Hematopoietic Stem Cell Transplantation for Familial Hemophagocytic Lymphohistiocytosis and Epstein–Barr Virus-Associated Hemophagocytic Lymphohistiocytosis in Japan

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Background. Post-transplant outcomes of hemophagocytic lymphohistiocytosis (HLH) patients were analyzed in Japan where Epstein–Barr virus (EBV)-associated severe forms are problematic. ***Methods.*** Fifty-seven patients (43 familial HLH [12 FHL2, 11 FHL3, 20 undefined], 14 EBV-HLH) who underwent stem cell transplantation (SCT) between 1995 and 2005 were enrolled based on the nationwide registration. ***Results.*** Fifty-seven patients underwent 61 SCTs, including 4 consecutive SCTs. SCTs were employed using allogeneic donors in 93% of cases (allo 53, twin 1, auto 3). Unrelated donor cord blood transplantation (UCBT) was employed in half of cases (21 FHL, 7 EBV-HLH). Reduced intensity conditioning was used in 26% of cases. The 10-year overall survival rates (median ± SE%) were 65.0 ± 7.9% in FHL and 85.7 ± 9.4% in EBV-HLH patients, respectively. The survival of UCBT recipients was >65% in both FHL and EBV-HLH patients. Three out of four patients were alive with successful engraftment after second UCBT. FHL patients showed a poorer outcome due to early treatment-related deaths (<100 days, seven patients) and a higher incidence of sequelae than EBV-HLH patients ($P = 0.02$). The risk of death for FHL patients having received an unrelated donor bone marrow transplant was marginally higher than that for a related donor SCT ($P = 0.05$) and that for UCBT ($P = 0.07$). ***Conclusions.*** EBV-HLH patients had a better prognosis after SCT than FHL patients. FHL patients showed either an equal or better outcome even after UCBT compared with the recent reports. UCB might therefore be acceptable as an alternate SCT source for HLH patients, although the optimal conditioning remains to be determined. Pediatr Blood Cancer

Key words: central nervous system disease; Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis; familial hemophagocytic lymphohistiocytosis; hematopoietic stem cell transplantation; reduced intensity conditioning; umbilical cord blood transplantation

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an immunohematologic emergency, characterized by fever, cytopenias, hepatosplenomegaly, hyperferritinemia, and disseminated intravascular coagulopathy (DIC) [1,2]. HLH comprises primary form of familial hemophagocytic lymphohistiocytosis (FHL) and secondary form occurring in association with infections, malignancies, and rheumatic diseases. FHL has currently been classified into FHL1 linked to chromosome 9, FHL2 with *PRF1* mutation, FHL3 with *UNC13D* mutation, and FHL4 with *STX11* mutation, although more than half of patients have no mutations of these genes [1]. HLH could also be a presenting symptom in patients with the other inherited disorders including X-linked lymphoproliferative disease (XLP), Griscelli syndrome, Hermansky–Pudlak syndrome, Chediak–Higashi syndrome and primary immunodeficiency diseases. HLH accounts for the common basis of hypercytokinemia arising from excessive immune activation, in which activated lymphocytes and hemophagocytosing-macrophages without malignant morphology infiltrate into systemic organs, including the bone

Additional Supporting Information may be found in the online version of this article.

Abbreviations: BM, bone marrow; BMT, bone marrow transplantation; CB, cord blood; CBT, cord blood transplantation; CNS, central nervous system; CT, computed tomography; EBV-HLH, Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis; EEG, electroencephalography; FHL, familial hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis; PB, peripheral blood; SCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; OS, overall survival; SCT, hematopoietic stem cell transplantation; TRM, treatment-related mortality; RIC, reduced intensity conditioning; VOD, venoocclusive disease; XLP, X-linked lymphoproliferative disease/syndrome.

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marrow (BM), liver, spleen, lymph nodes, skin, and central nervous system (CNS) [3,4]. FHL is a fatal disease if allogeneic hematopoietic stem cell transplantation (SCT) has not been successfully performed.

Epstein–Barr virus (EBV)-associated HLH (EBV-HLH) is a severe form of secondary HLH more frequently occurring in Asian children [5–7]. Activated EBV-infected $CD8^+$ T cells account for the disease process of EBV-HLH [8], however no predisposing factors have yet been clarified. EBV-HLH patients mostly respond to immunochemotherapy, but a small fraction of patients experience a fatal course without SCT. Therefore, although numbers were still small, SCT has been included in the salvage for refractory EBV-HLH cases [9–11]. The optimal timing of SCT, the source of donor cells and the conditioning are critical, particularly for young HLH patients. In this setting, the appropriate SCT for HLH patients needs to be established.

This study analyzed the outcomes of patients with FHL or EBV-HLH who underwent SCT in Japan over the past 10 years, in order to address the issues in the transplant-related problems including engraftment, late sequelae as well as to find out if there are distinct transplant strategies for FHL and EBV-HLH patients.

PATIENTS AND METHODS

Data Collection

The HLH/LCH Committee in the Japanese Society of Pediatric Hematology (JSPH) sent the first questionnaires to the hospitals administered by JSPH members based on the SCT registry in JSPH, asking if SCT was performed for any HLH patients between 1995 and 2005. The second questionnaires were sent to 57 hospitals with SCT cases, asking the patients' characteristics, treatment prior to SCT, donor sources, conditioning regimens, complications, and outcome. Of the 47 responses (recover rate 82%), 61 definite SCT cases from 33 hospitals were eligible for the study (mean 1.7 case/hospital, Supplemental Table). Forty-three FHL patients underwent 46 SCT, while 14 EBV-HLH patients underwent a total of 15 SCT. The majority of SCT (EBV-HLH 87%, FHL 89%) were performed between 2000 and 2005.

Diagnosis and Classification

All 57 patients fulfilled the diagnostic criteria of HLH [12]. FHL was diagnosed when the patient had a genetic abnormality, positive family history, and/or other evidence such as impaired natural killer cell activity [13]. The genetic study of FHL 2, 3, and 4, approved by the ethics committee of Kyushu University, Japan (No. 45), was partly completed postmortem according to our methods [14–17]. FHL2 and FHL3 determined by *PRF1* or *UNC13D* mutations accounted for 28% (n = 12), and 26% (n = 11), respectively, in this group. In addition, a total of eight patients were found with siblings diagnosed as having HLH. EBV infection might be associated with the development of HLH in four FHL patients (one FHL2, one FHL3, and two familial). These cases were classified as FHL, not as EBV-HLH. Other types of primary HLH such as XLP were excluded in this study.

EBV-HLH was diagnosed when a non-FHL patient had a primary infection or reactivation of EBV at the onset of HLH. EBV infection was assessed by the detection of EBV DNA and/or the pattern of serum EBV-specific antibody titers [18]. Cases with secondary HLH occurring in a chronic active EBV infection [19], and/or a histologically confirmed EBV-related lymphoma were excluded in this study. CNS involvement was determined when patients showed neurological manifestations, clinically as well as with any evidence of abnormality in the cerebrospinal fluids (CSF), neuroimagings (CT/MRI), and/or electroencephalography (EEG).

Prior Treatment to SCT

Treatment was based on the HLH-94 protocol using a combination of corticosteroid, cyclosporine-A (CSA), and etoposide (VP16) for both groups [20,21]. As the multidrug chemotherapy, CHOP-VP16-based regimen (VP16, vincristine, cyclophosphamide [CY], doxorubicin, and prednisolone) was chiefly employed. SCT was performed for all FHL patients, but limited for EBV-HLH patients who were resistant to any other treatments.

SCT

Allogeneic SCT was performed in 53 of the 57 patients (93%). Autologous SCT and identical-twin donor SCT were performed in three and one sporadic patients, respectively, because the molecular diagnosis was not available at the time of SCT. Donor sources, infused cell doses, conditioning regimens, and other SCT-related data are summarized in Table I. Allogeneic donor sources for EBV-HLH were HLA-matched sibling peripheral blood (PB) 1, haploidentical parent BM/PB 2, HLA-matched unrelated BM 1, HLA-matched unrelated cord blood (UCB) 2, and HLA-mismatched UCB 5, and those for FHL were HLA-matched related BM 7 (sibling 6), haploidentical parent BM/PB 2, HLA-matched unrelated BM 12, HLA-matched UCB 9, and HLA-mismatched UCB 12. All CBs were obtained from unrelated donors registered in the Japanese Cord Blood Bank Network. All unrelated donor BMs were obtained from the Japanese Marrow Donor Program. Myeloablative conditioning for EBV-HLH included VP16/busulfan (BU)/CY in 8 patients (4 in UCB transplantation [UCBT]) and other regimens in 3 patients, while those for FHL were VP16/BU/CY plus or minus anti-thymocyte globulin (ATG) in 23 patients (10 in UCBT) and others in 8 patients. Reduced intensity conditioning (RIC) for EBV-HLH included melphalan (MEL)/fludarabine (FLU) plus or minus thoracoabdominal irradiation in three patients (two in UCBT), and those for FHL were MEL/FLU plus or minus low-dose total body irradiation plus or minus ATG in eight patients (four in UCBT) and others in three patients. Donor chimerism was assessed by using short tandem repeats or sex chromosome analyses.

Evaluation of Late Sequelae

Long-term survivors were further questioned concerning their physical growth, endocrinological status, and neurological deficits. Neurological development including cognitive functions was assessed by Karnofsky score, developmental quotient and/or school performance.

