



Hematopoietic Cell Transplantation for Severe Combined Immunodeficiency Patients: a Japanese Retrospective Study

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Abstract

Purpose Hematopoietic cell transplantation (HCT) is a curative therapy for patients with severe combined immunodeficiency (SCID). Here, we conducted a nationwide study to assess the outcome of SCID patients after HCT in Japan.

Methods A cohort of 181 SCID patients undergoing their first allogeneic HCT in 1974–2016 was studied by using the Japanese national database (Transplant Registry Unified Management Program, TRUMP).

Results The 10-year overall survival (OS) of the patients who received HCT in 2006–2016 was 67%. Umbilical cord blood (UCB) transplantation was performed in 81 patients (45%). The outcomes of HCT from HLA-matched UCB ($n=21$) and matched sibling donors ($n=22$) were comparable, including 10-year OS (91% vs. 91%), neutrophil recovery (cumulative incidence at 30 days, 89% vs. 100%), and platelet recovery (cumulative incidence at 60 days, 89% vs. 100%). Multivariate analysis of the patients who received HCT in 2006–2016 demonstrated that the following factors were associated with poor OS: bacterial or fungal infection at HCT (hazard ratio (HR): 3.8, $P=0.006$), cytomegalovirus infection prior to HCT (HR: 9.4, $P=0.03$), ≥ 4 months of age at HCT (HR: 25.5, $P=0.009$), and mismatched UCB (HR: 19.8, $P=0.01$).

Conclusion We showed the potential of HLA-matched UCB as a donor source with higher priority for SCID patients. We also demonstrated that early age at HCT without active infection is critical for a better prognosis, highlighting the importance of newborn screening for SCID.

Keywords Severe combined immunodeficiency · Hematopoietic cell transplantation · Cord blood transplantation · Newborn screening · Retrospective study · Japan

Abbreviations

ADA	Adenosine deaminase	OS	Overall survival
CI	Confidence interval	ORD	Other related donor
CMV	Cytomegalovirus	PID	Primary immunodeficiency
GVHD	Graft-versus-host disease	SCID	Severe combined immunodeficiency
HR	Hazard ratio	TBI	Total body irradiation
HCT	Hematopoietic cell transplantation	TRUMP	Transplant Registry Unified Management Program
IS	Immunosuppression	UCB	Umbilical cord blood
IUIS	International Union of Immunological Societies	UCBT	Umbilical cord blood transplantation
MCB	Matched umbilical cord blood	UBM	Unrelated bone marrow
mMCB	Mismatched umbilical cord blood	VOD	Veno-occlusive disease
MSD	Matched sibling donor		
NBS	Newborn screening		

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Introduction

Severe combined immunodeficiency (SCID) is a hereditary disorder characterized by the severe dysfunction of cellular and humoral immunity owing to impaired T cell and B cell development or function. SCID comprises heterogeneous diseases caused by abnormalities in genes related to cytokine signaling, T cell receptor, VDJ recombination, and metabolism [1]. To date, 17 different diseases have been classified as SCID by the International Union of Immunological Societies (IUIS) [2]. Without any treatment, SCID patients develop opportunistic and/or severe infections during infancy, which normally leads to death within the first year.

Hematopoietic cell transplantation (HCT) has been widely applied as a curative therapy for patients with SCID since 1968 [3]. Particularly, in Japan, the first registered HCT for SCID was conducted in 1974. Upon the establishment of the Japanese Cord Blood Bank Network in 1999, umbilical cord blood (UCB) is commonly used in HCT for primary immunodeficiencies (PIDs) in Japan. Especially, umbilical cord blood transplantation (UCBT) can be prepared quickly and is considered beneficial for SCID patients, many of whom require relatively urgent transplantation. We previously analyzed 40 patients with SCID undergoing UCBT, showing its feasibility for SCID patients (5-year overall survival (OS); 71%) [4]. Although several other studies were reported from Japan [5–7], no Japanese study directly compared the outcomes of HCT for SCID patients between UCB and other donor sources. From Europe, Fernandes et al. demonstrated the transplant outcomes of SCID patients after HCT from UCB and mismatched related donors, showing similar 5-year OS ($57\% \pm 6\%$ vs. $62\% \pm 4\%$, respectively) and higher incidence of graft-versus-host disease (GVHD) in UCBT [8]. Since then, the utility of UCB as an alternative donor source has not been updated. In the present study, we conducted a Japanese nationwide retrospective analysis of SCID patients following HCT for the first time and described the characteristics of these patients, outcomes, and factors contributing to the survival of SCID patients, where nationwide newborn screening (NBS) is not available. We also demonstrated equivalent outcomes of HCT from HLA-matched UCB to those from matched sibling donors (MSDs), highlighting the potential of matched UCB as a donor source with higher priority for SCID patients.

Methods

Data Collection

This study was approved by the Institutional Ethics Committee of the Japan Society for Hematopoietic Cell Transplantation and Tokyo Medical and Dental University (approval number: M2018-067). The participants (and/or their guardians) provided written informed consent for research use of their data and were registered in the Transplant Registry Unified Management Program (TRUMP), the electronic database of all HCTs performed in Japan established by the Japanese Society of Hematopoietic Cell Transplantation [9]. Patients with SCID who underwent their first HCT were included. The diagnoses of the patients were collected according to the IUIS 2017 classification [10]. All transplant data were obtained from the TRUMP. Of note, the TRUMP database does not contain the data on the following: NK cell status at diagnosis, PK monitoring of alkylating agents, lineage-specific chimerism, and immunoglobulin supplementation after HCT.

