = bronchiolitis obliterans syndrome; cGVHD = chronic GVHD; F = female; IPS = idiopathic pneumonia syndrome; KL-6 = Kerbs von Lungren 6 Ag; M = male; MDS = myelodysplastic syndrome; mPSL = methylprednisolone; NHL = non-Hodgkin's lymphoma; SP-A = surfactant protein A; SP-D = surfactant protein D.
[a]cGVHD of the lung was excluded.
[b]Days after transplantation.

values of SP-A, -D and KL-6 in serum were 28.1 ng/ml (range, 6.7–83.7), 54.4 ng/ml (range, 17.2–159) and 242 U/ml (range, 104–725) in 49 patients without BOS/IPS, whereas 26.4 ng/ml (range, 13.8–32.3), 27.6 ng/ml (range, 17.2–45.5) and 165 U/ml (range, 106–310) in 5 patients with BOS, and 24.9 and 26.3 ng/ml, 17.2 and 43.4 ng/ml and 223 and 135 U/ml in 2 patients with IPS, respectively (Table 2).

In five BOS patients, post transplant SP-A, -D and KL-6 levels, when BOS was still active, specifically, obstructive abnormality in the examination of spirography sustained in all 5 patients, did not significantly change from the pretransplant values (median pre- vs post transplant values of SP-D, 27.6 vs 31.3 ng/ml; SP-A, 26.4 vs 36.55 ng/ml and KL-6, 165 vs 236.5 U/ml). On the other hand, in one IPS patient, respiratory dysfunction and abnormal opacity persisted during intubation, post transplant values of SP-A, -D and KL-6 apparently became higher than the pretransplant values (pre- vs post transplant SP-D in this patient, 43.4 vs 143 ng/ml; SP-A, 26.3 vs 136 ng/ml; KL-6, 135 vs 470 U/ml).

Risk factors for developing BOS and IPS

In the univariate analysis, pretransplant SP-D levels in serum were significantly lower and the incidence of extensive cGVHD was significantly more frequent in the patients with BOS/IPS as compared with the patients without BOS/IPS ($P = 0.03$ and 0.03, respectively) (Table 3). Pretransplant KL-6 levels in serum tended to be lower in the BOS/IPS group ($P = 0.09$). Thus, three factors, pretransplant SP-D and KL-6 level in serum and extensive type of cGVHD, were employed as covariates in multivariate logistic analysis. In multivariate analysis, the serum SP-D levels in the BOS/IPS group tended to be lower than those in the non-BOS/IPS group ($P = 0.08$) (Table 4).

Discussion

The major finding in our study is that low steady-state serum concentration of SP-D before allo-HSCT was closely associated with BOS/IPS. The following risk factors for BOS, advanced recipient or donor age, preceding acute or cGVHD, PBSCT, MTX for aGVHD prevention, female donor to male recipient, BU containing or intensive conditioning, lower serum IgG levels, lower pretransplant FEV_1/FVC ratio, respiratory viral infections within 100 days post-HSCT and an episode of interstitial pneumonitis have been reported.[5] Similar risk factors, greater patient age (>40 years), myeloablative regimens, aGVHD and high-dose TBI reportedly contribute to the development of IPS.[7,8] These reports suggest that the pathogenesis both of BOS and IPS involves compositive processes including non-allo-immune reaction affecting pulmonary function in allo-HSCT such as lung toxic conditioning, aging and a history of pulmonary infection and allo-immune reaction such as acute or cGVHD after allo-HSCT. However, in our study we found no significant association between age, donor source, conditioning regimen and aGVHD. Possible explanatory factors are (1) small population size, (2) various types of conditioning regimen and (3) only patients