Statistical Analysis

The 10-year overall survival (OS) rate with 95% confidence intervals were estimated by the Kaplan–Meier method. The OS was calculated for the period from the day of SCT until the death of any cause or the final observation. All results were updated to May 31,

TABLE I. Profiles of Patients Who Underwent Hematopoietic Stem Cell Transplantation

	EBV-HLH	FHL	*P*-value
Number, male:female	14, 4:10	43, 23:20	0.37
Age at onset (median, range)	5.5y, 6m–18y	0.5y, 6d–12y	<0.0001
Age at SCT (median, range)	5.9y, 1.4–18y	1.2y, 0.4–15y	0.0002
Observation period (median, range)	5.5y, 0.3–16y	4.8y, 0.2–19y	0.94
Manifestation at diagnosis (%)			
Fever	100	95	>0.99
Hepatosplenomegaly	86	86	>0.99
Lymphadenopathy	36	21	0.30
Skin eruption	7	14	0.67
Respiratory failure	36	14	0.12
DIC	50	33	0.26
Treatment prior to SCT (%)			
HLH94 only	36 (5/14)	60 (25/42)	0.14
Multidrug chemotherapy	57 (8/14)	19 (8/42)	0.017
Diagnosis to SCT (median, range)	5.8m, 1.8–24m	7.5m, 1.6–84m	0.18
SCT (n)			
Allogeneic	11	42	
Auto/Identical twin	3	1	
Nucleated cell doses ($\times 10^8$/kg)	1.3 (0.2–6.6)	2.5 (0.1–12.7)	0.14
Donor			
UCB	7	21	0.94
Others	7	22	
HLA disparity no	4	28	0.09
HLA disparity yes (>1 locus[a])	7	14	
Conditioning			
Myeloablative[b]	11	31	>0.99
RIC[c]	3	11	
Irradiation yes	4	11	0.73
Irradiation no	9	31	
ATG yes	0	8	0.18
ATG no	14	34	
CNS abnormality (%)			
At diagnosis	29[d] (4/14)	21[d] (9/42)	0.72
Before SCT	57 (8/14)	67 (28/42)	0.52
CSF pleocytosis	25 (2/8)	32 (7/22)	>0.99
MRI abnormality	36 (5/14)	51 (20/39)	0.36
Convulsion	43 (6/14)	41 (17/41)	0.93
Disturbed consciousness	36 (5/14)	24 (10/41)	0.49
Post-transplant state (n)			
Early death (<100 days)	2	7	0.48
Alive	12	29	0.31
Neurological deficit (%)	8[d] (1/12)	29[d] (7/24)	0.22
Late sequelae[e] (%)	8 (1/12)	52 (11/21)	0.022

ATG, anti-thymocyte globulin; BU, busulfan; CNS, central nervous system; CSF, cerebrospinal fluid; CY, cyclophosphamide; DIC, disseminated intravascular coagulopathy; EBV, Epstein–Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; FLU, fludarabine; HLH, hemophagocytic lymphohistiocytosis; MEL, melphalan; MRI, magnetic resonance imaging; SCT, hematopoietic stem cell transplantation; TAI, thoracoabdominal irradiation; TBI, total body irradiation; UCBT, unrelated donor cord blood transplantation; VP16, etoposide. Parenthesis means the positive number of patients per the evaluable number of patients. The observation period means the time from the onset to the last visit or death. [a]Human leukocyte antigen (HLA) disparity was assessed by the serotyping data of HLA-A, -B, and -DR; [b]Myeloablative conditionings for EBV-HLH were VP16/BU/CY 8 (4 in UCBT) and others 3, and those for FHL were VP16/BU/CY + ATG 23 (10 in UCBT) and others 8; [c]Reduced intensity conditionings (RIC) for EBV-HLH were MEL/FLU + TAI 3 (2 in UCBT), and those for FHL were MEL/FLU + low dose TBI + ATG 8 (4 in UCBT) and others 3; [d]The proportion of patients having neurological abnormality was lower in survived patients with EBV-HLH ($P = 0.0015$). Survived patients were neurodevelopmentally assessed at the last visit to the hospital; [e]Late sequela(e) in EBV-HLH was hemiparesis (n = 1), and those in FHL were short stature (n = 5), endocrinological abnormality (n = 1), psychomotor retardation with or without seizure (n = 5), brain atrophy (n = 1), and hearing difficulty (n = 1).

2008. An analysis of the risk factors for SCT outcome was possible for FHL, but not for EBV-HLH because of the small number of subjects. Age at onset of HLH or at the SCT, duration from the onset to SCT, CNS disease before SCT, donor sources, and the type of conditioning were tested using the log-rank method. Cox proportional-hazard model was employed to examine the association between selected clinical variables and the risk for death. A logistic regression model was used to investigate factors associated with neurological sequelae. Chi-square test or Fisher's exact test were employed in other comparisons. P values less than 0.05 were considered to be significant.

RESULTS

Profiles of EBV-HLH and FHL Patients

A comparison of the clinical profiles (Table I) revealed that the ages at disease onset and at the time of SCT were each higher in EBV-HLH than in FHL patients ($P < 0.0001$, $P = 0.0002$, respectively). No clinical manifestations differed between the two groups during the disease course, including respiratory failure as well as CNS abnormalities at diagnosis. The proportion of patients who failed VP16 and CSA therapy including HLH94 protocol and needed combination chemotherapy such as CHOP-VP16 before planning SCT was higher in EBV-HLH patients than FHL patients (57% vs. 19%, $P = 0.0168$).

Outcomes of SCT

Engraftment and survival. Post-transplant outcomes of 43 FHL patients and 14 EBV-HLH patients are summarized in Figures 1 and 2. The 10-year OS rates (median ± SE%) of FHL and EBV-HLH patients were 65.0 ± 7.9% and 85.7 ± 9.4%, respectively ($P = 0.24$; Fig. 3). In the allogeneic SCT cases with FHL (Fig. 1), 29 attained engraftment, 6 had rejection or graft failure, and 7 were undetermined. On the other hand, in EBV-HLH (Fig. 2), seven were engrafted, three were rejected, and one was undetermined. Of all 29 FHL patients engrafted after the first SCT, 26 were alive with no HLH relapse, but 3 died of treatment-related mortality (TRM). Seven engrafted patients with EBV-HLH were alive and well at the final follow-up. Among the nine rejection/graft failure patients (six FHL, three EBV-HLH), a second UCBT was successful in three of the four patients (three FHL, one EBV-HLH). Twelve of the UCBT recipients for FHL that received a graft with the first UCBT and two that received a second UCBT were alive at the last follow-up; while seven died; six were due to TRM and one was due to active HLH disease. Six of the seven UCBT recipients for EBV-HLH were alive and well at the last follow-up, while only one died of active HLH disease on day 18 post-transplant. A total of 29 FHL survivors after allogeneic SCT(s) had 17 complete donor chimera (2 patients after second UCBTs), 3 mixed chimera (1 had 42% donor chimera in remission 18 months after SCT, 2 attained >90% donor chimera until 6 months after SCT), 8 undefined, and 1 graft failure with CNS disease. Ten EBV-HLH survivors after allogeneic SCT attained eight complete donor chimera (seven patients after the first SCT and one patient after second SCT [UCBT]), and two with autologous recovery. Two of three EBV-HLH patients who rejected allogeneic cells were alive and disease free more than 6 years post-transplant. One of two EBV-HLH patients who underwent autologous SCT was alive and well 13 years post-transplant [22]. One EBV-HLH patient was alive and well 10 years after the identical twin donor BMT.

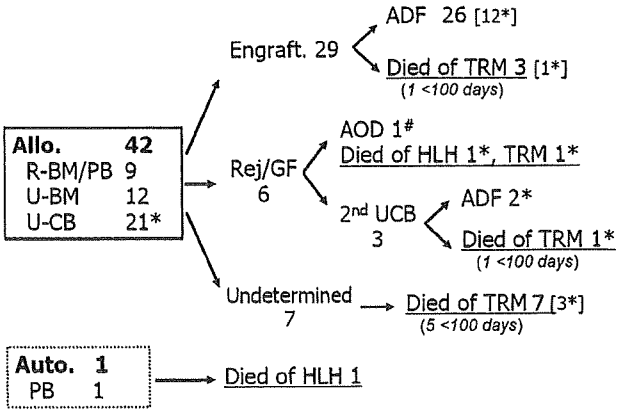

Fig. 1. Cohort diagram for the clinical outcome of 43 patients with familial hemophagocytic lymphohistiocytosis (FHL) who underwent stem cell transplantation (SCT). Of 42 patients after allogeneic SCT, 29 achieved engraftment (18 complete, 3 mixed) and 6 failed to engraft. One (#) with graft failure was alive with central nervous system disease 12 years after SCT. A total of 29 patients (67%) were alive after SCT. The underlined data indicate the number of deceased patients. Seven patients died within 100 days post-SCT (parenthesis). Asterisk (*) means UCB. R, related; U, unrelated; BM, bone marrow; PB, peripheral blood; CB, cord blood; ADF, alive with the disease free state; AOD, alive on disease; Rej/GF, rejection or graft failure; TRM, treatment-related mortality.

Causes of death. Of 14 deceased FHL patients, 12 died of TRM, including 3 chronic GVHD while 2 died of recurrent HLH. Seven patients experienced early death from TRM within 100 days after SCT (Fig. 1). One patient, later diagnosed with FHL2, died of CNS disease 5 years after autologous SCT [14]. Two EBV-HLH patients died of recurrent HLH within 50 days after SCT (Fig. 1). No TRM-related deaths were noted among the EBV-HLH patients.

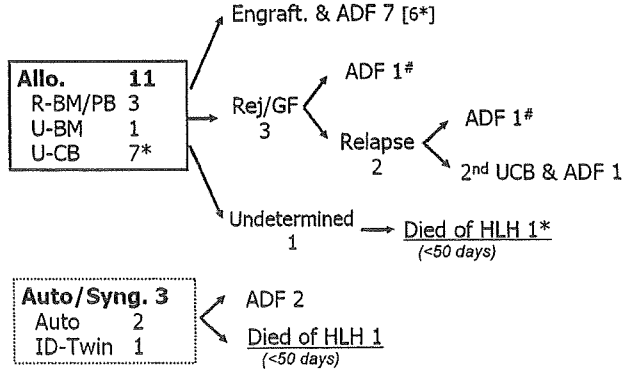

Fig. 2. Cohort diagram for the clinical outcome of 14 patients with Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) who underwent SCT. Among 11 patients after the first allogeneic SCT, 7 achieved successful engraftment and 3 failed to engraft. A total of 12 patients (86%) were alive after SCT. Two patients (#) were alive and well more than 6 years after SCT failure. The underlined data indicate the number of deceased patients. Two patients died within 50 days post-SCT (parenthesis). Asterisk (*) means UCB. Auto/Syng: autologous/syngeneic, ID: identical.