Study Endpoints

The conditioning regimens were classified as follows: fludarabine and busulfan (herein, Flu/Bu), fludarabine and melphalan (Flu/Mel), no chemotherapy (no conditioning), immunosuppression (IS, regimens containing one or more of the following: fludarabine, cyclophosphamide, anti-thymocyte globulin), and others (e.g., busulfan and cyclophosphamide [Bu/CY], cyclophosphamide and low-dose total body irradiation [TBI]). The conditioning regimens other than no conditioning or IS were also classified into myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC). Regimens containing one of the following were classified as MAC: TBI at a total dose of ≥ 700 cGy, busulfan at a total dose of ≥ 12 mg/kg, or melphalan at a total dose of > 140 mg/m², according to previous studies from North America [11, 12].

The definition of donor types is as follows: MSD, other related donor (ORD), matched cord blood (MCB), mismatched cord blood (mMCB), and unrelated bone marrow (UBM). HLA matching was determined by serology for earlier patients and was defined by genotype in more recent periods (among non-MSD recipients, 25% were determined by genotype before 2006 vs. 91% in 2006–2016). HLA-A, HLA-B, and HLA-DRB1 were registered in the

database for most of the cases, whereas HLA-C was only searched in the more recent patients. To strictly classify the HLA disparity, we used the term “matched” to refer to those 8/8 matched or 6/6 matched patients who lacked the HLA-C locus data (Table S1). Neutrophil recovery is defined as the achievement of an absolute neutrophil count of $\geq 0.5 \times 10^9/L$ for 3 consecutive days. Platelet recovery was defined as the achievement of an absolute platelet count of $\geq 50 \times 10^9/L$ for 3 consecutive days, unsupported by transfusion for 7 days. Retransplantation refers to both “boost” (reinfusion of stem cells from the same donor without conditioning) and “second HCT” (reinfusion of stem cells from a different donor with or without conditioning, or reinfusion from the same donor with conditioning). Whole blood cell chimerism was evaluated from 100 days to 1.5 years after HCT and the patients who died before achieving neutrophil recovery were excluded. We classified chimerism as follows: complete donor ($\geq 95\%$ donor chimerism), donor dominant ($< 95\%$ and $\geq 80\%$ donor chimerism), mixed chimerism ($< 80\%$ and $\geq 20\%$ donor chimerism), and low chimerism ($< 20\%$ donor chimerism or patients who required retransplantation). We defined short stature as a height at least 2 standard deviations below the mean height and gonadal dysfunction as an abnormality in either laboratory tests for gonadal hormones or semen analyses, or irregularity or absence of menstruation.

Statistical Analysis

Retransplantation, neutrophil recovery, platelet recovery, acute GVHD (aGVHD), and chronic GVHD (cGVHD) were analyzed using a cumulative incidence method. Death before retransplantation was considered a competing event for retransplantation. Death or retransplantation before neutrophil recovery was considered a competing event for neutrophil recovery. For platelet recovery, aGVHD, or cGVHD, death or retransplantation was considered a competing event as well. In the analyses for neutrophil and platelet recovery, we excluded patients who received no conditioning or IS. We calculated the cumulative incidence of cGVHD, limiting to the patients who survived more than 100 days after HCT. Gray’s test was used for the group comparisons of cumulative incidence. OS was calculated using Kaplan–Meier estimates, and Cox proportional hazard models were used to evaluate the impact of the independent risk factors on OS. Donor type, disease phenotype, age at HCT, bacterial and fungal infection at HCT, cytomegalovirus (CMV) infection prior to HCT, and conditioning regimen were considered variables because these factors have significant effects on OS according to previous reports [11–13]. For the multivariate analysis, we limited the patients to those who received HCT from 2006 onwards, this was when there were few missing values for each variable. The cumulative

incidence, OS, and hazard ratios (HRs) are reported with 95% confidence intervals (CIs). All statistical analyses were performed using Stata software v16.1 and EZR 1.42 [14]. Two-sided $p < 0.05$ was considered significant. All values enclosed in brackets [] represent 95% CIs.

Results

Patient Characteristics

A total of 181 SCID patients comprising 144 males (80%) and 37 females (20%) who underwent HCT between 1974 and 2016 were included in this study (a median time between HCT and last follow-up: 3.7 years; 1 day–28.5 years). The patient characteristics are shown in Table 1. The subtypes of SCID were identified in 100 participants (55%), with *IL2RG* as the most common, accounting for 55 patients (55%). Autosomal recessive SCID was relatively rare, reflecting the low rate of consanguineous marriage in Japan. The patients were diagnosed at a median age of 5 months (0 months–16 years) without improvement over time (Table S2) and received HCT at a median age of 7 months (1 month–17 years), with 65 days (0 days–11.0 years) as a median time between diagnosis and HCT.

HCT from related donors accounted for 89 cases (49%), whereas those from MSDs included 22 cases (12%). The remaining 92 cases (51%) were from unrelated donors, 81 (45%) of which were from UCB. Among the 81 cases receiving UCBT, 21 (12%) cases were from MCB. All UCBTs were single-unit unrelated cord blood transplantations. Once patients were diagnosed, UCBT could be performed as soon as HCT from related donor, whereas it took longer to perform HCT from URBM (Table S3). UCB became the most common donor source for SCID transplants in Japan, accounting for 53 cases (70%) in 2006–2016 (Table S2). The conditioning regimens and GVHD prophylaxes changed over time. More patients received Flu/Bu or Flu/Mel for conditioning and tacrolimus for GVHD prophylaxis in the later period (Table S2).