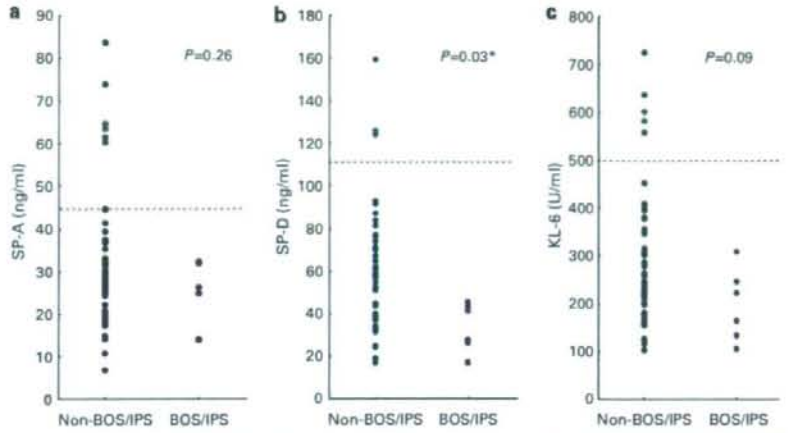

Figure 1 Distribution of serum markers (SP-A (**a**), SP-D (**b**) and KL-6 (**c**)) before transplantation for patients with/without BOS/IPS. SP-D values before SCT were significantly lower in patients with BOS/IPS than in those without BOS/IPS. In SP-A and KL-6, no statistical significance existed between patients with BOS/IPS and those without BOS/IPS. The dashed lines indicate the upper limit of the normal range for each marker. SP-A = surfactant protein A; SP-D = surfactant protein D; BOS/IPS = bronchiolitis obliterans syndrome/idiopathic pneumonia syndrome and KL-6 = Kerbs von Lungren 6 Ag.

Table 3 Comparison of risk factors between patients with and without BOS/IPS

Risk factor	*Median (range) or number*		P
	BOS/IPS	*Non-BOS/IPS*	
Age	32 (18–67)	42 (16–69)	0.96
High-risk disease	3/7	22/49	0.92
HLA mismatches	4/7	17/49	0.25
RIST	4/7	26/49	0.69
High-dose TBI containing regimen	3/7	12/49	0.30
BU containing regimen	4/7	34/49	0.52
aGVHD II–IV	3/7	27/49	0.54
cGVHD extensive (except lung)	7/7	21/49	0.03*
Serum SP-D levels before SCT (ng/ml)	27.6 (17.2–45.5)	54.4 (17.2–159)	0.03*
Serum SP-A levels before SCT (ng/ml)	26.3 (13.8–32.3)	28.1 (6.7–83.7)	0.26
Serum KL-6 levels before SCT (U/ml)	165 (106–310)	242 (104–725)	0.09

Abbreviations: BOS = bronchiolitis obliterans syndrome; IPS = idiopathic pneumonia syndrome; KL-6 = Kerbs von Lungren 6 Ag; RIST = reduced-intensity stem cell transplantation; SP-A = surfactant protein A; SP-D = surfactant protein D.
*$P<0.05$.

Table 4 Multivariate logistic analysis of risk factor for BOS/IPS

Risk factor	*Odds ratio (95% CI)*	P
Serum SP-D levels before SCT	0.95 (0.90–1.01)	0.08
Serum KL-6 levels before SCT	0.99 (0.98–1.01)	0.22
cGVHD extensive (except lung)	5.26 (0.49–56.0)	0.16

Abbreviations: cGVHD = chronic GVHD; CI = confidence interval; SP-D = surfactant protein D.

who survived more than 90 days after allo-HSCT in this study.

In clinical practice, elevated serum SP-D and KL-6 levels have been used as a marker of various lung diseases and activity of interstitial pneumonia.[10,12] Significant elevation in the serum level of SP-D and KL-6 in pulmonary inflammation is considered to be evoked by an activated secretion from the bronchiolar epithelium and/or an increase in the permeability of the lung/blood interface partly caused by the destruction of the bronchiolar epithelium and vascular endothelial cells. Also in this study, SP-A, -D and KL-6 were apparently elevated in IPS but not in BOS. Although we cannot conclude that surfactants and KL-6 increased in IPS but not in BOS based on the results in only one patient with IPS, in IPS the rapid and diffuse destruction of lung tissue may promote the release of SP-D into the circulation, while in BOS, which is a kind of chronic lung disease, the serum SP-D levels remained low. Although very little is known about the role of SP-D in chronic lung diseases, these results suggest that IPS and BOS have distinct etiologies.

