Hematopoietic Cell Transplantation for Inborn Errors of Immunity Other than Severe Combined Immunodeficiency in Japan: Retrospective Analysis for 1985–2016

Satoshi Miyamoto1,2 · Katsutsugu Umeda2,3 · Mio Kurata4 · Masakatsu Yanagimachi2,5 · Akihiro Iguchi2,6 · Yoji Sasahara2,7 · Keiko Okada2 · Takashi Koike9 · Reo Tanoshima10 · Masatake Ishimura11 · Masafumi Yamada12 · Maho Sato13 · Yoshiyuki Takahashi14 · Michiko Kajiwara15 · Hiroshi Kawaguchi16 · Masami Inoue13 · Yoshiko Hashii17 · Hiromasa Yabe1,18 · Koji Kato2,19 · Yoshiko Atsuta4,20 · Kohsuke Imai2,21 · Tomohiro Morio1,2

Received: 11 May 2021 / Accepted: 12 December 2021 / Published online: 4 January 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Purpose Hematopoietic cell transplantation (HCT) is a curative therapy for most patients with inborn errors of immunity (IEI). We conducted a nationwide study on HCT for patients with IEI other than severe combined immunodeficiency (non-SCID) in Japan.

Methods Data from the Japanese national database (Transplant Registry Unified Management Program, TRUMP) for 566 patients with non-SCID IEI, who underwent their first HCT between 1985 and 2016, were retrospectively analyzed.

Results The 10-year overall survival (OS) and event-free survival (EFS) were 74% and 64%, respectively. The 10-year OS for HCT from unrelated bone marrow (URBM), accounting for 39% of HCTs, was comparable to that for HCT from matched sibling donor (MSD), 79% and 81%, respectively. HCT from unrelated cord blood (URCB), accounting for 28% of HCTs, was also common, with a 10-year OS of 69% but less robust engraftment. The intensity of conditioning was not associated with OS or neutrophil recovery; however, myeloablative conditioning was more frequently associated with infection-related death. Patients who received myeloablative irradiation showed poor OS. Multivariate analyses revealed that HCT in 1985–1995 (hazard ratio [HR], 2.0; \( P = 0.03 \)), URCB (HR, 2.0; \( P = 0.01 \)), and related donor other than MSD (ORD) (HR, 2.9; \( P < 0.001 \)) were associated with poor OS, and URCB (HR, 3.6; \( P < 0.001 \)) and ORD (HR, 2.7; \( P = 0.02 \)) showed a higher incidence of retransplantation.

Conclusions We present the 1985–2016 status of HCT for non-SCID IEI in Japan with sufficient statistical power, highlighting the potential of URM as an alternative donor and the feasibility of reduced intensity conditioning.

Keywords Inborn errors of immunity · hematopoietic cell transplantation · umbilical cord blood transplantation · retrospective study · Japan

Abbreviations

aGVHD Acute graft-versus-host disease
BM Bone marrow
CGD Chronic granulomatous disease
cGVHD Chronic graft-versus-host disease
CI Confidence interval
CID Combined immunodeficiency
EFS Event-free survival
FHL Familial hemophagocytic lymphohistiocytosis
GVHD Gift-versus-host disease
HCT Hematopoietic cell transplantation
HLH Hemophagocytic lymphohistiocytosis
HR Hazard ratio
IEI Inborn errors of immunity
IUIS International Union of Immunological Societies
JSTCT Japanese Society for Transplantation and Cellular Therapy
MAC Myeloablative conditioning
MSD Matched sibling donor
ORD Other related donor
OS Overall survival
PB Peripheral blood
PGF Primary graft failure

Extended author information available on the last page of the article

© Springer
PIRD  Primary immune regulatory disorder
RIC  Reduced intensity conditioning
SCID  Severe combined immunodeficiency
SCN  Severe congenital neutropenia
SGF  Secondary graft failure
TBI  Total body irradiation
TRUMP  Transplant Registry Unified Management Program
URBM  Unrelated bone marrow
URCB  Unrelated cord blood
URCBT  Unrelated cord blood transplantation
WAS  Wiskott–Aldrich syndrome

Introduction

Inborn errors of immunity (IEI) comprise heterogeneous hereditary disorders affecting various components of innate and acquired immunity, including T and B lymphocytes, natural killer cells, phagocytes, macrophages, and complement proteins. Clinical manifestations of IEI are broad, including susceptibility to severe or opportunistic infections, autoimmunity, autoinflammation, allergic diseases, lymphoproliferation, and malignancies. They are increasingly being defined owing to recent advances in genetics and molecular sciences. In the most recent classification by the International Union of Immunological Societies (IUIS), 416 diseases have been enrolled as IEI [1]. In the present scenario, the collective prevalence of IEI is estimated to be at least 1 in 1,000 to 5,000 [2].

Hematopoietic cell transplantation (HCT) was first performed for a patient with severe combined immunodeficiency (SCID) in 1968 [3]. Since then, HCT has been widely applied as a curative therapy for patients with IEI, especially those with severe defects or dysregulation in cellular immunity. Unrelated cord blood (URCB) is commonly used in Japan and accounted for 33% of all allogeneic HCTs from 2009 to 2018 [4]. We previously performed a nationwide survey in Japan involving 88 patients with IEI who underwent unrelated cord blood transplantation (URCBT) and demonstrated an overall survival (OS) of 69% over 5 years [5]. However, no study has covered all HCTs for patients with IEI in Japan. Recently, we conducted a retrospective analysis of HCT for SCID in Japan. In this study, we conducted a nationwide retrospective analysis of HCT for patients with non-SCID IEI to provide an overview of the status and outcomes of HCTs and develop strategies for HCT in Japan.

Methods

Data Collection

This study was approved by the Institutional Ethics Committee of Tokyo Medical and Dental University. The participants (and/or their guardians) provided written informed consents and were registered in the Transplant Registry Unified Management Program (TRUMP), an electronic database of all HCTs performed in Japan established by the Japanese Society for Transplantation and Cellular Therapy (JSTCT) [6]. The patients with non-SCID IEI who underwent their first HCT were included. The diagnoses of patients were collected according to the IUIS 2017 classification [7]. All transplant data were obtained from the TRUMP.

Study Endpoints

Neutrophil recovery was 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. Primary graft failure (PGF) was defined as the failure to achieve neutrophil recovery, and secondary graft failure (SGF) was defined as the event of an absolute neutrophil count of \( < 0.5 \times 10^9/L \) for 3 consecutive days after achieving neutrophil recovery. Because data on PGF, SGF, and chimerism is not available for some patients, and because most cases of PGF or auto-recovery of recipient cells resulted in retransplantation or death, retransplantation or death was used as events for the analysis of event-free survival (EFS), to assess survival with sufficient donor cell engraftment. Only patients who achieved neutrophil recovery were included in the analysis for “late retransplantation” that was defined as a retransplantation after achieving neutrophil recovery.