Notably, 33 patients (33%) had an active bacterial or fungal infection at the time of HCT. Among those who received HCT in 2006–2016, active bacterial or fungal infection at HCT was correlated with the following conditions (Table S4): a shorter period between diagnosis and HCT (80 days for those without infection vs. 33 days for those with infection; $P = 0.001$), history of mechanical ventilation before HCT (11% for those without infection vs. 33% for those with infection; $P = 0.03$), and respiratory impairment at HCT (26% for those without infection vs. 56% for those with infection; $P = 0.02$). The patients who received no conditioning tended to be commonly chosen in the patients

Table 1 Details of the patient characteristics

Characteristics (number of patients evaluated)	
Patient sex (n = 181)	
Male	144 (80%)
Female	37 (20%)
Phenotype (n = 100)	
T – B + SCID	65 (65%)
<i>IL2RG</i> deficiency/X-linked	55 (55%)
<i>JAK3</i> deficiency	3 (3%)
CD3 component deficiency	2 (2%)
Unspecified T – B + SCID	5 (5%)
T – B – SCID	35 (35%)
<i>RAG1/RAG2</i> deficiency/Omenn syndrome	14 (14%)
ADA deficiency	6 (6%)
Artemis deficiency	6 (6%)
DNA ligase IV deficiency	3 (3%)
Reticular dysgenesis	1 (1%)
Unspecified T – B – SCID	5 (5%)
Age at diagnosis (n = 173)	
< 3 months	43 (25%)
≥ 3 months	130 (75%)
Median (range)	5 m (0 m–16 y)
Age at HCT (n = 175)	
< 4 months	25 (14%)
≥ 4 months	150 (86%)
Median (range)	7 m (1 m–17 y)
Time from diagnosis to HCT (n = 175)	
~ 3 months	114 (65%)
3~6 months	32 (18%)
6~months	29 (17%)
Median interval	2 m (0 m–11 y)
Year of HCT (n = 181)	
1974~2005	105 (58%)
2006~2016	76 (42%)
Bacterial or fungal infection at HCT (n = 99)	
Yes	33 (33%)
No	66 (64%)
GVHD prophylaxis (n = 158)	
Cyclosporine	87 (55%)
Tacrolimus	71 (45%)
Conditioning (n = 169)	
Flu/Bu	28 (17%)
Flu/Mel^a	34 (20%)
No conditioning	72 (43%)
Immunosuppression	7 (4%)
Flu/CY + ATG	3 (2%)
Flu	2 (1%)
CY	1 (0.6%)
ATG	1 (0.6%)
Others	28 (17%)
Bu/CY	18 (11%)
Flu/CY/ETP/Mel	3 (2%)

Table 1 (continued)

Characteristics (number of patients evaluated)	
Flu/Bu/Mel	2 (1%)
Flu + low-dose TBI	2 (1%)
Flu/CY + low-dose TBI	1 (0.6%)
TBI 8 Gy/CY	1 (0.6%)
AraC/ETP/CY	1 (0.6%)
In vivo T cell depletion (n = 166)	
Yes	23 (14%)
No	143 (86%)
Donor type (n = 181)	
BM	91 (50%)
MSD	22 (12%)
MORD	5 (3%)
mMORD	53 (29%)
UBM	11 (6%)
UCB	81 (45%)
MCB (unrelated)	21 (12%)
mMCB (unrelated)	59 (33%)
NA (unrelated)	1 (0.6%)
PB	9 (5%)
MORD	1 (0.6%)
mMORD	7 (4%)
NA (related)	1 (0.6%)

^aAmong Flu/Mel, 4 patients received Flu/Mel combined with low-dose TBI (3 Gy)

SCID, severe combined immunodeficiency; *ADA*, adenosine deaminase; *HCT*, hematopoietic cell transplantation; *GVHD*, graft-versus-host disease; *Flu*, fludarabine; *Bu*, busulfan; *Mel*, melphalan; *TBI*, total body irradiation; *CY*, cyclophosphamide; *ATG*, anti-thymocyte globulin; *ETP*, etoposide; *AraC*, cytarabine; *BM*, bone marrow; *MSD*, matched sibling donor; *MORD*, matched other related donor; *mMORD*, mismatched other related donor; *UBM*, unrelated bone marrow; *UCB*, umbilical cord blood; *MCB*, matched cord blood; *mMCB*, mismatched cord blood; *NA*, not applicable; *PB*, peripheral blood

with an active infection at HCT, although it did not reach significance ($P=0.06$).

Survival and Causes of Death

The summary of the transplant outcomes is shown in Table 2. The OS for 25 years was 44% [23–63%], and the median time of death from HCT was 51 days (1 day–24.3 years). The 10-year OS was 67% [55–77%] in 2006–2016 vs. 55% [45–64%] in 1974–2005 (Fig. 1a; $P=0.14$); the number of patients per period was low, and the difference did not reach significance.

Based on univariate analyses, there were significant differences in OS between the following: age at HCT (10 years: 84% [63–94%] for < 4 months vs. 56% [48–64%] for ≥ 4 months, Fig. 1b, $P=0.02$); bacterial and fungal

Table 2 Comparisons of the outcomes by the period of HCT

Outcome (number of patients evaluated)	Overall	~ 2005	2006~	<i>P</i> value
Overall survival (%) (<i>n</i> = 181)				0.14 ^a
1 year (95% CI)	70 (62–76)	65 (55–73)	76 (65–84)	
5 years (95% CI)	61 (53–67)	56 (46–65)	67 (55–77)	
10 years (95% CI)	59 (51–66)	55 (45–64)	67 (55–77)	
25 years (95% CI)	44 (23–63)	41 (21–59)	NA	
Retransplantation (<i>n</i> = 181)				0.47 ^b
Cumulative incidence (%) at 10 years (95% CI)	9 (6–14)	11 (6–17)	9 (3–19)	
Median days of retransplantation (range)	126.5 (31–2225)	125 (33–1323)	151 (31–2225)	
Neutrophil recovery (<i>n</i> = 90)^c				0.84 ^b
Cumulative incidence (%) at 30 days (95% CI)	78 (68–85)	78 (60–89)	78 (64–87)	
Cumulative incidence (%) at 42 days (95% CI)	83 (74–90)	81 (62–91)	85 (72–93)	
Median days of recovery (range)	17 (0–49)	16 (11–49)	17 (0–37)	
Platelet recovery (<i>n</i> = 82)^c				0.17 ^b
Cumulative incidence (%) at 30 days (95% CI)	49 (38–59)	35 (18–52)	57 (42–69)	
Cumulative incidence (%) at 60 days (95% CI)	73 (62–82)	66 (45–80)	77 (63–87)	
Median days of recovery (range)	28 (0–153)	36.5 (6–153)	26 (0–129)	
Acute GVHD				
Cumulative incidence (%) at 1 year (95% CI)				
Grades II–IV (<i>n</i> = 167)	16 (11–22)	13 (7–21)	20 (12–30)	0.28 ^b
Grades III–IV (<i>n</i> = 173)	6 (3–11)	5 (2–11)	8 (3–15)	0.46 ^b
Chronic GVHD				
Cumulative incidence (%) at 2 years (95% CI)				
Total (<i>n</i> = 125)	12 (7–19)	10 (4–19)	15 (7–25)	0.5 ^b
Extensive (<i>n</i> = 127)	6 (3–12)	4 (1–11)	9 (3–18)	0.28 ^b