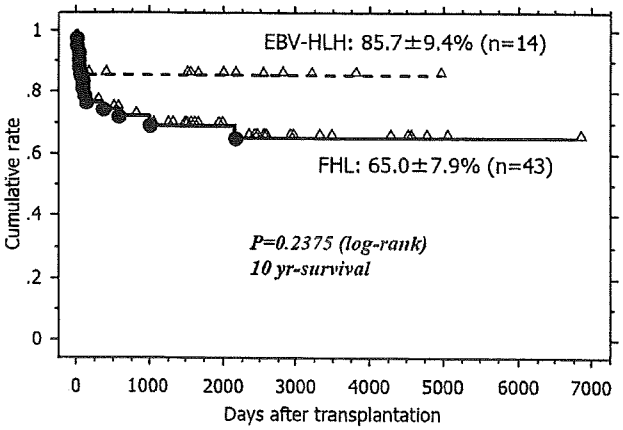

Fig. 3. Cumulative probability of post-transplant overall survival of FHL (*solid line*) and EBV-HLH patients (*dashed line*) who underwent SCT. Closed circle and open triangle represent deceased and alive patients, respectively. Each value indicates the 10-year overall survival rate plus or minus standard error assessed by the log-rank test.

Analysis of Prognostic Factors in FHL

A log-rank test on the OS rate did not show any significant difference in terms of age at SCT (<2 years vs. ≥2 years), time of SCT from HLH treatment (<6 months vs. ≥6 months), conditioning regimens (myeloablative vs. RIC) and various donor sources (R-PB/BM vs. UCBT vs. UBM; Table II). The Cox hazard model with adjustment for gender and age at engraftment indicated that the risk of death for UBM might be higher than that for R-PB/BM (adjusted hazard ratio = 0.07, 95% confidence interval [CI] = 0.01–1.02, $P = 0.05$) and that for UCB (0.27, 95% CI = 0.07–1.09, $P = 0.07$; Table II). No significant variables were found to predict the risk of early death within 100 days post-transplant, or the risk of neurological sequelae.

CNS Abnormalities and Late Sequelae

Table I shows that the frequency of CNS abnormalities at onset and the time of SCT did not differ between the EBV-HLH and FHL patients. Whereas, post-transplant CNS abnormalities were significantly higher in the FHL patients ($P = 0.0015$). Eleven FHL patients (52%) have had late sequelae including neurological as well as endocrinological problems, in comparison to only one EBV-HLH patient with left hemiparesis ($P = 0.022$). Late sequelae of FHL

TABLE II. Association Variables Influencing on the Risk of Mortality in FHL Patients

(A) Log-rank analysis Variables	No.	Survival (OS %)		*P*-value
Age				
<2 years	30	66.2 ± 8.7		0.56
≥2 years	12	75.0 ± 12.5		
Time from HLH treatment				
<6 months	14	62.9 ± 13.3		0.65
≥6 months	28	71.4 ± 8.5		
Conditioning				
Myeloablative	31	71.0 ± 8.2		0.50
RIC	11	60.6 ± 15.7		
Donor sources				
R-PB/BM, a	9	88.9 ± 10.5	a vs. b	0.22
UCB, b	21	65.6 ± 10.6	a vs c	0.15
UBM, c	12	58.3 ± 14.2	b vs c	0.61
(B) Cox's model analysis Variables	**No.**	**Adjusted hazard ratio**	**95% CI lower–upper limit**	***P*-value**
Stem cell source				
Unrelated BM	12	1.00	Reference	
Unrelated CB	21	0.27	0.07–1.09	0.07
Related PB/BM	9	0.07	0.01–1.02	0.05
Conditioning				
Reduced intensity	11	1.00	Reference	
Myeloablative	31	0.48	0.09–2.47	0.38
Radiation				
No	31	1.00	Reference	
Yes	11	0.52	0.11–2.52	0.41
Use of ATG				
No	34	1.00	Reference	
Yes	8	0.91	0.18–4.70	0.91
HLA disparity				
No	28	1.00	Reference	
Yes (>1 locus)	14	2.79	0.75–10.38	0.13

Both analyses (A, B) were performed for 42 FHL patients who underwent the first allogeneic SCT. The Cox model analysis was performed with adjustment for selected variables including sex and age at engraftment.

included psychomotor retardation with or without seizures (n = 5), brain atrophy (n = 1), hearing difficulty (n = 1), short stature (n = 5), and impaired sexual development (n = 1).

DISCUSSION

No underlying immunodeficiency has yet been identified for idiopathic EBV-HLH, which has been recognized to be distinct from familial or inherited disease-related HLH like FHL. However, EBV also acts as a trigger in the development of HLH episodes in FHL patients. Therefore, caution must be exercised in the differentiation of the two types of HLH disease. Strict use of the renewed diagnostic criteria for the registered cases in Japan enabled an analysis of the SCT results of 43 FHL and 14 EBV-HLH patients. The data first revealed a high survival rate in UCBT recipients in either type of HLH, indicating that CB could be preferable BM as the unrelated donor source in SCT for pediatric patients with refractory HLH. In addition, SCT in FHL patients was more problematic than that in EBV-HLH, where it was associated with a high incidence of post-transplant early death rate as well as late sequelae including neurological deficits. The EBV-HLH patients showed no apparent sequelae even if they had CNS involvement at diagnosis.

Information concerning SCT for HLH patients has been accumulated mostly in FHL, but little has been published in EBV-HLH except for sporadic case reports [10,11]. Previously published major studies on SCT in FHL patients are summarized in Table III. Because of the historical changes in the available genetic analyses, supportive care practices, donor sources and conditioning, the pre-2000 studies [23–27] might not be comparable to the current data. Henter et al. [21] showed the improved survival of patients treated with HLH-94 followed by BMT, in which the 3-year post-BMT survival was 62%. Horne et al. [28] noted significant TRM due to venoocclusive disease (VOD) after myeloablative conditioning, and that an active disease status at SCT was associated with a poor prognosis. Ouachee-Chardin et al. [29] reported 59% of OS in a series of 48 patients including 60% of haploidentical SCT, and indicated a high TRM due to VOD associated with young age. Recently, Baker et al. [30] reported that BU/CY/VP16 plus or minus ATG-conditioning provided a cure in 53% of patients after unrelated donor BMT, but a high mortality rate at day 100 (32 of 50 [64%] deceased patients). The present study showed a comparably high OS rate (69%) and similarly high incidence of early death until day 100 (7 of 13 [54%] deaths after allogeneic SCT) in Japan. Probably, the major distinction of the current study from the other reports is a higher usage of UCBT (50%) and RIC (26%). Unfortunately, the combined usage of RIC-UCBT was applied only in eight cases (14%) in this study, which was insufficient to fully evaluate its effectiveness. With regard to RIC-SCT with or without UCBT for FHL, Cooper et al. [31] reported a high disease free survival (75%) in 12 HLH patients (including 5 FHL) who underwent RIC-SCT from matched family/unrelated or haploidentical donor, in which 3 of 9 survivors had mixed chimerism but remain free of disease. The most recent report by Cesaro et al. [32] analyzed 61 cases including an appreciable number of RIC (18%) and UCBT (10%), but did not document the superiority of RIC-UCBT. In the present study, UCBT had a tendency to yield a more favorable outcome than UBMT, although the difference was not statistically significant. FHL infants received SCT early; however the fact that survival of FHL patients who underwent SCT at <2 years of age was not better than later SCT might reflect the difficulty in determining the optimal timing of SCT

TABLE III. Reports on the Clinical Outcome of Patients With HLH Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation

No. pts	Median age at SCT (months)	FH (%)	Major conditioning regimen	Donor	Source	OS (%)	Engraft. (%)	Causes of death	Refs.
9	13	45	Myeloab	VP16/BU/CY ±anti-LFA1	MRD/MMRD/haplo	BM	44.0	100	TR, HLH	[24]
29	NR	48	Myeloab	NR	MRD/MUD/haplo	BM	66.0	72	TR, HLH	[25]
20	9	30	Myeloab	VP16/BU/CY ±ATG	MSD/URD (80%)	BM	45.0	90	TR, HLH	[26]
14	14	36	Myeloab	VP16/BU/CY, ATG/BU/CY	MMRD/MUD	BM (T cell depleted)	64.3	65	TR, HLH	[27]
12	18	42	Myeloab	VP16/BU/CY	MSD/URD (67%)	BM	100	100	No	[33]
17	NR	NR	Myeloab	VP16/BU/CY ±ATG, TBI	MRD/URD/haplo	BM, CB (2), PB, CD34	58.0	94	TR, HLH, lymphoma	[8]
65[a]	13	31	Myeloab	VP16/BU/CY ±ATG	MRD/URD/haplo	BM, CB (5), PB, CD34	62.0	89	TR, HLH, AML	[21]
86[a]	13	34	Myeloab	VP16/BU/CY ±ATG, TBI	MRD/URD/haplo	BM, CB (7)	64.0	90	TR, HLH, 2nd AML	[28]
48	6	35	Myeloab	VP16/BU/CY, ATG/BU/CY	MSD/URD/haplo	BM, PB	58.5	78	HLH	[29]
12	14	17	RIC	FLU/MEL ± BUS, FLU/2GyTBI	MRD/URD/haplo	BM, CD34	75.0	100	TR	[31]
91	12	NR	Myeloab	VP16/BU/CY ±ATG	URD	BM, PB, CB (9)	45.0	83	TR, HLH	[30]
61	13	20	RIC (18%)	VP16 or MEL/BU/CY ±ATG	MRD/MMRD/URD	BM, PB, CB (6)	63.9	78	TR (68%), HLH (27%)	[32]
42	17	55	RIC (26%)	VP16/BU/CY ±ATG, TBI	MRD/MMRD/URD	BM, PB, CB (21)	69.0	78	TR (79%), HLH (21%)	Ours

AML, acute myelogeneous leukemia; BM, bone marrow; BU, busulfan; CB, cord blood; CY, cyclophosphamide; FHL, familial hemophagocytic lymphohistiocytosis; FH, family history; FLU, fludarabine; MEL, melphalan; MMRD, HLA-mismatched related donor; MRD, HLA-matched related donor; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; NR, not recorded; PB, peripheral blood; RIC, reduced intensity conditioning; TBI, total body irradiation; TR, transplantation-related events; URD, unrelated donor; VP16, etoposide. [a]Sixty four of 65 patients studied by Henter et al. [21] were included in 86 patients by Horne et al. [28].

or introducing appropriate RIC regimens in young infants. In UCBT, a major obstacle was thought to be early graft failure, but once engrafted no late graft failure could not be seen [29]. We confirmed this finding in our UCBT cases.