The diseases were classified into the following categories: Wiskott–Aldrich syndrome (WAS), combined immunodeficiency (CID), hemophagocytic lymphohistiocytosis (HLH), chronic granulomatous disease (CGD), non-CGD phagocytic disorder, and primary immune regulatory disorder (PIRD) (see Table 2 for details). Regimens containing one of the following were classified as myeloablative conditioning (MAC) and total body irradiation (TBI) at a total dose of \( \geq 800 \) cGy, busulfan at a total dose of > 8 mg/kg, or melphalan at a total dose of \( \geq 150 \) mg/m², according to the Center for International Blood and Marrow Transplant Research criteria [8] and previous studies [9, 10]. Other regimens were classified as reduced intensity conditioning (RIC), excluding 4 patients (DiGeorge syndrome, \( n = 3 \); and CHARGE syndrome, \( n = 1 \)) who did not receive any chemotherapy or radiation. HLA matching was determined by serology for patients from the initial years and by genotype for those in the more recent years. We used the term “matched” to refer to those 8/8, or 6/6 matched who lacked the HLA-C loci data, especially among patients from the initial years. The donor type was classified as matched sibling donor (MSD), other related donor (ORD, matched or mismatched non-MSD related donor), unrelated cord blood
We defined active bacterial or fungal infection at HCT as the infection that required systemic antibiotic therapy on the day of HCT. We defined respiratory impairment as conditions that met either of the following: hemoglobin adjusted DLCO < 80%, FEV1 < 80%, requirement of oxygen, or shortness of breath with/without mild exertion. The 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. Chimerism was classified as follows: complete (≥ 95% donor chimerism), donor dominant (< 95% and ≥ 80% donor chimerism), mixed (< 80% and ≥ 20% donor chimerism), and low (< 20% donor chimerism or patients who required retransplantation). Post-transplant short stature was defined as a stature at least 2 standard deviations below the mean height for age and sex, and data was requested to be updated annually.

Statistical Analysis

OS and EFS were calculated using the Kaplan–Meier estimates, and the impact of the independent risk factors on OS and EFS was evaluated using Cox proportional hazard models. Retransplantation, neutrophil recovery, platelet recovery, acute graft-versus-host disease (aGVHD), and chronic graft-versus-host disease (cGVHD) were analyzed using a cumulative incidence method. Death was considered a competing event for retransplantation. Death and retransplantation were considered competing events for neutrophil recovery, platelet recovery, aGVHD, and cGVHD. The cumulative incidence of cGVHD was calculated and was limited to the patients who survived more than 100 days after HCT. Gray’s test was used to compare the cumulative incidence, and the Fine–Gray model was used to evaluate the impact of independent risk factors on the cumulative incidence of retransplantation. For the final multivariate analysis, variables were selected by potential factors that are considered to affect the outcome or according to the results of the respective univariate analyses. The cumulative incidence, OS, EFS, and hazard ratios (HRs) are reported with 95% confidence intervals (CIs). All statistical analyses were performed using the Stata software v16.1 and EZR 1.42 [11]. Two-sided P < 0.05 was considered significant. All values enclosed in brackets represent 95% CI unless otherwise specified.

Results

Patient Characteristics

A total of 566 patients with non-SCID IEI comprising 451 (80%) males and 115 (20%) females who underwent HCT between 1985 and 2016 were included in this study. The median duration of follow-up was 4.2 years (1 day–30.8 years) for all participants and 5.4 years (52 days–30.8 years) for survivors. The characteristics of the participants with comparison according to time periods are shown in Table 1, and the precise diagnoses are shown in Table 2. The patients with CGD (126; 22%), WAS (118; 21%), familial hemophagocytic lymphohistiocytosis (FHL) (101; 18%), and SCN (59; 10%) commonly underwent HCT. The patients received HCT at a median age of 4 years (0–64 years), and the median time from diagnosis to HCT was 1.7 years (0–36.8 years). According to disease category, there was a significant difference in the interval between diagnosis and HCT, showing shorter intervals in patients with HLH, WAS, and longer and more varied intervals in those with CGD (P < 0.001; Fig. S1). Additionally, differences in various factors were observed between the disease categories (Table S1).

HCT from MSD accounted for 129 (23%) cases. Among 375 (66%) cases of HCT from unrelated donors, 157 (28%) were URBC, and 218 (39%) were URBM. All URCBTs were a single unit. Among 61 (11%) cases of HCT from ORD, 7 cases are from matched parents and 54 cases are from mismatched related donors (parent, n = 33; sibling, n = 20; uncle, n = 1), and 2 patients (CGD and CTLA4 deficiency) received post-transplant cyclophosphamide, and none received TCRαβ+/CD19+ depletion. Among evaluable patients (n = 442), the presence of respiratory impairment at HCT was observed in 41 (9%) cases whereas active bacterial or fungal infection at HCT was noted in 102 (23%) cases. There was a strong correlation between respiratory impairment and bacterial or fungal infection at HCT (P < 0.001).

Notably, the characteristics of HCT changed significantly over time (Table 1). More patients received RIC, especially melphalan-based RIC in the later period. The HCT from unrelated donors, especially from URBM, has increased in recent years, which may have been associated with increased in vivo T cell depletion. Furthermore, patients with CGD received HCT more frequently in the recent period. However, as a whole non-SCID IEI, there is no significant difference in the age at diagnosis, age at HCT, or time from diagnosis to HCT between each period.

Overall Survival and Event-Free Survival

The summary of the transplant outcomes over the entire period is shown in Table S2. The 10-year OS and EFS were 74% [69–78%] and 64% [60–69%], respectively. We did not observe a significant difference over time in OS or EFS (Fig. 1a, b).

There were significant differences in 10-year OS between respiratory impairments at HCT (61% [41–75%] for patients with respiratory impairment vs. 78% [72–83%] for those
without, Fig. 1c, \( P=0.01 \), but not between bacterial and fungal infection at HCT, or conditioning (Fig. 1d, e). HCT from bone marrow (BM) resulted in significantly better 10-year OS than that from cord blood (78% [72–82%] for BM vs. 68% [60–75%] for cord blood, Fig. 1f, \( P<0.001 \)).

HCT from MSD (81% [72–87%]) and URBM (79% [71–84%]) led to similar 10-year OS, providing better survival than HCT from the other donor types (69% [60–76%]).
for URCB, and 56% [41–68%] for ORD, \( P < 0.001, \text{Fig. 1g} \). The patients with HLH (62% [52–71%]) had worse OS than those with WAS (82% [74–88%], \( P = 0.009 \), pairwise comparison) or non-CGD phagocytic disorder (80% [67–89%], \( P = 0.005 \), pairwise comparison) (Fig. 1h). We did not observe any statistical difference in OS according to HLA disparities in URB M, as well as in URCB (Fig. S2a, b). Additional survival curves in each disease category are shown in Fig. S3. HCT from ORD showed a tendency toward poorer OS in all disease categories other than HLH. The OS of URCB was similar to that of MSD or URB M in WAS patients but not in the other disease categories. The intensity of conditioning did not show a significant difference in OS for any of the disease categories; however, MAC containing TBI \( \geq 800 \) cGy showed a trend of inferior OS in all disease categories.