^aLogrank test^bGray's test^cThe patients who received unconditioned HCT or immunosuppression were excluded from the analysis for hematologic recovery
HCT, hematopoietic cell transplantation; CI, confidence interval; NA, not applicable; GVHD, graft-versus-host disease

infection at HCT (10 years: 75% [62–84%] for those without infection vs. 50% [31–66%] for those with infection, Fig. 1c, $P=0.008$); CMV infection prior to HCT (5 years: 71% [60–79%] for those without infection vs. 33% [8–62%] for those with infection, Fig. 1d, $P<0.001$); and conditioning regimen (10 years: 80% [68–88%] for RIC, 55% [31–74%] for MAC, and 51% [39–61%] for no conditioning/IS, Fig. 1e, $P=0.007$). There was no difference in OS between the Flu/Bu and Flu/Mel regimens, with better survival than those who received no conditioning/IS or other regimens (Fig. 1f, $P=0.002$). Meanwhile, the SCID phenotype or genotype did not show a significant difference in OS (Fig. 1g, h). The 10-year OS of the HCT cases from MSD (91% [68–98%]) and those from MCB (91% [67–98%]) were similar, having better survival than the other donor type (Fig. 1i).

We additionally performed univariate analyses on the OS of patients who received HCT from 2006 onwards. Although these analyses may be less accurate owing to the smaller

sample size, similar trends were observed for each variable (Table 3).

Multivariate analysis of the patients who received HCT from 2006 onwards revealed that age at HCT ≥ 4 months (HR: 25.5 [2.2–293]; $P=0.009$), mMCB (HR: 19.8 [2.0–197]; $P=0.01$), bacterial and fungal infection at HCT (HR: 3.8 [1.5–9.8]; $P=0.006$), CMV infection prior to HCT (HR: 9.4 [1.3–66.4]; $P=0.03$), and no conditioning/IS (HR: 11.7 [2.7–50.7]; $P=0.001$) were associated with worse OS (Table 3). The SCID phenotype did not significantly affect OS.

The causes of death are shown in Table 4. Infection and non-infectious pulmonary complications were frequent, accounting for 27 cases (37%) and 15 cases (21%), respectively. The number of deaths due to infection was higher in the group with no conditioning ($P=0.05$, Table S5).