Dürken et al. [33] reported that six HLH patients with CNS disease underwent allogeneic BMT and three of them had no persistent neurological problems after transplant. More recently, SCT is thought to be preferable for FHL patients at the early stage of CNS disease with variable presentation [34,35]. Fludarabine-based RIC has been preferred in SCT for FHL patients in order to reduce late sequelae [36,37]. Since CNS disease itself had no impact on the OS in the current study, but nearly half of the long-term survivors of FHL had late sequelae associated with growth and development, further prospective studies should be focused on how to reduce late sequelae in SCT for FHL patients.

In the treatment of refractory EBV-HLH, no consensus has yet been reached concerning the treatment of patients who fail to respond to the HLH-2004 protocol type immunochemotherapy. Several reports documented that SCT led to a complete remission in such cases [8,10,11,28,38,39]. The present study revealed that use of pre-SCT combination chemotherapy might be associated with a better therapeutic impact on subsequent SCT in patients with EBV-HLH. Furthermore, long-term survival, that is, a probable cure, could be obtained even after autologous SCT [22] or identical twin donor BMT, suggesting that a reconstitution of allogeneic hematopoietic stem cells was not essential in the successful SCT for EBV-HLH patients as described in the autologous PBSCT success for lymphoma-associated HLH [40]. In addition, long-term survival even after graft failure or post-transplant relapse in EBV-HLH patients might suggest the possibility of resetting the adaptive immune response to the virus as postulated in autologous SCT for the treatment of autoimmune diseases [41,42]. Moreover, successful syngeneic SCT may imply that EBV-HLH is not a monogenic disease, since Chen et al. [43] observed that a primary infection of EBV incited HLH in a pair of the twins, but not in the identical twin counterpart. These observations implied that the genetic influence in patients with EBV-HLH might be distinct from that in patients with FHL on precipitating the excessive immune activation. Further prospective studies should therefore be directed toward not only the optimization of UCBT-RIC to improve survival of FHL patients, but to better understanding of the pathological interaction between cytotoxic granule disorders and EBV.

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Tacrolimus/Methotrexate versus Cyclosporine/ Methotrexate as Graft-versus-Host Disease Prophylaxis in Patients with Severe Aplastic Anemia Who Received Bone Marrow Transplantation from Unrelated Donors: Results of Matched Pair Analysis

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Tacrolimus (FK) and cyclosporine (CsA) have been shown to be effective in the prophylaxis of graft-versus-host disease (GVHD). However, no comparative studies have yet been conducted to examine the efficacy of FK/methotrexate (MTX) and CsA/MTX in patients with severe aplastic anemia (SAA) given unrelated donor bone marrow transplantation (U-BMT). We used matched-pair analysis to compare FK/MTX with CsA/MTX in patients with SAA who received U-BMT through the Japan Marrow Donor Program. Forty-seven pairs could be matched exactly for recipient age and conditioning regimens. Forty-five patients achieved engraftment in the FK group and 42 patients in the CsA group. The probability of grade II-IV acute GVHD (aGVHD) was 28.9% in the FK group and 32.6% in the CsA group ($P = .558$). The probability of chronic GVHD (cGVHD) was 13.3% in the FK group and 36.0% in the CsA group ($P = .104$). The 5-year survival rate was 82.8% in the FK group and 49.5% in the CsA group ($P = .012$). The study shows the superiority of FK/MTX over CsA/MTX in overall survival because of the lower incidence of transplantation-related deaths. A prospective randomized study comparing FK/MTX and CsA/MTX is warranted.

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KEY WORDS: Tacrolimus, Cyclosporine, Graft-versus-host disease, Prophylaxis, Aplastic anemia, Unrelated bone marrow transplantation

INTRODUCTION

Bone marrow transplantation (BMT) from a human-leukocyte antigen (HLA)-matched related donor is the treatment of choice for children and young adults with severe aplastic anemia (SAA) [1,2]. However, HLA-matched related donors are available for <30% of patients in developed countries. Immunosuppressive therapy (IST) has been used as an alternative treatment for patients without a HLA-matched related donor [3,4]. For nonresponders to IST, BMT from an unrelated donor (U-BMT) has been indicated [5]. Acute and chronic graft-versus-host disease (aGVHD, cGVHD) contribute to much of the morbidity and mortality associated with U-BMT. Effective prevention of these complications is therefore crucial for the success of U-BMT.

A combination of cyclosporine (CsA) and a short course of methotrexate (MTX) is the standard pharmacologic regimen for the prophylaxis of GVHD after BMT from both HLA-matched siblings and HLA-matched unrelated donors [6,7]. Tacrolimus (FK), a potent macrolide lactone immunosuppressant, inhibits T cell activation by forming a complex with FK binding protein-12, which blocks the serine-threonine phosphatase activity of calcineurin [8]. Although the mechanism of action is similar to that

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of CsA, the potency of FK in vitro is more than 100 times that of CsA [9]. This suggests that FK might also be more effective than CsA as GVHD prophylaxis in high-risk settings. In fact, in randomized studies of GVHD prophylaxis after matched related and unrelated BMT, the incidence of aGVHD was reduced in the treatment group receiving a combination of FK and a short course of MTX (FK/MTX) compared to the control group who received CsA/MTX [10-12]. However, although the number of deaths from GVHD was lower, an increased incidence of relapse was observed in the FK group, resulting in no difference in overall survival (OS) rate between the 2 groups. Nevertheless, because there is no risk of relapse in patients with nonmalignant disease, the results might be different in studies of malignant versus nonmalignant disease. Accordingly, FK/MTX could be associated with a lower incidence of aGVHD/cGVHD and better survival compared to CsA/MTX in patients with acquired SAA who received U-BMT.

METHODS

Patients and Controls

We collected U-BMT data from SAA patients who received FK/MTX for the prophylaxis of GVHD through the Japan Marrow Donor Program (JMDP) database. Forty-seven patients were recruited who underwent BMT between July 1997 and December 2002. For each patient receiving FK/MTX, we selected a control patient who received CsA/MTX for the prophylaxis of GVHD during the same period. Because our previous study identified that recipient age and conditioning regimens were the most important variables associated with treatment failure, we selected control patients matched for these 2 variables [13].

Transplantation data were collected using standardized forms provided by the JMDP. Baseline information and follow-up reports were submitted at 100 days, 6 months, 1 year, and then annually after transplantation. Analysis of patient outcome was performed using data from the last reported follow-up or the date of death.

Recipient-Donor HLA Matching

HLA matching between the recipient and donor was based on HLA serotyping according to the standard technique. In 69 (73%) of the 94 recipient-donor pairs, molecular analyses of HLA-A, -B, and -DRB1 loci were performed using DNA-based methods.

Transplantation Procedures

Various preconditioning regimens were used by individual transplantation centers and classified into 6 categories (Table 1): (1) cyclophosphamide (Cy; 120-200 mg/kg) + total body irradiation (TBI; 2-10 Gy) + limited field irradiation (LFI; 5-8 Gy) + antithymocyte globulin (ATG), (2) Cy + TBI + LFI, (3) Cy + TBI + ATG, (4) Cy + TBI, (5) Cy + LFI + ATG, and (6) Cy + LFI. For the prophylaxis of GVHD, FK was started at a dose of 0.03 mg/kg from day −1 and administered through continuous 24-hour i.v. infusion. Patients were converted from intravenous i.v. to oral intake when it could be tolerated at a ratio of 1:3 in 2 divided doses per day based on the last intravenous dose. Standard doses of CsA were 3 mg/kg by i.v. infusion and 6 mg/kg by oral intake. The MTX doses were 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11 after transplantation in both the FK and CsA groups.

Table 1. Patient/donor Characteristics and BMT Procedure

	Tacrolimus	Cyclosporine	P
Patient number	47	47	
Age (year)			.962
<10	11	11	
11-29	28	27	
>30	8	9	
Sex			.396
Male	31	27	
Female	16	20	
Recipient/donor sex			.71
Male/male	19	19	
Female/female	7	10	
Male/female	12	8	
Female/male	9	10	
HLA matching by DNA typing			.029
A, B, DRB1 match	20	34	
A mismatch	4	3	
B mismatch	7	0	
DRB1 mismatch	7	6	
2 alleles mismatch	3	2	
Unknown*	6	2	
Duration of disease before BMT			.359
1 year or less	6	11	
1-3 year	17	17	
3 year or more	24	19	
RBC transfusions before BMT			1
<20	7	7	
20 or more	38	38	
Unknown	2	2	
Platelet transfusions before BMT			.651
<20	9	7	
20 or more	36	36	
Unknown	2	4	
Conditioning regimens			1
Cy + TBI + LFI + ATG	3	3	
Cy + TBI + LFI	6	6	
Cy + TBI + ATG	18	18	
Cy + TBI	11	11	
Cy + LFI + ATG	3	3	
Cy + LFI	6	6	
Marrow cell dose			.764
<3 x 10^8/kg	14	13	
3 x 10^8/kg or more	30	32	
Unknown	3	2	

BMT indicates bone marrow transplantation; Cy, cyclophosphamide; TBI, total body irradiation; LFI, local field irradiation; ATG, antithymocyte globulin; RBC, red blood cell.
*HLA was serologically matched or 1-antigen mismatched in these donor-recipient pairs.

Definitions and Statistical Analysis

Engraftment was defined as achievement of a peripheral blood (PB) absolute neutrophil count (ANC) of more than 0.5×10^9/L for 3 consecutive days. In evaluation of engraftment, patients who died before day + 22 without engraftment were not considered evaluable. aGVHD and cGVHD were evaluated according to the standard criteria [14,15]. Patients who died before engraftment were excluded from the analysis of aGVHD. For analysis of cGVHD, only those who survived 100 days after transplantation were included. The probabilities of overall survival and aGVHD and cGVHD were estimated from the time of transplantation according to the Kaplan-Meier product-limit method. The χ^2 test and log-rank statistics were used to assess significance of differences in variables and outcomes between the 2 groups. All probability values were 2 sided, and $P < .05$ was considered significant.