Low production of surfactant protein and secretary protein in the alveoli is considered an important pathogenesis of certain types of lung disease such as adult respiratory distress and BOS.[15–17] SP-D is synthesized by non-ciliated Clara cells as well as pulmonary type II

pneumocytes. A decrease in the serum level of Clara cell secretary protein (CC16) was observed in BOS in both lung[16] and SCT.[17] The latter study also suggests that decreased serum levels of CC16 might permit early diagnosis of BOS. It was also reported that there is a protective effect of exogenous surfactant instillation to donor lungs before retrieval on post-lung transplantation surfactant function.[18] In addition, it was observed that absence or low levels of SP-D augment inflammation by acute oxidative stress in the mice model[19] and severe lung inflammation frequently occurred in SP-A-deficient mice receiving myeloablative allogeneic BM and spleen T-cells transplant.[11] Furthermore, in mice transtracheal human SP-A treatment attenuated the manifestation of IPS probably as a result of suppressed IFN-production by allo-activated lung-infiltrating T cells, and thereby, early survival was improved.[20]

The molecular weight of SP-D and -A is smaller than KL-6.[21] SP-D leaks more easily than SP-A because most of SP-A tightly bind to surfactant lipid aggregates in alveoli but SP-D appears to be lipid free.[22] In these points, a decrease in the serum SP-D level might reflect low production of SP-D in the alveoli of chronically damaged lung more than SP-A and KL-6. However, this is just speculation because it is unclear how the serum SP-D concentration is regulated and whether steady-state serum values of SP-D exclusively reflect constitutive synthesis levels of SP-D in the lung.

It has recently been shown that the constitutional SP-D serum levels are largely determined genetically based on the twin studies.[23,24] Moreover, it has been reported that, among the nine haplotypes of the human gene coding surfactant protein-D (SFTPD), the third most common haplotype of SFTPD (allele frequency 13.53%) is associated with a low serum level of SP-D.[25]

Therefore, we speculate that patients who have a certain SFTPD polymorphism will be put at higher risk of BOS/IPS when additive allo-immunological reaction or pulmonary infection occurs to them in allo-HSCT.

This study has the following limitations: (1) This study was retrospective in a single institution, (2) consisted of heterogeneous patient characteristics, diseases, conditioning regimens and GVHD prophylaxes and (3) we did not show decreased secretion or production of surfactant protein in the alveoli of the lung. To prove a causal linkage between the level of surfactant protein secretion in the alveoli and the pathogenesis of BOS/IPS in allo-HSCT patients, we need to directly measure the surfactant protein production level in the alveoli by BAL in allo-HSCT patients. However, measurement with BAL is an invasive examination for routine practice and has artifacts related to the instillation of fluid into the airway. Therefore, it may be a better alternative to address the association between single nucleotide polymorphism in SP-D in allo-HSCT recipients and LONIPCs.

In conclusion, pretransplant serum SP-D level may be a noninvasive and useful predictive marker for the development of BOS/IPS following allo-HSCT. To establish the usefulness of constitutive serum SP-D in allo-HSCT, a prospective trial in a large number of patients is needed.

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宛先ラベルに変更・訂正がある場合ご記入下さい

(〒　　－　　)

造血幹細胞移植患者の長期フォローに関する実態調査

ご回答に際してのお願い

■ ご回答の記入は、
① 該当する項目番号に○印をつける。
② 記入欄に数字を記入する。
③ 記入欄に文字を記入する。
以上の方法でお願いいたします。

■ このアンケートについて、ご不明な点などがございましたら、ご遠慮なく下記の担当者まで、ご連絡下さい。

■ 尚アンケート用紙は、 7月 7日(月)までに ご投函頂きますようお願い致します。

＊ 本アンケートへのご回答は、移植業務に従事されている医師にご記入をお願いします。
＊ 同封いたしました看護師用アンケートは、移植業務にたずさわる看護師にご記入いただくものです。該当する看護師のご協力も心よりお願いいたします。

ご記入頂きましたら、同封の返信用封筒にて、切手を貼らずにそのままご返送下さい。
看護師向けのアンケートも同封あるいは別便でご返送ください。

連絡先
国立国際医療センター血液内科
〒162-8655 東京都新宿区戸山1－21－1.
電話03-3202-7181FAX03-3207-1038
担当者：萩原（5274）
shagiwar@imcj.hosp.go.jp