Multivariate analyses of data from patients of entire period (Table 3, \( n = 565 \)) revealed that the earliest period (1985–1995) was associated with poor OS (HR: 2.0 [1.1–3.8]; \( P = 0.03 \)). URCB and ORD were associated with poor OS (URCB, HR 2.0 [1.2–3.5], \( P = 0.01 \); ORD, HR 2.9 [1.6–5.2], \( P < 0.001 \) and EFS (URCB, HR 2.7 [1.7–4.4],

### Table 1 (continued)

| Disease category (n = 566) | Overall | '95 | '96–'05 | '06– | \( P \) value |
|---------------------------|---------|-----|--------|------|-------------|
| OS                        |         |     |        |      |             |
| Wiskott–Aldrich syndrome  | 118 (21%) | 15 (42%) | 45 (28%) | 58 (16%) | <0.001<sup>a</sup> |
| Combined immunodeficiency | 108 (19%) | 5 (14%) | 38 (23%) | 65 (18%) |
| Hemophagocytic lymphohistiocytosis | 99 (17%) | 8 (22%) | 24 (15%) | 67 (18%) |
| Chronic granulomatous disease |        |     |        |      |             |
| Non-CGD phagocytic disorder |        |     |        |      |             |
| Primary immune regulatory disorder |        |     |        |      |             |

<sup>a</sup>Fisher’s exact test; <sup>b</sup>Kruskal–Wallis test; <sup>c</sup>including MAC containing Bu and Mel (\( n = 10 \)); <sup>d</sup>including RIC containing Bu and Mel (\( n = 3 \)); <sup>e</sup>including Flu + CY ± LD-TBI (\( n = 66 \), CY ± LD-TBI (\( n = 9 \), Flu + LD-TBI (\( n = 1 \), and LD-TBI (\( n = 1 \)).
Compared to the patients with WAS, those with HLH, CID, and PIRD were associated with worse OS (HLH, HR 2.7 [1.5–4.6], P < 0.001; CID, HR 2.6 [1.4–5.0], P = 0.003; PIRD, HR 2.3 [1.1–4.6], P = 0.02), as well as worse EFS. Patients with CGD showed poor EFS (HR 1.8 [1.1–3.0], P = 0.02), but not significant for OS. As in univariate analyses, URBM did not show significant difference in impact for OS or EFS.
Fig. 1 Kaplan–Meier survival curves. a OS and b EFS according to the period in which HCT was performed. The subsequent analyses for OS were applied to the patients in all periods, according to c RI at HCT, d the presence of bacterial and fungal infection at HCT, e conditioning regimens, f donor source, g donor type, and h disease category. OS, overall survival; HCT, hematopoietic cell transplantation; EFS, event-free survival; RI, respiratory impairment; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; BM, bone marrow; CB, cord blood; PB, peripheral blood; MSD, matched sibling donor; URCB, unrelated cord blood; URBM, unrelated bone marrow; ORD, other related donor; WAS, Wiskott–Aldrich syndrome; CID, combined immunodeficiency; HLH, hemophagocytic lymphohistiocytosis; CGD, chronic granulomatous disease; PCD, phagocytic disorder; PIRD, primary immune regulatory disorder.
compared to MSD. If limiting to the patients in the recent period (2006–2016, \(n=362\)), respiratory impairment at HCT was associated with poor OS (HR: 2.0 [1.1–3.9]; \(P=0.03\), Table 4). During this period, the risk for OS in URCB and ORD was not significant compared to MSD, which indicates the risk for OS may have been reduced. However, URCB and ORD still showed poor EFS (URCB, HR 2.6 [1.4–5.0], \(P=0.004\); ORD, HR 2.6 [1.1–5.8], \(P=0.02\), Table 4) in the recent period.

### Hematologic Recovery, Graft Failure, and Retransplantation

Among evaluable patients, PGF was observed in 44 (8%, out of 564) cases and SGF was 33 (7%, out of 487) cases (Fig. 2). Retransplantation was performed in 61 (11%) cases with a median interval of 178 days (20 days–9.8 years) from HCT. Only one patient with FHL, one with hyper IgE syndrome, and one with CD40L deficiency survived without retransplantation even though they did not achieve sufficient donor engraftment.

The HCT from URCB was associated with slower hematologic recovery than the other donor types (median days [range] of neutrophil recovery: 15 [0–130] for MSD vs. 17 [9–46] for URCB vs. 17 [9–37] for ORD vs. 19 [0–49] for URBM; Fig. 3a; \(P<0.001\); median days [range] of platelet recovery: 27.5 [0–128] for MSD vs. 30 [8–356] for URCB vs. 26 [9–118] for ORD vs. 47 [0–278] for URBM; \(P<0.001\); Fig. 3b). The incidence of retransplantation was high in HCT from URCB or ORD (10-year: 11% [5–18%] for MSD vs. 6% [3–10%] for URCB vs. 20% [10–31%] for ORD vs. 21% [14–29%] for URBM; \(P<0.001\); Fig. S4a). However, the difference in the incidence of late retransplantation was not significant between URCB and MSD, or URBM (Fig. S4b). The incidence of HCT from URBM with two or more locus mismatches was associated with frequent retransplantation (10-year: 4% [1–9%] for matched URBM; 5% [1–12%] for 1 mis URBM; 16% [6–31%] for \(\geq 2\) mis URBM; \(P=0.04\); Fig. S2c). The HLA disparities in URCBT were associated with a tendency of higher incidence of retransplantation (Fig. S2d). Patients with HLH had slower platelet recovery than those with other diseases (Fig. 3d), which is probably due to the high frequency of URCBT (60%) for HLH (Table S1), and URCBT in HLH patients showed a tendency of higher incidence of retransplantation (Fig. S5b). URCBT in CGD patients also showed an increased incidence of