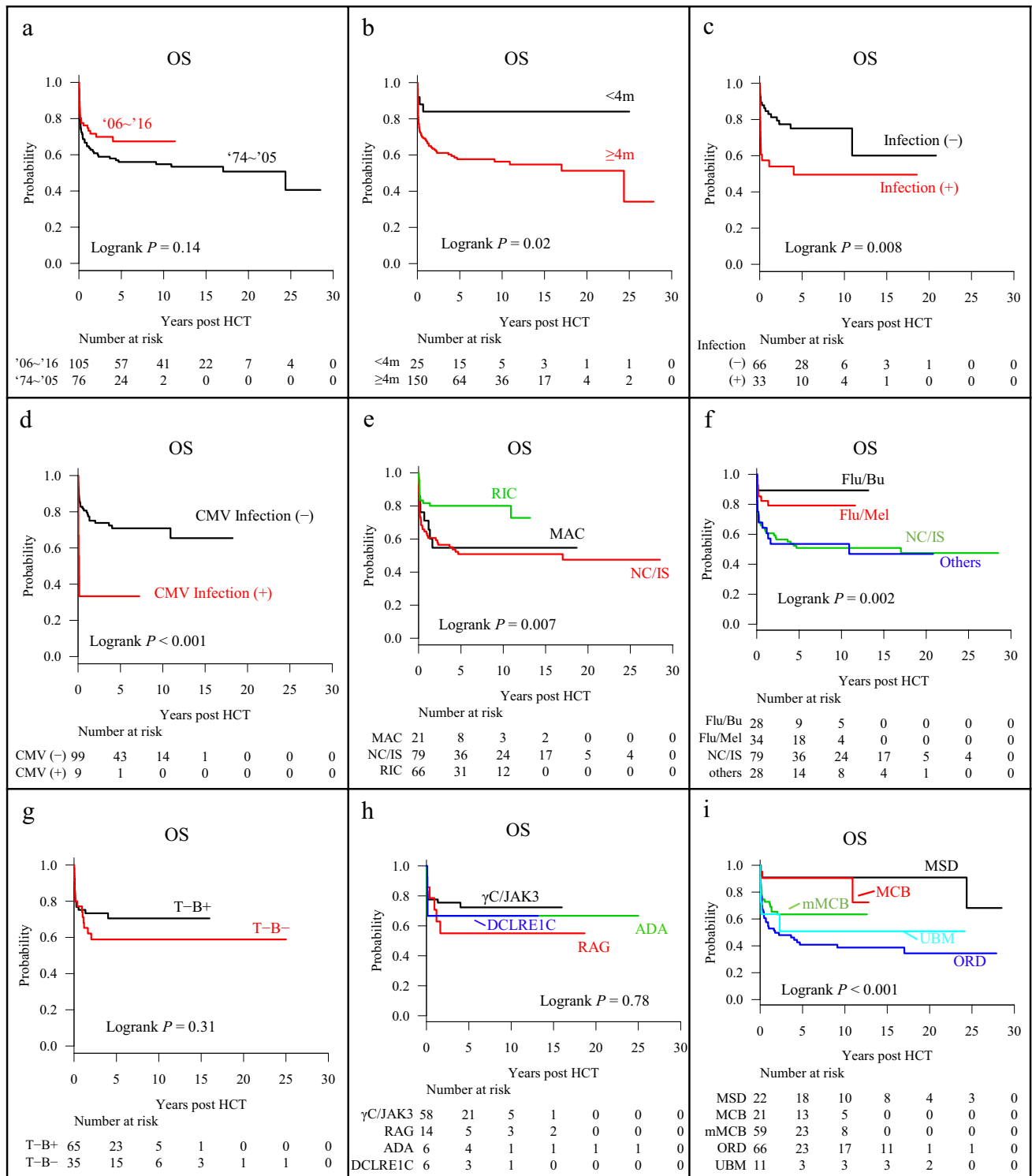


Fig. 1 Kaplan–Meier survival curves. **a** OS according to the period when transplanted. The subsequent analyses for OS were applied to the patients in all periods, according to **b** age at HCT diagnosis, **c** the presence of bacterial or fungal infection status at HCT, **d** CMV infection prior to HCT, **e** intensity of conditioning, **f** conditioning regimen, **g**, **h** SCID phenotype, and **i** donor type. OS, overall survival;

HCT, hematopoietic cell transplantation; CMV, cytomegalovirus; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; NC, no conditioning; IS, immunosuppression; Flu, fludarabine; Bu, busulfan; Mel, melphalan; MSD, matched sibling donor; MCB, matched cord blood; mMCB, mismatched cord blood; ORD, other related donor; UBM, unrelated bone marrow

Table 3 Factors affecting OS after HCT between 2006 and 2016

Factors	<i>n</i>	Univariate analysis		Multivariate analysis	
		5-year OS (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
SCID phenotype			0.45		
T – B + SCID	53	69% (53–81%)		1	
T – B – SCID	21	60% (35–78%)		0.37 (0.12–1.1)	0.08
Age at HCT			0.046		
< 4 m	14	93% (59–99%)		1	
≥ 4 m	61	62% (47–74%)		25.5 (2.2–293)	0.009
Donor type			0.61		
MSD	7	86% (33–98%)		1	
MCB (unrelated)	13	85% (51–96%)		7.4 (0.5–100)	0.13
mMCB (unrelated)	39	66% (48–78%)		19.8 (2.0–197)	0.01
ORD	11	48% (9–80%)		5.9 (0.6–54.7)	0.12
UBM	5	NA		22.3 (1.4–357)	0.03
Bacterial or fungal infection at HCT			0.005		
No	47	79% (64–89%)		1	
Yes	27	49% (28–67%)		3.8 (1.5–9.8)	0.006
CMV infection prior to HCT			0.45		
No	70	69% (56–79%)		1	
Yes	5	60% (13–88%)		9.4 (1.3–66.4)	0.03
Conditioning			0.04		
Flu/Bu	22	86% (63–95%)		1	
Flu/Mel	26	77% (55–89%)		2.0 (0.5–8.5)	0.33
No conditioning/immunosuppression	21	41% (18–63%)		11.7 (2.7–50.7)	0.001
Others	6	67% (20–90%)		3.6 (0.5–24.1)	0.2

OS, overall survival; CI, confidence interval; SCID, severe combined immunodeficiency; HCT, hematopoietic cell transplantation; MSD, matched sibling donor; MCB, matched cord blood; mMCB, mismatched cord blood; ORD, other related donor; UBM, unrelated bone marrow; NA, not applicable; CMV, cytomegalovirus; Flu, fludarabine; Bu, busulfan; Mel, melphalan

Hematologic Recovery and Retransplantation

The cumulative incidence of neutrophil and platelet recovery did not differ over time (Table 2). The HCT from MSD showed the fastest hematologic recovery (Fig. 2a, b). MCB also showed relatively robust neutrophil recovery (cumulative incidence at 30 days; 89% [57–98%]) and platelet recovery (cumulative incidence at 60 days; 89% [57–98%]). Retransplantation was performed in 16 cases (9%) with an interval from the HCT of 126.5 days (31 days–6.1 years). We showed an increased incidence of retransplantation in the HCT from ORD and mMCB (Fig S2a). However, no case required retransplantation after the HCT from MCB, suggesting substantially stable engraftment of MCB. Among the UCBT cases, HLA disparity tended to result in slower platelet recovery and increased incidence of retransplantation (Fig. 2b, Fig. S1c, and Fig. S2a, b).

In terms of conditioning regimens, the Flu/Bu and Flu/Mel regimens similarly showed robust hematologic recovery (Fig. 2c, d), as well as a low incidence of retransplantation in these groups (Fig. S2c).

Chimerism

The whole blood cell chimerism according to donor type is shown in Fig S3a. Among patients with HCT from MCB, 67% had donor chimerism of 80% or higher, while none had donor chimerism of less than 20%. Chimerism according to a type of conditioning regimen is also shown in Fig. S3b. Complete or donor-dominant chimerism was significantly more frequently seen in patients who received RIC than no conditioning/IS ($P=0.01$). Among RIC regimens, complete or donor-dominant chimerism might have been more frequent in Flu/Bu than Flu/Mel, although the difference was not significant.