【造血幹細胞移植および移植後長期フォローの実施状況について】

【全員の先生へ】

Q1. 貴施設の（診療科ではなく施設全体の）病床数をお教え下さい。（○は１つ）

1. 300床未満
2. 300～500床
3. 500～1000床
4. 1000床以上

Q2. 貴科の移植用病床数をお教え下さい。

移植用病床数	床

Q3. 貴科の移植に携わっている医師数をそれぞれお教え下さい。

（1） 常勤医師	名
（2） レジデント	名
（3） 非常勤医師	名

Q4. 昨年（2007年度）１年間の「造血幹細胞移植」の実施総数をそれぞれお教え下さい。

（1） 自家移植	例／2007年
（2） 血縁同種移植	例／2007年
（3） 非血縁骨髄移植	例／2007年
（4） 臍帯血移植	例／2007年

Q5. 貴施設で定期的にフォローしている移植後長期生存患者（以下、長期フォロー患者と略す）の人数をお教え下さい。（○は１つ）

1. 50名未満
2. 50～99名
3. 100～299名
4. 300～499名
5. 500名以上

Q6. 長期フォローの必要な患者１人あたりの診療時間は平均何分でしょうか。

長期フォローに必要な診療時間	分／1患者

Q7. 関係各科との連携についてお伺いします。
長期フォロー患者のコンサルトを依頼する科を選び、依頼頻度が高い順に順位をお教え下さい。
依頼することのない科は空白のままで結構です。

消化器内科		位	脳神経外科		位
呼吸器内科		位	心臓血管外科		位
内分泌・代謝科		位	外科／乳腺外科		位
腎臓内科		位	呼吸器外科		位
循環器科		位	産婦人科		位
膠原病科		位	泌尿器科		位
精神科		位	整形外科		位
心療内科		位	耳鼻咽喉科		位
緩和ケア科		位	歯科口腔外科		位
神経内科		位	眼科		位
皮膚科		位			

Q8. 医師以外のスタッフの関与についてお伺いします。
長期フォローにおいて、医師以外のスタッフが関与することはございますか？（○は１つ）

1. 関与することがある（⇒Q9へ）
2. 関与することはない（⇒Q11へ）

Q9. 【Q9＝1「関与することがある」先生へ】
長期フォローに関与する医師以外のスタッフの職種をお教え下さい。（○はいくつでも）

1. 看護師
2. 薬剤師
3. 栄養士
4. 理学療法士
5. 歯科衛生士
6. ソーシャルワーカー
7. 臨床心理士
8. その他（具体的に:　　）

Q10. 【Q9＝1「関与することがある」先生へ】
長期フォローに関与する医師以外のスタッフに対して、長期フォロー患者に関する
多職種カンファレンスを開いていますか？（○は１つ）

1. 開いている
2. 開いていない

【全員の先生へ】

Q11. 移植患者のために、特化した外来枠を設けていますか？（○は１つ）

1.	設けている
2.	設けていない

Q12. 移植後、長期フォローのための外来枠を設けていますか？（○は１つ）

1.	設けている
2.	設けていない

Q13. 長期フォローは、連携病院でも行っていますか？（○は１つ）

1.	行っている（⇒Q14へ）
2.	行っていない（⇒Q15へ）

Q14. 【Q13＝1「行っている」先生へ】

関連病院と長期フォローをどのように連携していますか？（自由回答）

具体的に：

【移植後の長期フォロー患者のクリニカルプロセスについて】

【全員の先生へ】

Q15. 貴施設での、長期フォロー患者の診療指針をお教え下さい。（○は１つ）

1.	診療マニュアルを定めている
2.	マニュアルはないがカンファレンス等でコンセンサスを作っている
3.	各医師の判断にまかせている
4.	その他（具体的に：　　）