RESULTS

Patient, Donor, and Transplantation Characteristics

Patient, donor, and transplantation characteristics of the study population are summarized in Table 1. There was an imbalance in HLA-A, -B, and -DRB1 allele mismatches, with 21 of the mismatch pairs observed in the FK group and 11 in the CsA group ($P = .029$). Other variables were comparable between the 2 groups.

Engraftment

Engraftment took place in 45 patients (96%) in the FK group and 42 patients (89%) in the CsA group. Three patients, 1 in the FK group and 2 in the CsA group, died before day 21 and were considered not evaluable for engraftment. One of the 46 evaluable patients in the FK group and 3 of the 45 evaluable patients in the CsA group failed to engraft. Another patient in the CsA group experienced late graft failure. The median time to neutrophil recovery was 18 days in the FK group (range: 10-28 days) and 17 days in the CsA group (range: 12-26 days) ($P = .400$).

aGVHD

The probability of grade II-IV aGVHD was 28.9% (range: 15.3%-42.5%) in the FK group and 32.6% (range: 18.4%-46.8%) in the CsA group at 100 days (Figure 1; $P = .558$). aGVHD developed at a median of 30 days (range: 7-76 days) in the FK group and 13 days (range: 5-28 days) in the CsA group after transplantation. The distribution of GVHD grade and organ involvement is presented in Table 2. Despite the imbalance in HLA disparity, the incidence of grade II-IV aGVHD in the FK group was equal to that in the CsA group.

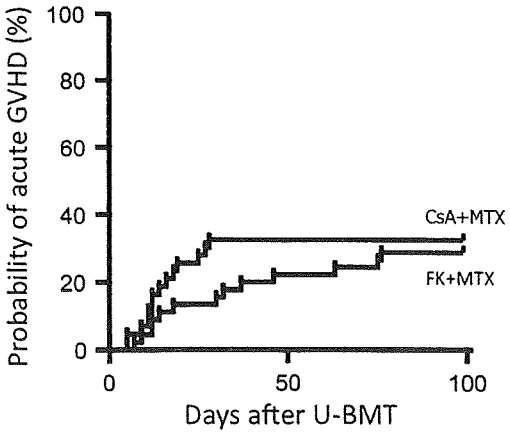

Figure 1. The probability of grade II-IV aGVHD in the FK/MTX group and the CsA/MTX group (28.9% versus 32.6%, $P = .558$).

cGVHD

Thirty-eight patients in the FK group and 35 in the CsA group were evaluable for cGVHD. Five patients in the FK group developed cGVHD at a median period of 4 months (range: 3-5 months) and 10 patients in the CsA group developed cGVHD at a median period of 4 months (range: 2-40 months). Overall, the probability of cGVHD was 13.3% (range: 2.1%-24.5%) in the FK group and 36.0% (range: 15.2%-56.8%) in the CsA group (Figure 2; $P = .104$). Three patients in the FK group and 4 in the CsA group developed an extensive type of cGVHD.

Survival

Of 47 patients in each group, 39 in the FK group survived at 4 to 61 months (median: 26 months), whereas 25 in the CsA group survived at 3 to 61 months (median: 38 months) after transplantation. The OS at 5 years was 82.8% (range: 71.9%-93.6%) in the FK group and 49.5% (range: 32.5%-66.4%) in the CsA group (Figure 3; $P = .012$). Eight patients in

Table 2. Distribution of Grade and Organ Involvement in Acute GVHD

	Tacrolimus (n = 47)	Cyclosporine (n = 47)
Grade		
0	22 (47%)	26 (55%)
I	7 (15%)	3 (6%)
II	8 (17%)	7 (15%)
III	4 (8%)	6 (13%)
IV	2 (5%)	1 (2%)
unevaluable	4 (8%)	4 (8%)
Organ involvement		
skin	5 (38%)	3 (21%)
skin + gut	6 (46%)	7 (50%)
gut + liver	1 (8%)	0 (0%)
skin + gut + liver	1 (8%)	4 (29%)

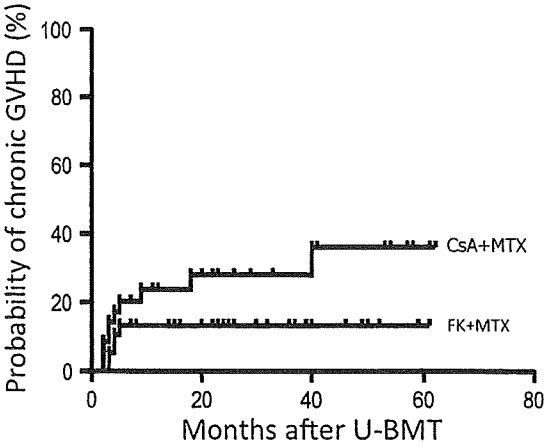

Figure 2. The probability of cGVHD in the FK/MTX group and the CsA/MTX group (13.3% versus 36.0%, $P = .104$).

the FK group and 22 in the CsA group died from transplantation-related toxicities ($P = .002$). Causes of death are summarized in Table 3. Graft failure and bacterial/fungal infection were the major causes of death.

DISCUSSION

Analyses of registration data suggest that the outcome of U-BMT in AA patients has substantially improved over the past 10 years. In analysis of 498 patients registered to the European Group for Blood and Marrow Transplantation (EBMT), 5-year survival increased from 32% ± 8% before to 57% ± 8% after 1998 [16]. Similarly, Maury et al. [17] analyzed the outcome of 89 patients in the French registry and found that 5-year survival increased from 29% ± 7% before and 50% ± 7% after 1998. An optimum conditioning regimen, GVHD prophylaxis and better donor selection may be responsible for these improvements.

In the late 1990s, HLA typing using molecular methods was introduced into clinical use. Matching for 10 alleles by high resolution technology replaced

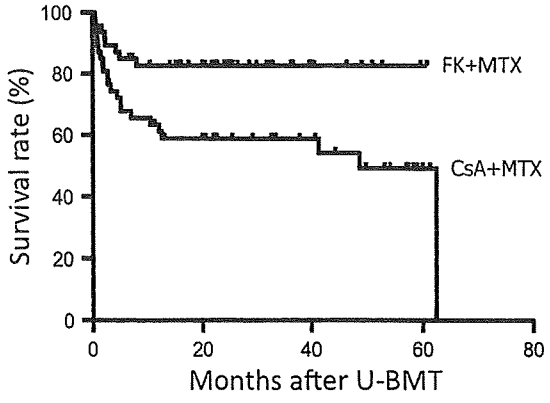

Figure 3. Kaplan-Meier estimates of OS in the FK/MTX group and the CsA/MTX group (82.8% versus 49.5%, $P = .012$).

Table 3. Primary Causes of Death

	Tacrolimus (n = 47)	Cyclosporine (n = 47)
Bacterial/fungal infection	4	4
Graft failure	1	4
Acute GVHD	1	2
Interstitial pneumonitis	0	3
Hemorrhage	1	1
EBLPD	1	1
Heart failure	0	2
Others	0	3
Total	8	22

EBLPD indicates Epstein Barr virus associated lymphoproliferative disorder; GVHD, graft-versus-host disease.

matching for 6 antigens by low resolution technology. A French study revealed that improved survival was associated with high-resolution HLA matching, suggesting that better donor selection might be a major factor in improving prognosis [17]. Recent attempts to improve the outcome in SAA patients include the use of low-dose TBI or a nonirradiation-fludarabine (Flu)-based regimen. In a prospective multicenter study sponsored by the National Marrow Donor Program (NMDP) using low-dose TBI, a low graft rejection rate of 5% and 5-year survival of 55% were achieved in 87 patients [18]. Moreover, a study by the EBMT using Flu, low-dose Cy and ATG showed a lower incidence of aGVHD and cGVHD and 5-year survival of 73% [19]. Although these novel pretransplant conditioning regimens are promising, all analyses failed to show the contribution of new regimens to the improved outcomes because of the small number of patients.

Different from patients with hematologic malignancies, there is no obvious benefit of GVHD for patients with AA. In fact, many studies have indicated adverse effects of aGVHD on the outcome of AA patients, suggesting that the most effective prophylactic regimen for GVHD should be employed for patients with AA. However, trials involved with lessening severe GVHD are limited in patients with AA. In a small number of studies, ex vivo T cell depletion by monoclonal antibodies (mAbs) or in vivo use of alemtuzumab instead of ATG has been attempted with encouraging results [20,21]. Although pharmacologic prevention with CsA/MTX is used as GVHD prophylaxis in the majority of AA patients, the role of alternative pharmacologic agents remains undetermined. Although previous randomized studies comparing CsA/MTX and FK/MTX did not show any survival benefits of FK despite a reduction in the incidence of aGVHD, most patients had malignant disease and only a few with AA were included [10-12].

The aim of the present study was to compare FK and CsA in the prophylaxis of GVHD using matched pair analysis. One drawback was the imbalance of HLA disparity between the 2 groups, with 21 mismatched pairs in the FK group and 11 in the CsA group. Our previous study showed that allelic mismatching of

HLA-A and -B antigens, but not HLA-DRB1 is the most crucial risk factor for survival of AA patients who received transplants from an unrelated donor [13]. More HLA class I mismatched pairs (HLA-A; 4, HLA-B; 7) were included in the FK group than in the CsA group (HLA-A; 3). Despite this disadvantage in terms of HLA disparity, the probability of grade II-IV aGVHD did not differ between the 2 groups. The probability of cGVHD tended to be marginally less in the FK group than in the CsA group ($P = .104$). The duration of CsA or FK after U-BMT may affect the incidences of cGVHD. However, we did not compare the difference of duration in this study because the actual duration of administration of these immunosuppressants was not available in our database.