HCT-Related Complications

The cumulative incidences of aGVHD II–IV and cGVHD did not change over time (Table 2). In the HCT from MSD, there was no occurrence of grades II–IV aGVHD or cGVHD. The HCT from MCB or mMCB showed similar incidence of GVHD to that from ORD (grades II–IV and grades III–IV

Table 4 Causes of death

Cause of death	<i>n</i> (%)
Infection	27 (37%)
Non-infection	46 (63%)
Pulmonary (non-infection)	15 (21%)
Others (non-infection)	31 (42%)
Veno-occlusive disease	4 (5%)
Unknown	4 (5%)
Multi-organ failure	3 (4%)
Cardiac failure/cardiomyopathy	3 (4%)
Secondary malignancy	2 (3%)
Renal failure	2 (3%)
CNS dysfunction	2 (3%)
Acute GVHD	2 (3%)
Chronic GVHD	2 (3%)
Adrenal	2 (3%)
Hemorrhage	2 (3%)
Liver failure	1 (1%)
Hemophagocytic syndrome	1 (1%)
Thrombotic microangiopathy	1 (1%)
total	73

CNS, central nervous system; GVHD, graft-versus-host disease

aGVHD at 1 year: 19% [6–38%] and 10% [2–27%] for MCB vs. 21% [11–32%] and 12% [5–22%] for mMCB vs. 16% [8–27%] and 3% [0.6–10%] for ORD, respectively; total and extensive cGVHD at 2 years: 6% [0.3–23%] and 6% [0.3–23%] for MCB vs. 22% [11–36%] and 12% [4–24%] for mMCB vs. 13% [5–25%] and 5% [0.9–15%] for ORD, respectively; Fig. 2e–h). Among the UCBT cases, HLA disparity showed a trend towards more frequent GVHD occurrence (Fig. S1d–g), although it was not statistically significant. A similar trend was observed between GVHD and donor type in HCT cases performed after 2006 (data not shown).

The other HCT-related complications identified are listed in Table 5. CMV infection was observed in 15% of the patients. Among the various infections that complicated during the pre- or post-transplant course, CMV infection was correlated with poorer OS ($P < 0.001$; Table S6). However, other viral infections were not associated with poor OS. The number of evaluable patients was small, and we could not show an association of donor type selection and viral clearance or occurrence of viral infection after HCT (data not shown).

Referring to the dose of busulfan, 28 patients received Flu/Bu regimen with a median busulfan dose of 9.9 mg/kg (4–19 mg/kg), among which only four patients received more than 12 mg/kg of busulfan, which was considered to be myeloablative. In contrast, 18 patients received Bu/CY regimen with a median busulfan dose of 16 mg/kg (8–20 mg/

kg). Veno-occlusive disease (VOD) was developed in eight patients, six of whom received Bu/CY as the conditioning regimen (data not shown). Among 110 evaluable patients, 24 (22%) reported short stature. The patients with short stature were significantly associated with extensive cGVHD (22% [8–40%] for those with short stature vs. 3% [0.5–8%] for those without, $P = 0.002$). In addition, short stature was more frequently observed in patients who received “others” conditioning (Table S7; $P = 0.06$), especially in patients receiving the Bu/CY regimen. There was no significant association between the higher dose of alkylating agents and the higher incidence of short stature either in the Flu/Bu ($P = 0.39$) or Flu/Mel ($P = 0.82$) regimen group. However, in this registry, there were no serum concentration data of alkylating agents, which is highly variable especially in infants, and we could not analyze the association between their toxicity and the actual exposure.

Discussion

In 2006–2016, 67% of HCT patients had a 10-year OS, which is comparable to that reported elsewhere (North America [12], Europe [13], and Turkey [15]: 10-year OS, 71%, 71%, and 66%, respectively; Australia and New Zealand: 5-year OS, 70% [16]. The HCT from MSD showed a 10-year OS of 91%, which is also consistent with these reports.

Unlike other studies, we could not detect an OS difference in OS between T – B + SCID and T – B – SCID. The sample size may have been insufficient, and the influence of other factors may have been too strong to clearly assess the risk of confounding SCID phenotypes. Another reason could be differences in the distribution of T – B – SCID diseases. Among T – B – SCID, the percentage of adenosine deaminase deficiency (ADA-SCID), with a similar 10-year OS of ~60% in North America and this cohort, was lower in Japan than in western countries (17.1% in our study, whereas 35.7% in North America [11], and 25.0% in Europe [13]). This may have reduced the negative impact of T – B – SCID on OS.

UCBT for SCID has been frequently performed in Japan, representing 70% of recent cases. This is due to accessibility to UCB, declining birth rates that lead to decreased MSD availability, and long waits for unrelated donors in Japan. In contrast, UCBT is performed less in Western countries: 11% in North America [11] and 12% of unrelated donors including UCBT in Europe [13]. Although GVHD of MCB recipients was more frequent than that of MSD, we confirmed that the survival and engraftment after HCT from MCB and MSD were almost equivalent.

Other studies in Western countries have shown that MCB accounted for 20–30% of unrelated UCBT [17, 18], which is

Fig. 2 Cumulative incidence of outcomes. The cumulative incidences of neutrophil recovery and platelet recovery according to (a and b, respectively) donor types and (c and d, respectively) conditioning regimens, and the cumulative incidences of e grades II–IV acute GVHD, f grades II–IV acute GVHD, g chronic GVHD, and h extensive chronic GVHD according to donor types are shown. *HCT*, hematopoietic cell transplantation; *MSD*, matched sibling donor; *MCB*, matched cord blood; *mMCB*, mismatched cord blood; *ORD*, other related donor; *UBM*, unrelated bone marrow; *Flu*, fludarabine; *Bu*, busulfan; *Mel*, melphalan; *NC*, no conditioning; *IS*, immunosuppression; *GVHD*, graft-versus-host disease