Q16. 移植後の慢性GVHD（移植片対宿主反応病）の定義には議論があるところと思いますが、貴施設での診断基準をお教え下さい。（○は１つ）

1.	NIH consensus development projectによるcriteria
2.	発症時期を問わない慢性GVHD所見
3.	Day100以降のGVHD所見
4.	その他（具体的に：　　）

Q17. 慢性GVHDの重症度分類は、どのようにされていますか。実際にカルテに記載している分類法をお教え下さい。（○は１つ）

1. Limited or Extensive
2. Scoring system: NIH consensus development projectによるスコア
3. その他（具体的に: ）

Q18. 貴施設での、慢性GVHDなどの晩期合併症のスクリーニング頻度を、検査や評価項目毎にそれぞれお教え下さい。（○はそれぞれ１つずつ）

		3ヵ月毎	6ヵ月毎	12ヵ月毎	症状があれば施行	施行しない
歯科口腔検査	⇒	1.	2.	3.	4.	5.
眼科検査	⇒	1.	2.	3.	4.	5.
呼吸機能検査	⇒	1.	2.	3.	4.	5.
胸部CT	⇒	1.	2.	3.	4.	5.
甲状腺機能	⇒	1.	2.	3.	4.	5.
生殖機能検査	⇒	1.	2.	3.	4.	5.
骨代謝・骨密度	⇒	1.	2.	3.	4.	5.
心機能	⇒	1.	2.	3.	4.	5.
神経学的検査	⇒	1.	2.	3.	4.	5.
皮膚生検	⇒	1.	2.	3.	4.	5.
皮膚硬化度評価	⇒	1.	2.	3.	4.	5.
婦人科がん検診	⇒	1.	2.	3.	4.	5.
乳がん検診	⇒	1.	2.	3.	4.	5.
消化器がん検診	⇒	1.	2.	3.	4.	5.
SF36/FACT等ツールによるQOL評価	⇒	1.	2.	3.	4.	5.

Q19. 慢性GVHDの病状/症状あるいは治療効果の評価の方法をお教え下さい。（○は１つ）

1. NIH consensus development projectによるcriteriaに準じた評価
2. 医師の経験に基づいた判断
3. その他（具体的に: ）

Q20. 貴施設では、全身型慢性GVHDの治療薬として、通常カルシニューリンインヒビターを使用されますか。（○は１つ）

1.	通常使用する（⇒Q21へ）
2.	通常使用しない（⇒Q22へ）

Q21. 【Q20＝1「通常カルシニューリンインヒビターを使用する」先生へ】
では、予防薬と治療薬で使用するカルシニューリンインヒビター（CSPあるいはTacro）は、同じ薬剤を使用しますか、それとも変更しますか。（○は１つ）

1.	GVHD予防薬と治療薬は同じ （予防薬がCSPで治療薬もCSP、または、予防薬がTacroで治療薬もTacro）
2.	GVHD予防薬と治療薬は異なる （予防薬がCSPで治療薬はTacro、または、予防薬がTacroで治療薬はCSP）

【全員の先生へ】

Q22. 全身型慢性GVHDの治療において、ステロイドの代表的な使用方法を、各項目毎にお教え下さい。

種類（○は1つ）	⇒	**1.** PSL	**2.** mPSL	
初期投与量（○は1つ）	⇒	**1.** ≧2mg /kg/day	**2.** 1mg /kg/day	**3.** 0.5mg /kg/day
		4. その他（具体的に:		）
服用方法（○は1つ）	⇒	**1.** 朝1回	**2.** 朝夕2分割	**3.** 朝昼2分割
減量時の服用方法（○は1つ）	⇒	**1.** 毎日投与	**2.** 隔日投与	
減量開始の時期（記入）	⇒			
減量速度（記入）	⇒			
中止の目安（記入）	⇒	服用開始後		ヵ月で中止

Q23. 全身型慢性GVHDの治療において、カルシニューリンインヒビターやステロイドの他に使用経験がある薬剤をお教え下さい。（○はいくつでも）

1.	サリドマイド
2.	MMF
3.	PUVA
4.	その他（具体的に: ）

Q24. 全身型慢性GVHDの治療において、貴科で使用している代表的なレジメンをお教え下さい。

具体的に:

Q25. 慢性GVHDの以下の障害や症状について、先生が実施される「局所療法」を、それぞれ具体的にお教え下さい。

ドライアイ	⇒
口腔粘膜障害	⇒
呼吸器症状	⇒
皮膚症状	⇒

【同種移植後の長期フォロー患者の感染予防について】

【全員の先生へ】

Q26. 同種移植後のニューモシスティス肺炎の予防的抗生剤として、「バクタ」を投与していますか。

1. バクタを投与している(⇒Q28へ)
2. バクタを投与していない(⇒Q30へ)

Q27. 【Q27＝1「バクタを投与している」先生へ】
バクタの予防的投与期間をお教え下さい。（○は１つ）

1. 3ヵ月
2. 6ヵ月
3. 12ヵ月
4. ステロイド投与中
5. CSP/Tacro投与中
6. すべての免疫製剤が終了するまで

Q28. 【Q27＝1「バクタを投与している」先生へ】
予防投与の際のバクタの１日投与量をお教え下さい。（○は１つ）

1. 2錠　**2.** 3錠　**3.** 4錠
4. その他(具体的に:　　)

Q29. 【Q27＝1「バクタを投与している」先生へ】
その予防投与の際のバクタの投与間隔をお教え下さい。（○は１つ）

1. 毎日　**2.** 週2日　**3.** 週3日
4. その他(具体的に:　　)