The duration of follow-up in the FK506 group is less than in the CSP group. Although it may introduce a significant bias in the analysis, the current study showed that 5-year survival was significantly higher in the FK group than in the CsA group. Patients in the FK group showed a significant reduction in treatment-related mortality (TRM), resulting in better OS. To date, results of 3 previous randomized studies comparing FK and CsA have indicated a significantly lower incidence of aGVHD among patients receiving FK, but with no survival benefits having been demonstrated [10-12].

Yanada et al. [22] conducted a retrospective study comparing an FK-based regimen and CsA-based regimen for the prophylaxis of GVHD using registration data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). In their study, 777 patients who underwent BMT from an unrelated donor were analyzed (FK group: n = 191, CsA group; n = 586). Although the distribution of different diseases was not specified, the majority of the patients appeared to have hematologic malignancies. FK significantly reduced the risk of aGVHD and TRM without any increase in relapse, thus improving OS.

In conclusion, our matched pair analysis showed the superiority of FK/MTX over CsA/MTX in OS. However, our study was retrospective and a further study comparing FK/MTX and CsA/MTX as a prophylaxis of GVHD in AA patients who will receive U-BMT may be warranted.

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造血幹細胞移植委員会

小児期造血幹細胞移植全国集計（1983～2005）

——細胞源ドナー別移植成績——

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Japan National Registry of Hematopoietic Stem Cell Transplantation in Japan 1983-2005: Analysis of Hematopoietic Stem Cell Transplantation According to Donor and Stem Cell Source

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Abstract The Hematopoietic Stem Cell Transplantation Committee of the Society conducted an annual registry of hematopoietic stem cell transplantation (HSCT) in children in Japan from 1983 until 2005. 8,889 transplants were reported to the registry. This report describes the results of the main disease after transplantation between 1998 and 2005. Among patients with acute myeloid leukemia who underwent transplants in first complete remission (CR), the 5-year disease-free survival probabilities (5y-DFS) are 65.9% [95% confidence interval (CI): 56.5-76.9] for bone marrow transplantation (BMT) from HLA identical sibling donors (n=88), 60.9% (95%CI: 49.9-74.2) for BMT from unrelated donors (n=65), and 60% (95%CI: 46.3-77.8) for cord blood transplantation from unrelated donors (n=42). Among patients with acute lymphoblastic leukemia who underwent transplants in first CR, the 5y-DFS are 69.5% (95%CI: 60.6-79.7) for BMT from HLA identical sibling donors (n=95), 68.1% (95%CI: 59.4-78.2) for BMT from unrelated donors (n=105) and 58.7% (95%CI: 49-70.3) for cord blood transplantation from unrelated donors (n=88). Among patients with aplastic anemia who received allogeneic BMT, the 5y-DFS are 83.2% (95%CI: 76.3-90.6) for HLA identical sibling donors (n=110), 90.7% (95%CI: 81.2-100) for other related donors (n=33) and 78.1% (95% CI: 70.2-86.9) for unrelated donors. HLA-identical siblings were used as donors for less than 30% of the recipients. The prognosis of patients transplanted using bone marrow from unrelated donors is comparable and satisfactory. Cord blood transplant is avaluable alternative source of HSCT in children with acute leukemia in first or second CR.

要　旨　日本小児血液学会造血幹細胞移植委員会では，1983年から2006年まで，毎年，わが国の小児における造血幹細胞移植登録集計を行ってきた．8,889件の移植が登録された．本稿では，1998年から2005年までの8年間の成績をおもな疾患で検討した．第1寛解期（CR）の急性骨髄性白血病の移植種類別5年無病生存率は，HLA一致同胞間骨髄移植（n=88）65.9%［95%信頼区間（CI）56.5～76.9］，非血縁者間骨髄移植（n=65）60.9%（95%CI: 49.9～74.2），非血縁者間臍帯血移植（n=42）60%（95%CI: 46.3～77.8）であった．第1CRの急性リンパ性白血病の移植種類別5年無病生存率は，HLA一致同胞間骨髄移植（n=95）69.5%（95%CI: 60.6～79.7），非血縁者間骨髄移植（n=105）68.1%（95%CI: 59.4～78.2），非血縁者間臍帯血移植（n=88）58.7%（95%CI: 49～70.3）であった．再生不良性貧血の移植別5年無病生存率は，HLA一致同胞間骨髄移植（n=110）83.2%（95%CI: 76.3～90.6），その他の血縁者間骨髄移植（n=33）90.7%（95%CI: 81.2～100），非血縁者間骨髄移植（n=109）78.1%（95%CI: 70.2～86.9）であった．HLA一致同胞間移植は，同種移植の30%未満を占めるに過ぎない．非血縁者間骨髄移植は，ほとんどの同種移植適応疾患で，HLA適合同胞間移植に次ぐ安定した成績を上げるようになっている．臍帯血移植は，第1～2CRの急性白血病では有用である．

Key words: hematopoietic stem cell transplantation, unrelated bone marrow transplantation, unrelated cord blood stem cell transplantation, allogeneic peripheral stem cell transplantation

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I. はじめに

日本における小児科領域の造血幹細胞移植登録事業は，日本小児血液学会造血幹細胞移植委員会により，1983年（第25回小児血液研究会）から2005年までの間，年1回，新規症例の登録と既登録症例の追跡調査（最終追跡調査は2007年1月）という形で行われてきた．集計結果の公表は，日本小児血液学会総会において行われ，翌年の「日本小児血液学会雑誌」に報告されてきた（最終2000年）[1-16]．

内科領域の造血幹細胞移植登録事業は，1993年（第16回日本骨髄移植研究会），1991年移植分まで遡って，小児科領域と同様な形式で開始され，小児科領域とは独立のデータベースとして管理され，その後日本造血細胞移植学会に引き継がれた．1998年，日本小児血液学会と日本造血細胞移植学会の協力により，小児科領域と内科領域の造血幹細胞移植データの基本情報がはじめて結合され，1999年の以降の移植の集計は，日本造血細胞移植学会のモノグラフ「日本造血細胞移植全国調査報告書」として報告されることになった．平成14年版と17年版には小児科領域の成績が特集された．

しかしregistryの並立状態は続き，日本骨髄移植推進財団や日本臍帯血バンクネットワークでも独自のregistryを確立したため，registry間のデータ整合性や臨床現場での煩雑さなどの問題が生じ，登録システム一元化が強く要請されるようになった．さまざまな議論を経て，データマネージャーやIT技術者を備えた本格的なデータセンターが名古屋大学に造血細胞移植情報管理学講座として設置され，2006年，移植登録一元管理プログラム（Transplant Registry Unified Management Program: TRUMP）が公表された．小児科領域の造血幹細胞移植は，2006年移植分の新規登録（2007年）からTRUMPに移行し，2005年までの移植データは，2008年末までにTRUMPへの変換が完了し，TRUMP稼働施設には，当該データが日本造血細胞移植学会データセンターから送付された．

従来の小児造血幹細胞移植登録事業は，すべての移植を対象として登録されてきたため，registryの違いに伴うバイアスはない．1990年代終わり頃からは，移植の適応や移植種類の選択の形式が現在の形にほぼ落ち着いた．そこで，今回の解析は，1998年から2005年に行われた移植成績を中心に報告する．

II. 方　法

1. 対　象

対象は，2005年12月31日までに小児科領域で実施された造血幹細胞移植のうち，日本小児血液学会に登録された移植である．登録は，前年に行われた移植が，毎年，日本小児血液学会雑誌に綴じ込まれた登録票雛形を用いて行われた．2006年以降実施の移植は対象外である．登録票雛形以外の形式で記載された移植は，追跡調査等で移植実施が確認されれば含めた．また，2007年1月までにTRUMPにて2005年までの移植として登録された分は含めた．対象となる移植は8,889件となった．造血幹細胞移植一元化に伴い，小児科領域のデータの追跡調査は2007年1月が最終となった．

2. データベース

登録票のデータは，事務局にてコンピュータ入力し，電子ファイルのデータベースとして管理した．1997年までは管理集計ソフトウェアBeccelを用いてきたが，1998年に内科領域のデータと基本情報を結合する際に，汎用ソフトウェアで入出力可能なデータ形式に変換し，その後，移植ごとの情報を基本とし，患者テーブルを参照できるリレーショナルデータベースとした．

TRUMPは，移植ごとの情報を管理するデータベースであるが，元となった4つのregistryとの整合性のために，フィールド数は小児科領域の移植データベースの3倍以上に増加し，同一内容項目であっても，フィールドの定義は，異なるものが存在する．これらを考慮に入れて，TRUMP ver.1.3.1のフィールドに対応可能なデータ形式に変換した．従来の小児移植登録データには，TRUMPのフィールドの多くは冗長のため，本解析では有意味なデータフィールドに限定したデータセットを用意した．

複数回移植症例は，移植回数および個人を推定できる複数のフィールドの同一性ないし類似性より推定し，追跡調査で各施設に一覧リストで確認を求めた．

3. 統計解析

統計処理には，「R ver.2.8.1」（2008-12-22）を用いた．

移植患者数は，複数回移植の2回目以降の移植のみが登録されている患者を考慮して集計した．複数回移植の登録漏れがなければ，移植患者数は初回移植患者と一致し，複数回移植患者数は2回目移植患者と一致するはずであるが，実際には，さまざまな段階での登録漏れがあるため一致しない．移植種類の定義では，複数の幹細胞を用いている場合には，骨髄と末梢血幹細胞の併用は「末梢血幹細胞移植」とし，臍帯血移植を含む移植は「臍帯血移植」とした．

生存率は，「R」のsurvivalパッケージで計算した．生存解析の開始点は，造血幹細胞移植日とし，粗生存率は「死亡」をイベントとし，無病生存率は，「死亡」，「拒絶・

生着不全日」，「再発」，「二次がん診断日」をイベントとした．生存率の比較は，log-rank検定を行った．累積発現率（cumulative incidence function）の計算には，「R」のパッケージcmprskを用いた．再移植率と二次がん累積発生率の計算には，「死亡」を競合リスクとして計算した．