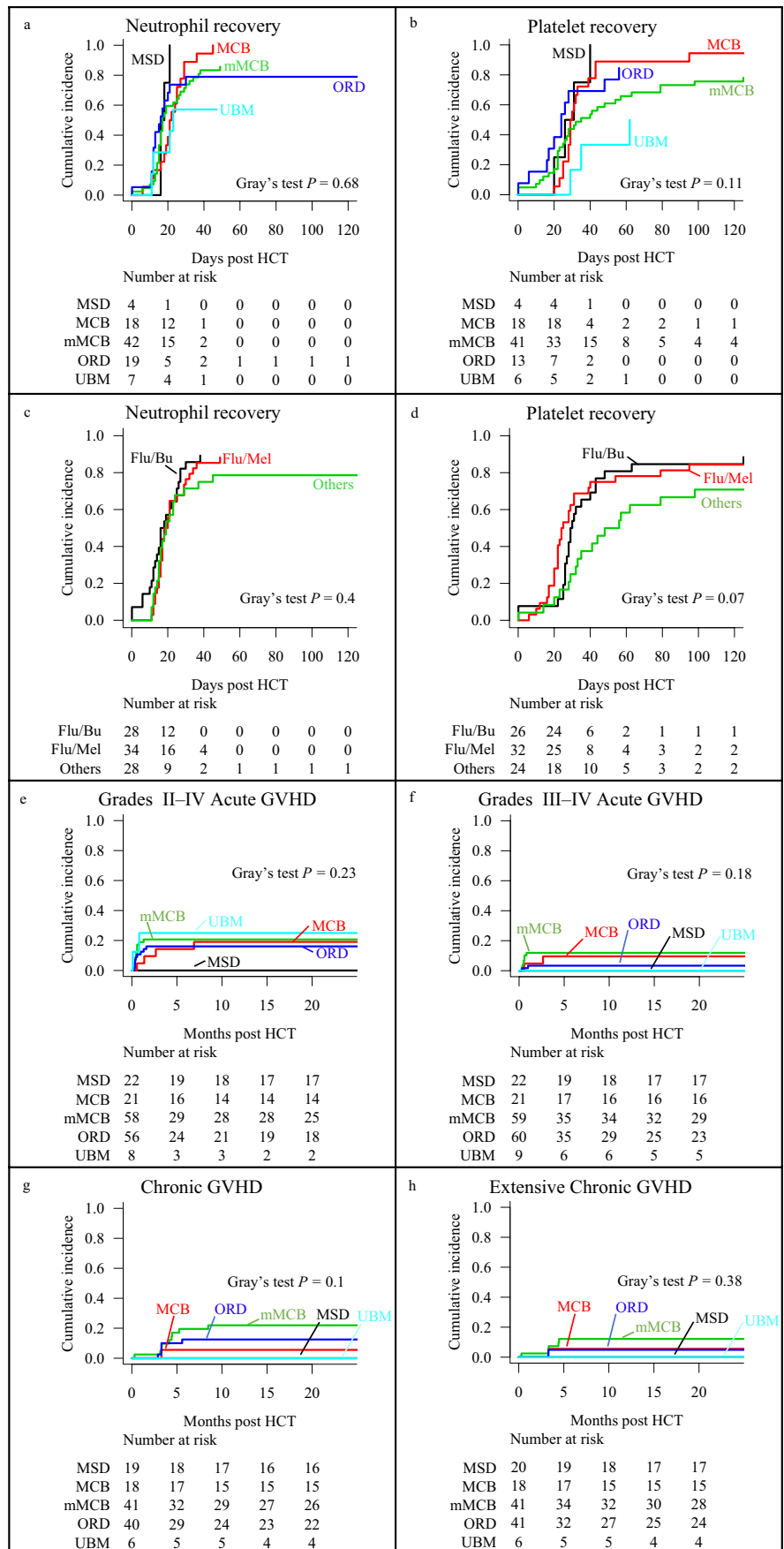


Table 5 Transplant-associated complications

	n (%)	Number of patients evaluated
Infection		
CMV antigenemia	19 (20%)	96
CMV infection	17 (15%) ^a	116
Pneumonia	14 (12%) ^a	116
Hepatitis	4 (3%) ^a	116
Enterocolitis	3 (3%) ^a	116
Retinitis	4 (3%) ^a	116
Encephalitis/meningitis	3 (3%) ^a	116
Myocarditis/nephritis	1 (0.9%) ^{a,b}	116
Other viral infection	17 (15%) ^a	111
Norovirus	4 (4%) ^a	110
RSV	3 (3%) ^a	110
EBV	3 (3%) ^a	111
HHV6/adenovirus/coronavirus/rotavirus/VZV/Rhinovirus	1 (0.9%) ^b	110
Fungal infection	5 (3%) ^c	173
Candidiasis	1 (0.6%) ^c	173
Aspergillosis	4 (2%) ^c	173
Bacterial infection	28 (26%) ^c	106
Non-infection		
Interstitial pneumonitis (non-infectious)	9 (5%)	178
ARDS	8 (4%)	178
Thrombotic microangiopathy	4 (2%)	178
Veno-occlusive disease	8 (4%)	178
Central nervous system disorder	3 (2%)	178
Hemorrhage	7 (4%)	178
Bronchiolitis obliterans	1 (0.6%)	178
Malignancy (NHL)	2 (1%)	178
Short stature ($\leq -2SD$)	24 (22%)	110
Gonadal dysfunction	3 (9%)	33
Hypothyroidism	4 (7%)	56

^aIncluding those who were diagnosed to have an infection before HCT, after HCT, and the date of diagnosis is not available

^bThe number (and percentage) of each item on the left is shown

^cIncluding only those who were diagnosed to have an infection after HCT

CMV, cytomegalovirus; RSV, respiratory syncytial virus; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; VZV, varicella zoster virus; ARDS, acute respiratory distress syndrome; NHL, non-Hodgkin lymphoma; SD, standard deviation

similar to our study. However, another study analyzing SCID patients from Eurocord [8] demonstrated cumulative incidences of $34\% \pm 6\%$ for grades II–IV aGVHD and $22\% \pm 5\%$ for cGVHD in UCBT recipients, which are higher than our cohort. These findings, which showed a similar HLA matching but less frequent GVHD in Japanese than in Western

countries, imply that DPB1, DQB1, other minor histocompatibility antigens, or non-HLA gene polymorphisms, including drug metabolism, are probably more homogenous in the Japanese population, as suggested previously [17, 19]. Unsurprisingly, greater mismatch in UCB was associated with worse OS and a tendency for unstable engraftment. While HCT from MCB produced good results, caution must be exercised when HCT from mMCB is performed.