---

**Table 3** Factors affecting OS and EFS of patients in the entire periods

| Factors                        | \(n\) | Overall survival | Event-free survival |
|--------------------------------|------|------------------|---------------------|
|                                |      | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                                |      | 10-year (95% CI) | HR (95% CI) | \(P\) value | HR (95% CI) | \(P\) value |
| **Donor type**                 |      |                  |                  |                  |                  |                  |
| MSD                            | 129  | 81% (72–87%)     | 1                | \(<0.001\)       | 74% (63–82%)    | \(<0.001\)       |
| URCB                           | 157  | 69% (60–76%)     | 2.0 (1.2–3.5)    | 0.01             | 54% (45–62%)    | 2.7 (1.7–4.4)    | \(<0.001\)       |
| ORD                            | 61   | 56% (41–68%)     | 2.9 (1.6–5.2)    | \(<0.001\)       | 43% (29–57%)    | 3.1 (1.9–5.3)    | \(<0.001\)       |
| URBM                           | 218  | 79% (71–84%)     | 1.4 (0.8–2.4)    | 0.22             | 74% (66–80%)    | 1.3 (0.8–2.1)    | 0.28             |
| **Periods of HCT**             |      |                  |                  |                  |                  |                  |
| 2006–2016                      | 367  | 75% (68–81%)     | 1                | \(0.27\)         | 65% (58–72%)    | 1                |
| 1996–2005                      | 163  | 73% (65–79%)     | 1.2 (0.8–1.7)    | 0.45             | 66% (58–73%)    | 0.95 (0.7–1.3)   | 0.78             |
| 1985–1995                      | 36   | 63% (45–77%)     | 2.0 (1.1–3.8)    | 0.03             | 55% (37–69%)    | 1.6 (0.9–2.9)    | 0.10             |
| **Disease category**           |      |                  |                  |                  |                  |                  |
| Wiskott–Aldrich syndrome       | 118  | 82% (74–88%)     | 1                | \(<0.001\)       | 74% (65–81%)    | 1                |
| Combined immunodeficiency      | 65   | 68% (54–79%)     | 2.6 (1.4–5.0)    | 0.003            | 63% (49–75%)    | 2.0 (1.1–3.5)    | 0.02             |
| Hemophagocytic lymphohistiocytosis | 108 | 62% (52–71%)   | 2.7 (1.5–4.6)    | \(<0.001\)       | 55% (44–64%)    | 2.0 (1.2–3.2)    | 0.005            |
| Chronic granulomatous disease  | 126  | 75% (64–83%)     | 1.7 (0.95–3.2)   | 0.07             | 65% (54–74%)    | 1.8 (1.1–3.0)    | 0.02             |
| Non-CGD phagocytic disorder    | 99   | 80% (67–89%)     | 1.0 (0.5–2.0)    | 1.0              | 62% (47–74%)    | 1.4 (0.8–2.4)    | 0.20             |
| Primary immune regulatory disorder | 50  | 67% (46–81%)     | 2.3 (1.1–4.6)    | 0.02             | 63% (42–78%)    | 1.9 (1.01–3.6)   | 0.045            |

**OS**, overall survival; **EFS**, event-free survival; **HCT**, hematopoietic cell transplantation; **CI**, confidence interval; **HR**, hazard ratio; **MSD**, matched sibling donor; **URCB**, unrelated cord blood; **ORD**, other related donor; **URBM**, unrelated bone marrow; **CGD**, chronic granulomatous disease.
### Table 4 Factors affecting OS and EFS after HCT in 2006–2016

| Factors                        | n  | Overall survival | Event-free survival |
|-------------------------------|----|-----------------|---------------------|
|                               |    | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                               |    | 5-year (95% CI) | P value | HR (95% CI) | P value | 5-year (95% CI) | P value | HR (95% CI) | P value |
| Donor type                  |    |                 |         |             |         |                 |         |             |         |
| MSD                         | 70  | 84% (72–91%)    | 0.046   | 1           | <0.001  | 81% (69–89%)    | 1       |
| URCB                        | 104 | 71% (61–79%)    | 1.7 (0.8–3.7) | 0.15 | 56% (45–65%)    | 2.6 (1.4–5.0) | 0.004 |
| ORD                         | 26  | 68% (42–84%)    | 1.7 (0.6–4.4) | 0.31 | 53% (31–71%)    | 2.6 (1.1–5.8) | 0.02  |
| URBMM                       | 167 | 83% (76–89%)    | 1.1 (0.5–2.3) | 0.78 | 77% (69–83%)    | 1.5 (0.8–2.6) | 0.17  |
| Respiratory impairment at HCT|    |                 | 0.005   | 1           | 0.05    |                 |         |             |         |
| No                          | 326 | 81% (76–85%)    | 1       | 72% (66–77%) | 1       |
| Yes                         | 36  | 64% (45–78%)    | 2.0 (1.1–3.9) | 0.03 | 58% (39–73%)    | 1.5 (0.8–2.6) | 0.17  |
| Disease category            |    |                 | 0.001   | 0.045       | 1       |
| Wiskott–Aldrich syndrome    | 58  | 89% (77–95%)    | 1       | 82% (69–90%) | 1       |
| Combined immunodeficiency   | 42  | 75% (58–86%)    | 2.4 (0.9–6.7) | 0.10 | 67% (50–79%)    | 2.0 (0.9–4.5) | 0.11  |
| Hemophagocytic lymphohistiocytosis | 65 | 66% (53–76%)    | 3.5 (1.4–8.8) | 0.008 | 58% (44–69%)    | 2.3 (1.1–4.8) | 0.03  |
| Chronic granulomatous disease | 99 | 78% (67–85%)    | 2.2 (0.8–5.6) | 0.11 | 67% (56–77%)    | 2.2 (1.04–4.7) | 0.04  |
| Non-CGD phagocytic disorder | 67  | 87% (72–95%)    | 0.9 (0.3–2.9) | 0.84 | 75% (60–85%)    | 1.7 (0.8–4.0) | 0.18  |
| Primary immune regulatory disorder | 36 | 77% (57–89%)    | 2.1 (0.7–6.5) | 0.20 | 71% (51–84%)    | 1.9 (0.7–4.8) | 0.19  |

OS, overall survival; EFS, event-free survival; HCT, hematopoietic cell transplantation; CI, confidence interval; HR, hazard ratio; MSD, matched sibling donor; URCB, unrelated cord blood; ORD, other related donor; URBMM, unrelated bone marrow; CGD, chronic granulomatous disease

---

**Fig. 2** Flow-chart of the events of the study patients. The number of patients with neutrophil recovery, graft failure, retransplantation, and survival is shown in each square. *One patient with familial hemophagocytic lymphohistiocytosis developed primary graft failure but survived without reHCT; 10 patients were associated with donor chimerism of mixed or less; two patients who were diagnosed with auto-recovery of recipient cells and survived without reHCT were included (hyper IgE syndrome, n = 1; CD40L deficiency, n = 1); 4the patients in which initial neutrophil recovery was not evaluable but survived without reHCT were included (n = 2); 5among them, 5 patients were associated with auto-recovery of recipient cells. HCT, hematopoietic cell transplantation; w/o, without; reHCT, retransplantation; SGF, secondary graft failure; DLI, donor lymphocyte infusion"
Fig. 3 Cumulative incidence of hematologic recovery and graft-versus-host disease.

The cumulative incidences of neutrophil recovery and platelet recovery according to (a and b, respectively) donor type, (c and d, respectively) disease category, and (e and f, respectively) conditioning regimen are shown. The patients who received no conditioning were excluded from these analyses.

The cumulative incidences of (g) grade II–IV acute GVHD and (h) chronic GVHD according to donor type are also shown. HCT, hematopoietic cell transplantation; MSD, matched sibling donor; URCB, unrelated cord blood; URBM, unrelated bone marrow; ORD, other related donor; WAS, Wiskott–Aldrich syndrome; CID, combined immunodeficiency; HLH, hemophagocytic lymphohistiocytosis; CGD, chronic granulomatous disease; PCD, phagocytic disorder; PIRD, primary immune regulatory disorder; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease.
retransplantation or late retransplantation (Fig. S5c,i). However, the association of URCBT and retransplantation was not significant in the other disease categories.