III. 結　　果

1. 移植件数と複数回移植

Table 1に，登録された移植種類と移植回別件数を示す．データベースから同定できた患者数は7,676名であり，2005年までに複数回移植を受けたのは1,079名であった．登録データのみで，死亡を競合リスクとして累積複数回移植率を計算すると，5年で13.6%（95%CI: 12.8～14.4），10年で14.3%（95%CI: 13.5～15.1），20年で14.8%（95%CI: 13.9～15.7）であった．

再移植1,250件の再移植理由は，計画的移植が324件（25.9%），生着不全・拒絶が208件（16.6%），再発が665件（53.0%），二次がんが18件（1.4%）であった．

2. 移植種類の年代別変遷

登録された移植の，移植年ごとの移植種類別推移をTable 2に示す．移植年別件数は1981年にはわずか年11件であったが，1986年105件，1994年521件，2001年643件と増加したが，その後漸減傾向にある．

同種移植におけるHLA一致同胞間骨髄移植の割合は，1985年以降80%以上を占め，1988年に88.8%とピークに達したが，2000年以降20%以下まで減少した．末梢血幹細胞移植は，自家移植で1987年から，同種移植では1993年から小児登録上出現し，自家移植では，2000年以降8割以上が末梢血幹細胞移植となったが，血縁者間移植中に占める同種末梢血幹細胞移植の割合は，2002年の45.1%をピークに2005年は24.0%まで低下した．非血縁者間末梢血幹細胞移植は2件登録されているが，海外バンクからの提供である．

臍帯血移植は，血縁者間で1994年から，非血縁者間で1997年から現れ，2005年には同種移植の26.1%を占めた．非血縁者間移植は，骨髄バンク，臍帯血バンクの発足後にそれぞれ急激に増加し，同種移植に占める非血

Table 1 Total transplants registered

Type of transplant		First SCT	Second SCT	Third SCT	Forth or later SCT	Total
HLA-id sibling	BM	2,013	146	7	0	2,166
	PB	134	89	15	5	243
	CB	29	7	0	0	36
Related donor other than HLA-id sibling	BM	626	100	14	3	743
	PB	201	118	20	4	343
	CB	16	7	1	1	25
Syngeneic	BM	43	9	2	0	54
	PB	4	0	0	0	4
Unrelated donor	BM	1,235	128	12	3	1,378
	PB	2	0	0	0	2
	CB	546	104	17	3	670
	Fetal liver	5	0	0	0	5
Autologous	BM	989	103	14	8	1,114
	PB	1,806	255	29	10	2,100
Others or unknown		3	2	1	0	6
Subtotal		7,652	1,068	132	37	8,889
Not registrated		24	11	2	0	37
Total		7,676[1)]	1,079[2)]	134	37	8,926
Registered retransplants				1,237		
Retransplants containing not registered transplants				1,250		

[1)] Number of total patients registered. [2)] Number of patients with multiple stem cell transplants. BM: bone marrow, PB: peripheral blood stem cell, CB: cord blood.

Table 2 Trend of all transplants listed by donor type and stem cell source

Year of transplant	HLA-id sib.			Related donor other than HLA-id sib.			Syngeneic		Unrelated				Autologous		Others	Total			
	BM	PB	CB	BM	PB	CB	BM	PB	BM	PB	CB	Fetal liver	BM	PB		Allo	Auto	Syn	Total
-1979	2	0	0	1	0	0	0	0	0	0	0	2	0	0	0	5	0	0	5
1980	3	0	0	0	0	0	2	0	0	0	0	1	1	0	0	4	1	2	7
1981	4	0	0	0	0	0	1	0	0	0	0	2	4	0	0	6	4	1	11
1982	13	0	0	3	0	0	1	0	0	0	0	0	9	0	0	16	9	1	26
1983	19	0	0	7	0	0	5	0	1	0	0	0	7	0	0	27	7	5	39
1984	25	0	0	7	0	0	3	0	0	0	0	0	6	0	0	32	6	3	41
1985	46	0	0	11	0	0	2	0	0	0	0	0	19	0	0	57	19	2	78
1986	52	0	0	14	0	0	2	0	1	0	0	0	36	0	0	67	36	2	105
1987	56	0	0	13	0	0	1	0	0	0	0	0	25	3	0	69	28	1	98
1988	69	0	0	12	0	0	1	0	0	0	0	0	38	10	0	81	48	1	130
1989	103	0	0	12	0	0	0	0	1	0	0	0	58	19	0	116	77	0	193
1990	117	0	0	24	0	0	2	0	0	0	0	0	75	56	0	141	131	2	274
1991	129	0	0	29	0	0	3	0	6	0	0	0	88	64	0	164	152	3	319
1992	127	0	0	33	0	0	4	0	10	0	0	0	100	88	0	170	188	4	362
1993	129	1	0	35	0	0	10	0	34	0	0	0	105	132	0	199	237	10	446
1994	181	0	2	44	0	0	3	0	49	0	0	0	80	162	0	276	242	3	521
1995	149	5	4	48	16	1	2	0	93	0	0	0	71	164	0	316	235	2	553
1996	163	19	6	67	24	3	1	0	121	0	0	0	65	168	0	403	233	1	637
1997	140	18	3	54	33	0	4	2	114	0	11	0	57	152	0	373	209	6	588
1998	111	12	4	34	36	7	2	1	114	0	50	0	56	166	0	368	222	3	593
1999	109	24	4	39	23	3	1	0	110	0	77	0	49	174	0	389	223	1	613
2000	89	45	6	28	26	4	1	1	139	1	106	0	37	162	1	444	199	2	646
2001	70	42	3	38	39	2	1	0	150	0	93	0	34	170	1	437	204	1	643
2002	64	37	1	39	50	1	1	0	143	0	79	0	26	108	0	414	134	1	549
2003	68	21	1	49	42	2	1	0	101	1	92	0	31	109	2	377	140	1	520
2004	69	9	0	47	27	1	0	0	115	0	85	0	15	95	0	353	110	0	463
2005	59	10	2	55	27	1	0	0	76	0	77	0	22	98	2	307	120	0	429
Total	2,166	243	36	743	343	25	54	4	1,378	2	670	5	1,114	2,100	6	5,611	3,214	58	8,889

BM: bone marrow, PB: peripheral blood stem cell, CB: cord blood, Auto: autologous, Allo: allogeneic, Syn: syngeneic.

縁者間移植は，2000年以降過半数を超えた．非血縁者間移植に占める臍帯血移植の割合は，臍帯血バンク発足後年々増加し，2005年には過半数に達した．

胎児肝移植は1981年以前の登録である．自家および同系臍帯血移植は，登録されていない．

1998～2005年期における初回同種移植2,552件中，HLA同胞間骨髄移植は602件（23.6%），HLA同胞からの骨髄移植と末梢血幹細胞移植を合わせた数は718件（28.1%）であるのに対して，非血縁者間骨髄移植844件（33.1%），非血縁者間臍帯血移植537件（21.0%）であった．また，初回自家移植1,107件中，自家骨髄移植227件（20.5%），自家末梢血幹細胞移植880件（79.5%）であった．

3. 造血幹細胞移植の適応

Table 3に初回造血幹細胞移植の適応を年代別に示す．全移植における各疾患の適応の割合をみると，急性骨髄性白血病（AML）は，1990～1997年期は全移植の20.6%を占めたが，1998～2005年期には15.8%に低下，第1寛解期移植（CR1）は12.7%から7.6%まで急減した．急性リンパ性白血病（ALL）は，1990～1997年期には30.3%を占めたが，1998～2005年期には26.1%と低下した．骨髄異形成症候群（MDS）は1990～1997年期の4.2%から1998～2005年期には4.8%まで増加し，とくに若年性骨髄単急性白血病（JMML）は0.7%から1.9%まで増加した．悪性リンパ腫は，1990～1997年期に7.3%から1998～2005年期に4.8%まで減少，とくに成熟型B細胞性/バーキットリンパ腫は，1.4%から0.4%と減少した．慢性骨髄性白血病（CML）は，1993年から2003年までは年間10件以上の新規移植が行われてきたが，2003年から2005年の3年間の新規移植の合計は18件と減少した．固形腫瘍は，年代ごとに適応が増加し，1998年以降は26.0%と急性リンパ性白血病と肩を並べた．とくに