Regarding the conditioning regimen, no conditioning/IS had a negative impact on survival in this study. Considering that SCID-X1 and ADA-SCID are known to achieve great outcomes after HCT from MSDs without conditioning [20, 21], conditioning is often avoided for these patients with active infections at HCT. In this study, patients with such infections tended to receive unconditioned HCT, and death from infection was associated with not receiving conditioning. Therefore, the risk for no conditioning/IS may have been caused by concurrent active infections, which also worsened prognosis. Moreover, from 2006–2016, nine patients without active infection at HCT received no conditioning/IS, but four eventually died. We could not find a consistent trend for this mortality. Therefore, we cannot exclude the possibility that this small number of deaths influenced the multivariate analysis, showing that no conditioning/IS had an “independent” impact on poor OS.

In this study, we showed that post-transplant VOD and short stature were more common in the Bu/CY regimen, implying toxicity of myeloablative busulfan doses, particularly in combination with a second alkylating agent. Short stature was relatively more common in our cohort than in another cohort (14%) [22]. However, we speculate that conditioning was not a major cause of short stature for some patients because of the association between extensive cGVHD and short stature and four patients with documented short stature received no conditioning. We did not find any differences in outcomes between the Flu/Bu and Flu/Mel regimens. Busulfan-containing regimens have been reported to be significantly associated with normal B cell function as compared with other regimens [23]. However, those who received busulfan-containing regimens exhibited an increased incidence of transplant-related late effects, such as gonadal dysfunction and infertility, which occurred more often than in the Flu/Mel regimens [24, 25]. Since the optimal conditioning regimen for SCID patients without MSD remains controversial, studies on the pharmacokinetics and pharmacodynamics of conditioning agents, studies on limiting doses of alkylating agents, and development of non-chemotherapeutic agents are being conducted with high priority [26]. The prognosis of T–B + SCID patients after HCT was good with low-dose busulfan (30 mg-h/L) combined with fludarabine [27]. Ongoing clinical trials determining the optimal doses of busulfan (NCT03619551) or anti-CD117 (NCT02963064) will also help to refine the

guidelines on the optimal conditioning regimens for SCID. Furthermore, haploidentical transplantation with ex vivo T cell receptor $\alpha\beta$ and CD19 depletion [28–30] or lentiviral gene therapy [31, 32] is reportedly feasible and efficacious for SCID patients. These novel methods will undoubtedly be important for developing future treatment strategies.

As in other large studies [11, 13], active infection at HCT and later age of HCT were associated with poor survival in this study. Active bacterial or fungal infection at HCT correlated with a shorter interval between diagnosis and HCT. However, we do not have any data in the registry to clearly explain this result. In our cohort, although the median time between diagnosis and HCT was almost equal to that in North America, the median age at diagnosis was 5 months, which is later than that in North America, where NBS for SCID is available [33]. Therefore, once nationwide NBS is implemented, we anticipate that infections will be managed more appropriately and HCT will be performed at an earlier age, which should improve survival.

There are several limitations to this study. First, because our sample size is relatively small, we could not exclude bias. Second, the TRUMP did not contain busulfan pharmacokinetics, which reduced regimen-related toxicity analyses. Third, we did not evaluate immunological reconstitution and lineage-specific chimerism due to the lack of available information, which weakened our results and discussion. Fourth, we did not have NK cell status at the time of diagnosis. Future studies in Japan are expected to collect more specific PID information by interactively using the TRUMP and the Primary Immunodeficiency Database in Japan [34], which is currently in preparation.

In conclusion, we demonstrated that OS of HCT from MCB and MSD was similar, suggesting that a MCB donor can be an alternative for SCID patients without MSD. Better diagnostic methods for SCID, namely NBS, are also indispensable for better outcomes, as infection and later age at HCT were independent survival risks. In most areas in Japan, NBS is limited and availability should be expanded to improve prognosis after HCT.

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Authorship Contributions S.M. designed the research, analyzed the data, and wrote the manuscript. K.U., A.N., M.Y., H.Y., and K.K. revised the manuscript. M.Ku. and Y.A. verified the analytical method and analyzed the data. M.I., M.S., T.S., M.Kat., Y.S., A.I., T.K., Y.T., and M.Kaj. recruited the patients and collected the data. M.I., Y.H., and K.K. contributed to transplantation data management as members of the Japanese Data Center for Hematopoietic Cell Transplantation. K.I. and T.M. designed the research and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Availability of Data and Material The datasets presented in this article are not readily available because the dataset belongs to the JSTCT and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT). Requests to access the datasets should be directed to <http://www.jdchct.or.jp/>.

Code Availability All statistical analyses were performed using Stata software v16.1 and EZR 1.42.

Declarations

Ethics Approval The studies involving human participants were reviewed and approved by the Institutional Review Boards at the Japanese Society for Transplantation and Cellular Therapy (JSTCT) and Tokyo Medical and Dental University.

Consent to Participate/Publication All participants (and/or their guardians) provided written informed consent for research use of their data and publication.

Competing Interests The authors declare no competing interest.

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