Platelet recovery was faster in the patients who received RIC conditioning (Fig. 3f). Although retransplantation was not correlated with the intensity of conditioning (Fig. S4e), late retransplantation was more frequent in RIC than MAC (Fig. S4f). For patients with WAS or HLH, the melphalan-based regimen tended to have a higher incidence of retransplantation than the busulfan-based regimen (Fig. S5s,t). Of note, the incidence of URCBT in the RIC group was common in HLH (72%) but not in WAS patients (29%). The high incidence of retransplantation in HLH patients who received RIC regimens was probably influenced by the frequent use of URCB for these patients.

Multivariate analysis (n = 565) revealed that URCB (HR: 3.6 [1.7–7.6]; P < 0.001), ORD (HR: 2.7 [1.2–6.3]; P = 0.02), and CGD (HR: 2.3 [1.01–5.2]; P = 0.047), compared to WAS, were associated with an increased incidence of retransplantation (Table 5), as observed in the multivariate analysis for EFS.

**Chimerism**

More robust whole blood donor chimerism was achieved in patients who received HCT from MSD or URBM than those who received HCT from ORD or URCB (Fig. S6a). The donor dominance in chimerism was not significantly different between MAC and RIC regimens (Fig. S6b). The HLA disparity in URBM or URCB and disease category did not show a significant difference in terms of donor chimerism (data not shown).

### HCT-Related Complications

The cumulative incidence of aGVHD II–IV at 1 year was higher for HCT from URBM than for HCT from MSD (33% [27–40%] vs. 16% [10–23%], P = 0.005, Fig. 3g), and cGVHD at 2 years was more frequent in HCT from ORD than in HCT from MSD (33% [20–46%] vs. 15% [9–22%], P = 0.01, Fig. 3h). The cumulative incidence of GVHD in URCBT was 24% [17–31%] for aGVHD II–IV at 1 year and 13% [8–20%] for cGVHD at 2 years, which did not show a statistical difference when compared to that in HCT from MSD. The HLA disparities in URBM or URCB were not significantly associated with GVHD incidence (Fig. S2e-h).

Other HCT-related complications and the details of the post-transplant infections are shown in Tables S3 and S4, respectively. Bacterial infection (P = 0.005) and gonadal dysfunction (P = 0.006) were more commonly seen in patients who received MAC regimens, whereas the frequency of other complications did not significantly differ between different intensities of conditioning (Table S5). Viral and fungal infection was observed in 24% and 10% of the patients evaluated, respectively. Bacterial infections were observed in 37% of the evaluable patients at a median of 9 days (1–335) after HCT, and 72% of them developed infections before the neutrophil recovery was achieved. URCBT tended to have a slightly higher incidence of post-HCT bacterial infection (P = 0.006), but not of post-HCT viral infection (Table S6). Of note, serotherapy was used in

---

**Table 5** Factors affecting the incidence of retransplantation

| Factors                          | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | Cumulative incidence at 10-year (95% CI) | P value | 95% CI | P value |
| Donor type                       |                     |                      |        |
| MSD                              | 129                 | 11% (5–18%)          | <0.001 | 1       |
| URCB                             | 157                 | 21% (14–29%)         | 3.6 (1.7–7.6) | <0.001 |
| ORD                              | 61                  | 20% (10–31%)         | 2.7 (1.2–6.3) | 0.02   |
| URBM                             | 218                 | 6% (3–10%)           | 0.8 (0.3–1.8) | 0.54   |
| Disease category                 |                     |                      | 0.62   |
| Wiskott–Aldrich syndrome         | 118                 | 10% (5–16%)          | 1      |
| Combined immunodeficiency        | 65                  | 10% (4–19%)          | 1.1 (0.4–3.0) | 0.86   |
| Hemophagocytic lymphohistiocytosis| 108                | 13% (7–22%)          | 0.9 (0.4–2.1) | 0.86   |
| Chronic granulomatous disease    | 126                 | 15% (9–23%)          | 2.3 (1.01–5.2) | 0.047  |
| Non-CGD phagocytic disorder      | 99                  | 22% (11–34%)         | 2.1 (0.9–4.9) | 0.07   |
| Primary immune regulatory disorder| 50                  | 6% (2–15%)           | 0.95 (0.3–3.6) | 0.94   |

CI, confidence interval; HR, hazard ratio; MSD, matched sibling donor; URCB, unrelated cord blood; ORD, other related donor; URBM, unrelated bone marrow; CGD, chronic granulomatous disease
42% of the URCBT, less frequent than HCT from URBM (74%). Among evaluable patients (n = 541), 14 (3%) patients developed malignancy, most of which were associated with post-transplant lymphoproliferation. Short stature occurred in 18% of the patients. The patients with short stature at HCT were more likely to develop post-transplant short stature than those without (P < 0.001, Fig. S7a). Among patients with normal stature at HCT, 7% of them developed short stature after HCT. On the contrary, among patients with short stature at HCT, 66% of them improved after HCT. We did not observe a significant difference in the incidence of short stature between conditioning; however, MAC regimen containing TBI ≥ 800 cGy tended to cause post-transplant short stature more frequently than other regimens (Fig. S7b).

**Cause of Death**

Death from infection was the most common, accounting for 43 (33%) cases (Table S7). Among the patients who died, the MAC regimen was commonly associated with death from infection (P = 0.02, Table 6). In contrast, the death from organ dysfunction was relatively common in the patients who received RIC regimens (Tables 6 and S8). Notably, some of these deceased patients, including those with CGD or FHL, presented with poor immunologic reconstitution or failure to control the primary disease, suggesting that the toxicity of conditioning was not directly responsible for deaths in certain cases. The donor type or disease category did not correlate with differences in the cause of death (data not shown).

**Discussion**

Our results show a 10-year OS of 74% for patients with non-SCID IEI, who underwent their first HCT between 1985 and 2016, which is comparable to that from multicenter studies in other countries (Europe, 69% over 10 years [12]; Australia and New Zealand, 72% over 5 years [13]; Brazil, 72% over 5 years [14]; Colombia, 62% over 5 years [15]). Multivariate analysis revealed that the earliest period was a risk for poor OS. The various advances including management for infection, HLA testing, GVHD prophylaxis, and better conditioning choices (e.g., avoiding TBI-based MAC regimen) would have benefited patients in the earliest period. However, the difference in OS or EFS was not significant between 1996–2005 and 2006–2016, which would require further improvement.

We demonstrated the effect of URBM and URCB on the outcome of HCT for non-SCID IEI in Japan. The HCT from URBM was the most frequently performed, showing comparable 10-year OS to that for HCT from MSD (79% vs 81%, respectively). The equivalent outcome for HCT from URBM and MSD has also been reported from other countries [12, 13]. Although the incidence of aGVHD was high with HCT from URBM, the excellent survival was partly due to robust hematologic recovery and sufficient donor engraftment. The preparation for HCT from URBM takes several months in Japan, and our analysis reconfirms that URBM can be considered a useful alternative donor source for stable patients who have enough time to prepare for HCT.