Table 3 Trends of indication for first transplant by disease

Disease or disease status	-1989		1990-1997		1998-2005		Total	
	No.	%	No.	%	No.	%	No.	%
Acute myeloid leukemia	137	19.9	680	20.6	579	15.8	1,396	18.2
CR1	84	12.2	419	12.7	280	7.6	783	10.2
CR2	28	4.1	114	3.5	109	3.0	251	3.3
NeitherCR1 nor CR2	22	3.2	141	4.3	174	4.7	337	4.4
Unknown status	3	0.4	6	0.2	16	0.4	25	0.3
Acute lymphoblastic leukemia	170	24.6	998	30.3	958	26.1	2,126	27.8
CR1	44	6.4	342	10.4	371	10.1	757	9.9
CR2	66	9.6	369	11.2	286	7.8	721	9.4
NeitherCR1 nor CR2	55	8.0	284	8.6	274	7.5	613	8.0
Unknown status	5	0.7	3	0.1	27	0.7	35	0.5
Chronic myeloid leukemia	36	5.2	100	3.0	93	2.5	229	3.0
CP1	23	3.3	74	2.2	68	1.9	165	2.2
Not-CP1	13	1.9	26	0.8	25	0.7	64	0.8
Myelodysplastic syndrome/Myeloproliferative disorders	14	2.0	138	4.2	176	4.8	328	4.3
MDS(RA/RARS)	1	0.1	36	1.1	36	1.0	73	1.0
MDS(RAEB)	2	0.3	21	0.6	35	1.0	58	0.8
MDS(RAEB in t)	4	0.6	35	1.1	20	0.5	59	0.8
MDS(CMMoL)	2	0.3	17	0.5	10	0.3	29	0.4
MDS(JMML)	5	0.7	24	0.7	70	1.9	99	1.3
Other MDS/MPD	0	0.0	5	0.2	5	0.1	10	0.1
Other leukemia	0	0.0	3	0.1	22	0.6	25	0.3
Malignant lymphoma	51	7.4	240	7.3	177	4.8	468	6.1
Non-Hodgkin lymphoma (T/B-precursor)	31	4.5	145	4.4	112	3.1	288	3.8
Non-Hodgkin lymphoma (mature B/Burkitt)	17	2.5	47	1.4	16	0.4	80	1.0
Non-Hodgkin lymphoma (Ki-1)	1	0.1	29	0.9	23	0.6	53	0.7
Non-Hodgkin lymphoma (others)	0	0.0	3	0.1	11	0.3	14	0.2
Hodgkin disease	2	0.3	16	0.5	15	0.4	33	0.4
Solid tumors	136	19.7	729	22.1	955	26.0	1,820	23.8
Neuroblastoma	71	10.3	348	10.6	297	8.1	716	9.4
Rhabdomyosarcoma	7	1.0	119	3.6	141	3.8	267	3.5
Ewing sarcoma family tumor	5	0.7	54	1.6	106	2.9	165	2.2
Hepatoblastoma	4	0.6	28	0.9	58	1.6	90	1.2
Wilms tumor	1	0.1	8	0.2	26	0.7	35	0.5
Osteosarcoma	3	0.4	13	0.4	18	0.5	34	0.4
Retinoblastoma	6	0.9	7	0.2	19	0.5	32	0.4
Germ cell tumor	7	1.0	36	1.1	33	0.9	76	1.0
CNS tumor (Medulloblastoma/PNET)	3	0.4	34	1.0	103	2.8	140	1.8
CNS tumor (Germ cell tumor)	1	0.1	17	0.5	23	0.6	41	0.5
Other CNS tumor	22	3.2	21	0.6	80	2.2	123	1.6
Other solid tumors	6	0.9	44	1.3	51	1.4	101	1.3
Bone marrow failure	102	14.8	274	8.3	369	10.1	745	9.7
Aplastic anemia (without congenital disease)	92	13.3	229	7.0	273	7.4	594	7.8
Fanconi anemia (not MDS/AML)	5	0.7	17	0.5	49	1.3	71	0.9
Pure Red Cell Anemia	2	0.3	16	0.5	23	0.6	41	0.5
Kostmann disease	1	0.1	8	0.2	10	0.3	19	0.2
Other bone marrow failure	2	0.3	4	0.1	14	0.4	20	0.3
Chronic active EBV	0	0.0	3	0.1	44	1.2	47	0.6
HLH/LCH	3	0.4	17	0.5	53	1.4	73	1.0
Hemophagocytic lymphohistiocytosis	1	0.1	12	0.4	39	1.1	52	0.7
LCH/Other histiocytosis	2	0.3	5	0.2	14	0.4	21	0.3
Congenital metabolic disease	10	1.4	54	1.6	94	2.6	158	2.1
MPS-II(Hunter disease)	0	0.0	16	0.5	30	0.8	46	0.6
Adrenoleukodystrophy	1	0.1	10	0.3	36	1.0	47	0.6
Other congenital metabolic disease	9	1.3	28	0.9	28	0.8	65	0.8
Primary immune deficiency	31	4.5	56	1.7	135	3.7	222	2.9
SCID	27	3.9	30	0.9	49	1.3	106	1.4
Wiskott-Aldrich syndrome	3	0.4	15	0.5	40	1.1	58	0.8
Hyper IgM syndrome	0	0.0	1	0.0	13	0.4	14	0.2
Chronic granulomatous disease	0	0.0	3	0.1	20	0.5	23	0.3
Other primary immune deficiency	1	0.1	7	0.2	13	0.4	21	0.3
Autoimmune disease	0	0.0	1	0.0	11	0.3	12	0.2
Others	0	0.0	1	0.0	2	0.1	3	0.0
Total	690	100	3,294	100	3,668	100	7,652	100

MDS: myelodysplastic syndrome, MPD: myeloproliferative disorders, JMML: Juvenile Myelomonocytic Leukemia, CNS: central nerve system, PNET: primitive neuroectodermal tumor, CR1: first complete remission, CR2: second complete remission, CP1: first chronic phase.

髄芽腫・PNET（primitive neuroectodermal tumor）等を中心に中枢神経系腫瘍の増加は著明で，5.6%を占めた．非悪性疾患では，先天性造血障害，慢性活動性EBウイルス感染症（CAEBV），血球貪食性リンパ増殖ヒスチオサイトース（HLH)/ランゲルハンス細胞組織球症（LCH），先天性代謝疾患，先天性免疫不全症など，小児特有の疾患で増加した．

4. 疾患別移植種類別移植成績

本項では，1998年から2005年に行われた初回移植のおもな疾患別・移植前状態別生存率を述べる．個別の結果はTable 4A～4Dに示した．

全体としてみた移植種類別の初回移植の5年無病生存率（5y-DFS）をみると，HLA一致同胞間移植（n＝600）は，65.6%（95%CI: 61.7～69.7）で，これは他の移植種類と比較して有意に高い．次いで，非血縁者間骨髄移植（n＝841）は，58.6%（95%CI: 55.2～62.3）であり，HLA一致同胞間骨髄移植以外の移植種類と比較して有意に高い．HLA一致同胞間末梢血幹細胞移植（n＝115），HLA一致同胞ドナー以外の血縁者間骨髄移植（n＝261），臍帯血移植（n＝531）は，それぞれ48.4%（95%CI: 39.9～58.8），52.5%（95%CI: 46.5～59.2），47.8%（95%CI: 43.5～52.4）であった．HLA一致同胞以外の血縁者間末梢血幹細胞移植（n＝158）は，28.5%（95%CI: 22～36.9）と他の移植種類より有意に低い生存率に留まるが，CD34陽性細胞選択純化の有無を考慮すると，処理群（n＝62）は19%（95%CI: 11.3～31.9）で，非処理群（n＝96）の34.5%（95%CI: 25.7～46.3），と比較して有意に低い（p＝0.0031）．HLA一致同胞以外での骨髄移植においても，処理群（n＝16）31.2%（95%CI: 15.1～64.6）は，非処理群（n＝245）53.8%（95%CI: 47.7～60.7），より有意に低い（p＝0.0072）．

1） AML

AML第1寛解期（CR1）の初回移植（n＝280）のおもな移植を5y-DFSで比較すると，HLA一致同胞間骨髄移植（n＝88）65.9%（95%CI: 56.5～76.9），非血縁者間骨髄移植（n＝65）60.9%（95%CI: 49.9～74.2），非血縁者間臍帯血移植（n＝42）60%（95%CI: 46.3～77.8）であり，これらの間には有意差を認めなかった．HLA一致同胞間末梢血幹細胞移植（n＝10）は80%（95%CI: 58.7～100）であったが，それ以外の血縁者間末梢血幹細胞移植（n＝18）は42.4%（95%CI: 24.4～73.8）と，HLA一致同胞間骨髄移植と有意に劣っていた．第2寛解期（CR2）の初回移植（n＝109）の移植の5y-DFSは，HLA一致同胞間骨髄移植（n＝17）が64.2%（95%CI: 44.8～91.9），非血縁者間骨髄移植（n＝34）が55.2%（95%CI: 40.6～75.1），非血縁者間臍帯血移植（n＝27）が49.2%（95%CI: 32.8～73.9）であり，これらの間にも有意差を認めなかった．

第1～2寛解期（CR1-2）以外の初回移植（n＝174）の5y-DFSは，非血縁者間骨髄移植（n＝46）25.3%（95%CI: 15.3～41.9），非血縁者間臍帯血移植（n＝47）24.8%（95%CI: 14.9～41.1）であった．HLA一致同胞以外の血縁者間の末梢血幹細胞移植（n＝27）は11.1%（95%CI: 3.8～32.3），同骨髄移植（n＝17）は11.8%（95%CI: 3.2～43.2）であった．件数は少ないが，HLA一致同胞間骨髄移植（n＝18）は50%（95%CI: 31.5～79.4）であり，他の血縁者間移植や非血縁者間臍帯血移植とは有意差を認めた．HLA一致同胞間末梢血幹細胞移植（n＝10）は30%（95%CI: 11.6～77.3）であった．

2） ALL

ALL-CR1の初回移植（n＝371）の5y-DFSは，HLA一致同胞間移植（n＝95）69.5%（95%CI: 60.6～79.7），非血縁者間骨髄移植（n＝105）68.1%（95%CI: 59.4～78.2），非血縁者間臍帯血移植（n＝88）58.7%（95%CI: 49～70.3）であり，これらの間には有意差を認めなかった．CR2の初回移植（n＝286）の5y-DFSは，HLA一致同胞間骨髄移植（n＝63）53.8%（95%CI: 42～69），HLA一致同胞間末梢血幹細胞移植（n＝20）55%（95%CI: 37～81.8），その他血縁者間骨髄移植（n＝24）56.3%（95%CI: 39～81.4），非血縁者間骨髄移植（n＝88）54%（95%CI: 44.2～66），非血縁者間臍帯血移植（n＝57）51.7%（95%CI: 39.7～67.2）で，これらにも有意差を認めなかった．

CR1-2以外の初回移植（n＝174）の5y-DFSは，HLA一致同胞間骨髄移植（n＝35）24.1%（95%CI: 12.6～45.8），同末梢血幹細胞移植（n＝19）27.8%（95%CI: 13.2～58.5），その他血縁者間骨髄移植（n＝31）24.2%（95%CI: 12.5～46.6），同末梢血幹細胞移植（n＝26）7.7%（95%CI: 2～29.1），非血縁者間骨髄移植（n＝89）28.3%（95%CI: 19.6～41），非血縁者間臍帯血移植（n＝64）15.1%（95%CI: 8.3～27.6）であり，HLA一致同胞以外の血縁者間末梢血幹細胞移植と非血縁者間臍帯血移植は，HLA一致同胞間移植や非血縁者間骨髄移植より有意に低く，CD34細胞純化非処理群（n＝13）の5y-DFSは15.4%（95%CI: 4.3～55）であったが，処理群（n＝13）は全例1年以内に死亡した．

Ph陽性ALLのCR1での初回移植（n＝80）の5y-DFSは，HLA一致同胞間骨髄移植（n＝23）40.5%（95%CI: 24～68.3），非血縁者間骨髄移植（n＝29）52.1%（95%CI: 35.8～76），非血縁者間臍帯血移植（n＝14）55.1%