The OS for URCBT over 10 years was 69%. Although the OS was inferior to that for HCT from MSD, this might be acceptable for patients who require urgent transplantation and do not have MSD. A similar incidence of GVHD in URCBT and HCT from MSD also suggested its utility in Japan. However, the engraftment after URCBT was not robust, as evident from a slow hematologic recovery and less sufficient donor engraftment. While the risk for OS in URCBT in the recent period may have been reduced, multivariate analyses consistently demonstrated that URCB was an independent risk for poor EFS and retransplantation. URCBT for SCID patients in Japan showed excellent outcomes, including OS and engraftment [16]. However, the disadvantage for engraftment is well known in the HCT for hematologic disorders other than SCID [17–21]. Despite the ready availability and feasibility of URCBT, we recognize the risk for poor engraftment for non-SCID IEI as a whole.

For patients who received HCT from ORD, most of which are mismatched relatives, we observed a poor OS/EFS, as well as poor engraftment and a high incidence of cGVHD. In our cohort, post-transplant cyclophosphamide or TCRαβ+/ CD19+ depletion, which are beginning to be adopted in haploidentical HCTs for IEIs worldwide [22–27] as well as in Japan [28], was not used in most of the cases. The introduction of these novel techniques would be expected to expand donor options and improve the outcome of HCT from ORD in the coming decades. Furthermore, gene therapy for

---

**Table 6** Association between cause of death and intensity of conditioning in the deceased patients

| Cause of death         | MAC  | RIC  | P value |
|------------------------|------|------|---------|
| n=54                   | n=60 |      |         |
| Infection              | 25 (46%) | 13 (22%) | 0.02a |
| Pulmonary (non-infection) | 12 (22%) | 16 (27%) |         |
| Others (non-infection) | 17 (31%) | 31 (15%) |         |

Patients who received no conditioning (n = 3) or unspecified intensity of conditioning (n = 9) and patients with unknown cause of death (n = 5) were excluded from this analysis; aFisher’s exact test; bAmong them, death by organ dysfunction occurred in 16 patients (multi-organ failure, n = 5; liver failure, n = 5; cardiac failure, n = 2; central nervous system dysfunction, n = 2; renal failure, n = 2; also see Table S8).

MAC, myeloablative conditioning; RIC, reduced intensity conditioning.
numerous IEIs, including SCID, WAS, CGD, and leukocyte adhesion deficiency, is being developed [29]. Promising results for these novel approaches should improve the prognosis of IEI patients without suitable donors.

We analyzed the association of conditioning regimens and the outcomes of HCT. In the recent decade, RIC regimens have been commonly chosen. Although RIC regimens may have been associated with late retransplantation, the OS and donor chimerism for RIC regimens were not significantly different from those for MAC regimens, indicating sufficient efficacy of RIC regimens. In our cohort, MAC regimens were more commonly associated with death from infection. Considering the higher incidence of bacterial infection in patients who received MAC regimens, we speculate that strong tissue injury associated with MAC, such as mucosal damage, probably contributed to infection-related deaths. Furthermore, TBI-based MAC regimens specifically showed poor OS in all disease categories, as well as a higher tendency toward post-transplant short stature. RIC regimens potentially reduce short- and/or long-term conditioning-related toxicities and are considered suitable in HCT for IEI.

We showed the risk of respiratory impairment at HCT on OS. The strong association between respiratory impairment and infection implied that the infection was responsible for dyspnea in most patients. The presence of infection alone was not associated with poor survival, but infection and subsequent pulmonary damage could be a risk. The pre-HCT management for non-infectious manifestations, as well as infectious events, is equally important. For instance, it is well known that the remission status of HLH is associated with good survival after HCT [30, 31]. Several targeted therapies have been developed for IEI in recent years, such as anti-interferon-γ antibody for HLH [32], JAK inhibitor for HLH [33], or STAT1 or STAT3 gain-of-function [34], CTLA4-Fc fusion protein for CTLA4 haploinsufficiency [35] or LRBA deficiency [36], and PI3K inhibitor for activated PI3Kδ syndrome [37]. Those novel pharmacological treatments are expected to control the disease activity as bridging therapies before HCT.

Besides the results for non-SCID IEI as a whole, IEI comprises heterogeneous diseases. Each disorder is associated with different backgrounds of the patients (Fig. S1 and Table S1) or outcomes of HCT (Fig. S3, S5). In patients with WAS, similar outcomes for URBMT, URCB, and MSD confirmed that URBMT and URCB were preferable alternative donors, in agreement with the finding from other studies [38, 39]. RIC regimens showed equivalent OS but increased incidence of retransplantation in this study. In contrast, busulfan-based regimens were associated with less incidence of retransplantation than melphalan-based regimens, which is also consistent with the findings of a previous report [38].

The interval between diagnosis and HCT was the shortest for patients with HLH compared with that for patients with other diseases, indicating the urgency for HCT. URCB was the most commonly chosen for these diseases probably owing to rapid availability. The 10-year OS for URCB was 58%, which was similar to that reported from Europe [40] and Japan [41]; however, OS was not satisfactory compared to that of MSD (10-year OS: 79%), and we also observed a higher incidence of retransplantation after URCB. Further approaches, including optimal conditioning regimen, exploring indication of haplo-HCT with post-transplant cyclophosphamide [23], or better pre-HCT disease control using molecular-targeted therapies [32, 33], would be necessary for improving the management of HCT in the coming decades.

In patients with CGD, the outcome for HCT from URBMT and MSD was equivalent. Multivariate analysis showed that CGD was a risk for retransplantation as well as poor EFS, and URCB for CGD showed a high incidence of retransplantation. The patients were more commonly complicated with infection or respiratory impairment at HCT (Table S1), which may also pose a risk for infection, concerning poor engraftment in URCB. As this study has shown, URCB for CGD patients is also reported to have poor engraftment [42, 43]. Because the time between diagnosis and HCT was relatively long, URCB may be used for these diseases only on limited occasions. The intensity of conditioning showed no difference in outcomes in this study, and prospective clinical trials have also shown that a fludarabine/busulfan-based RIC regimen is effective in CGD patients [44, 45]. Thus, RIC is recommended for these diseases to reduce regimen-related toxicity, especially in recipients with concurrent infection.

Our study has several limitations. First, some important information, such as the precise genotype of the diseases, was not available in the TRUMP registry for the patients in the earlier period, which might have reduced the sample size and affected the analyses. The data such as genotype of the HLA or donor chimerism are also partially unavailable, especially in some early patients. Second, the TRUMP registry was not oriented for the HCT for IEI; active viral infection at HCT or disease-specific complications that might affect the outcome of HCT were missing. The data of immunologic reconstitution after HCT, such as lineage-specific chimerism or discontinuation of immunoglobulin, as well as sequential data for chimerism were also unavailable. Third, a precise analysis of each disease was not performed. We provided some insights for the preferred management of HCT for some disease categories. However, to establish better disease-specific management, it is important to conduct a precise evaluation for each disease through retrospective analyses, prospective studies, or trials for novel therapeutic modalities. For further detailed analysis, we have already published retrospective studies for each IEI from Japan [42, 46, 47] and plan to...
perform such studies for other diseases in the future on behalf of the Hereditary Disorder Working Group of the JSTCT, collaborating with the Primary Immunodeficiency Database in Japan [48] and the TRUMP.

In conclusion, we present an overview of the back-grounds and outcomes of HCT for non-SCID IEIs in Japan with a large number of patients for sufficient statistical power. We demonstrate that the OS for HCT from URBM and MSD was almost equivalent in Japan, confirming URBM as an alternative donor source in HCT for non-SCID IEI. URCBT, which was also commonly performed in Japan, showed substantial applicability for some diseases but posed a high risk for poor engraftment. We also demonstrate the efficacy of RIC regimens and highlight the importance of disease control before HCT. These results should contribute to the development of future management strategies for IEIs in Japan. Furthermore, detailed evaluation for individual IEI, along with recent advances in novel therapeutic approaches, needs to be addressed for establishing an optimal HCT strategy for each disease.

**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1007/s10875-021-01199-w](https://doi.org/10.1007/s10875-021-01199-w).

**Acknowledgements** We thank the Japan Marrow Donor Program, the cord blood banks in Japan, and the staff at the participating hospitals who attended to the patients and provided information for the TRUMP registry. We also thank Soichi Adachi, Shunichi Kato, Yasuo Horikoshi, Miharu Yabe, Nao Yoshida, Hiromitsu Takakura, Sae Ishimaru, Shinya Osone, Hidetoshi Takada, Nozomu Kawashima, Shinobu Tamura, Ayako Yamamori, Koji Kawaguchi, Akira Nishimura, Risa Matsumura, and Takako Miyamura, who supported this study as members of the Hereditary Disorder Working Group of the Japanese Society for Transplantation and Cellular Therapy. We would also like to thank Kay Tanita for her support in preparing the figures.

**Author Contribution** SM designed the research, analyzed the data, and wrote the manuscript. KU, MYan, AI, YS, HY, and KK revisited the manuscript. MKu and YA verified the analytical method and analyzed the data. KO, TK, RT, MI, MYam, MS, YT, MKa, and HK recruited the patients and collected the data. MI, YH, and KK contributed to transplantation data management as members of the Japanese Data Center for hematopoietic cell transplantation. KI and TM designed the research and revised the manuscript. All authors contributed to the article and approved the submitted version.

**Funding** This work was supported by the Japanese Ministry of Health, Labor, and Welfare [grant number 20FC1053], and Japan Agency for Medical Research and Development [grant numbers JP19Hk0201100 and JP19jk0110041].

**Data Availability** The datasets presented in this article are not readily available because they belong 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/](http://www.jdchct.or.jp/).

**Code Availability** All statistical analyses were performed using the 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.

**Conflict of Interest** The authors declare no competing interests.

**References**

1. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020;40:24–64. [https://doi.org/10.1007/s10875-019-00737-x](https://doi.org/10.1007/s10875-019-00737-x).
2. Zhang Q, Frange P, Blanche S, Casanova JL. Pathogenesis of infections in HIV-infected individuals: insights from primary immunodeficiencies. Curr Opin Immunol. 2017;48:122–33. [https://doi.org/10.1016/j.coi.2017.09.002](https://doi.org/10.1016/j.coi.2017.09.002).
3. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstruction of sex-linked lymphoproliferative immunological deficiency. Lancet. 1968;2:1366–9. [https://doi.org/10.1016/s0140-6736(68)92673-1](https://doi.org/10.1016/s0140-6736(68)92673-1).
4. Hematopoietic Cell Transplantation in Japan. Annual Report of Nationwide Survey 2019. The Japanese Data Center for Hematopoietic Cell Transplantation/The Japan Society for Hematopoietic Cell Transplantation. Available at: [http://www.jdchct.or.jp/data/report/2019/2-10-2.pdf](http://www.jdchct.or.jp/data/report/2019/2-10-2.pdf). Accessed 23 Dec 2020.
5. Morio T, Atsuta Y, Tomizawa D, Nagamura-Inoue T, Kato K, Ariga T, et al. Outcome of unrelated umbilical cord blood transplantation in 88 patients with primary immunodeficiency in Japan. Br J Haematol. 2011;154:363–72. [https://doi.org/10.1111/j.1365-2141.2011.08735.x](https://doi.org/10.1111/j.1365-2141.2011.08735.x).
6. Atsuta Y, Suzuki R, Yoshimi A, Gondo H, Tanaka J, Hiraoka A, et al. Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. Int J Hematol. 2007;86:269–74. [https://doi.org/10.1038/sj.ijsa.2900822](https://doi.org/10.1038/sj.ijsa.2900822).
7. Bousfiha A, Jeddane L, Picard C, Ailal F, Gaspar HB, Al-Herz W, et al. The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2018;38:129–43. [https://doi.org/10.1007/s10875-017-0465-8](https://doi.org/10.1007/s10875-017-0465-8).
8. Baciagalupo A, Ballen K, Rizzo D, Giral S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15:1628–34. [https://doi.org/10.1016/j.bbmt.2009.07.004](https://doi.org/10.1016/j.bbmt.2009.07.004).
9. Pai S-Y, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med. 2014;371:434–46. [https://doi.org/10.1056/NEJMoa1401177](https://doi.org/10.1056/NEJMoa1401177).
10. Haddad L, Logan BR, Griffith LM, Buckley RH, Parrott RE, Pookop SE, et al. SCID genotype and 6-month post-transplant CD4 count predict survival and immune recovery. Blood. 2018;132:1737–49. [https://doi.org/10.1182/blood-2018-03-840702](https://doi.org/10.1182/blood-2018-03-840702).
11. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant. 2013;48:452–8. [https://doi.org/10.1038/bmt.2012.244](https://doi.org/10.1038/bmt.2012.244).
12. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol. 2010;126:602–10. https://doi.org/10.1016/j.jaci.2010.06.015.

13. Mitchell R, Niven-Smith I, Anazodo A, Tiedemann K, Shaw P, Teague L, et al. Outcomes of hematopoietic stem cell transplantation in primary immunodeficiency: a report from the Australian and New Zealand Children’s Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. Biol Blood Marrow Transplant. 2013;19:338–43. https://doi.org/10.1016/j.bbmt.2012.11.019.

14. Fernandes JF, Nichele S, Daude LT, Tavares RB, Seber A, Kerbauy FR, et al. Transplantation of hematopoietic stem cells for primary immunodeficiencies in Brazil: challenges in treating rare diseases in developing countries. J Clin Immunol. 2018;38:917–26. https://doi.org/10.1007/s10875-018-0564-1.

15. Olaya M, Franco A, Chaparro M, Estupiñan M, Aristizabal D, Builes-Restrepo N, et al. Hematopoietic stem cell transplantation in children with inborn errors of immunity: a multi-center experience in Colombia. J Clin Immunol. 2020;40:1116–23. https://doi.org/10.1007/s10875-020-00856-w.

16. Miyamoto S, Umeda K, Kurata M, Nishimura A, Yanagimachi M, Ishimura M, et al. Hematopoietic stem cell transplantation for severe combined immunodeficiency patients: A Japanese retrospective study. J Clin Immunol. 2021. https://doi.org/10.1007/s10875-021-01112-5.

17. Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang M-J, Arcese W, et al. Effect of graft source on unrelated donor haematopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol. 2010;11:653–60. https://doi.org/10.1016/S1470-2045(10)70127-3.

18. Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang M-J, Champlin RE, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med. 2004;351:2265–75. https://doi.org/10.1056/NEJMoa041276.

19. Peffault de Latour R, Purtill D, Ruggeri A, Sanz G, Michel G, Gandemer V, et al. Influence of nucleated cell dose on overall survival of unrelated cord blood transplantation for patients with severe aplastic acquired anemia: a study by eurocord and the aplastic anemia working party of the European group for blood and marrow transplantation. Biol Blood Marrow Transplant. 2011;17:78–85. https://doi.org/10.1016/j.bbmt.2010.06.011.

20. Rocha V, Labopin M, Sanz G, Arcese W, Schwedtfeger R, Bosi A, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med. 2004;351:2276–85. https://doi.org/10.1056/NEJMoa041469.

21. Ruggeri A, Eapen M, Scaradavou A, Cairo MS, Bhatia M, Kurtzberg J, et al. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant. 2011;17:1375–82. https://doi.org/10.1016/j.bbmt.2011.01.012.

22. Kurzay M, Hauck F, Schimid M, Wiebking V, Eichinger A, Jung E, et al. T-cell replete haploidentical bone marrow transplantation and post-transplant cyclophosphamide for patients with inborn errors. Haematologica. 2019;104:e748–82. https://doi.org/10.3324/haematol.2018.215285.

23. Neven B, Diana J-S, Castelle M, Magnani A, Rossain J, Touzot F, et al. Haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide for primary immunodeficiencies and inherited disorders in children. Biol Blood Marrow Transplant. 2019;25:1363–73. https://doi.org/10.1016/j.bbmt.2019.03.009.

24. Uppuluri R, Sivasankaran M, Patel S, Swaminathan VV, Ramanan KM, Ravichandran N, et al. Haploidentical stem cell transplantation with post-transplant cyclophosphamide for primary immune deficiency disorders in children: Challenges and outcome from a tertiary care center in South India. J Clin Immunol. 2019;39:182–7. https://doi.org/10.1007/s10875-019-00600-z.

25. Balasahv D, Shcherbina A, Maschan M, Trakhtman P, Skvortsova Y, Shelikhova L, et al. Single-center experience of unrelated and haploidentical stem cell transplantation with TCRαβ and CD19 depletion in children with primary immunodeficiency syndromes. Biol Blood Marrow Transplant. 2015;21:1955–62. https://doi.org/10.1016/j.bbmt.2015.07.008.

26. Elfrey K, Shah RM, Unni MNM, Ottaviano G, Rao K, Chiesa R, et al. New graft manipulation strategies improve the outcome of mismatched stem cell transplantation in children with primary immunodeficiencies. J Allergy Clin Immunol. 2019;144:280–93. https://doi.org/10.1016/j.jaci.2019.01.030.

27. Shah RM, Elfrey R, Nademi Z, Qasim W, Amrolia P, Chiesa R, et al. T-cell receptor αβ+ and CD19+ cell-depleted haploidentical and mismatched hematopoietic stem cell transplantation in primary immune deficiency. J Allergy Clin Immunol. 2018;141:1417–26. https://doi.org/10.1016/j.jaci.2017.07.008.

28. Osumi T, Yoshimura S, Sako M, Uchiyama T, Ishikawa T, Kawai T, et al. Prospective study of allogeneic hematopoietic stem cell transplantation with post-transplantation cyclophosphamide and antithymocyte globulin from HLA-mismatched related donors for nonmalignant diseases. Biol Blood Marrow Transplant. 2020;26:e286–91. https://doi.org/10.1016/j.bbmt.2020.08.008.

29. Fischer A, Hacein-Bey-Abina S. Gene therapy for severe combined immunodeficiencies and beyond. J Exp Med. 2020;217:e20190607. https://doi.org/10.1084/jem.20190607.

30. Horne A, Janka G, Maarten Egeler R, Gadner H, Imashuku S, Ladisch S, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol. 2005;129:622–30. https://doi.org/10.1111/j.1365-2457.2005.05501.x.

31. Ouachée-Chardin M, Elie C, de Saint BG, Le Deist F, Mahlaoui N, Picard C, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics. 2006;117:e743–50. https://doi.org/10.1542/peds.2005-1789.

32. Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. N Engl J Med. 2020;382:1811–22. https://doi.org/10.1056/NEJMoa1911326.

33. Ramanan KM, Uppuluri R, Ravichandran N, Patel S, Swaminathan VV, Jayakumar I, et al. Successful remission induction in refractory familial hemophagocytic lymphohistiocytosis with ruxolitinib as a bridge to hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2020;67:e28071. https://doi.org/10.1002/pbc.28071.

34. Forbes LR, Vogel TP, Cooper MA, Castro-Wagner J, Schussler E, Weinacht KG, et al. Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. J Allergy Clin Immunol. 2018;142:1665–9. https://doi.org/10.1016/j.jaci.2018.07.020.

35. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol. 2018;142:1932–46. https://doi.org/10.1016/j.jaci.2018.02.055.

36. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulos C, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science. 2015;349:436–40. https://doi.org/10.1126/science.aac1663.

37. Rao VK, Webster S, Dalm VASH, Šedivá A, van Hagen PM, Holland S, et al. Effective “activated PI3Ko
Authors and Affiliations

Satoshi Miyamoto1,2 · Katsutsugu Umeda2,3 · Mio Kurata4 · Masakatsu Yanagimachi2,5 · Akihiro Iguchi2,6 · Yoji Sasahara2,7 · Keiko Okada8 · Takashi Koike9 · Reo Tanoshima10 · Masatake Ishimura11 · Masafumi Yamada12 · Maho Sato13 · Yoshiyuki Takahashi14 · Michiko Kajiwara15 · Hiroshi Kawaguchi16 · Masami Inoue13 · Yoshiko Hashii17 · Hiromasa Yabe2,18 · Koji Kato2,19 · Yoshiko Atsuta4,20 · Kohsuke Imai2,21 · Tomohiro Morio1,2

1 Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan
2 Hereditary Disorder Working Group of the Japanese Society for Transplantation and Cellular Therapy, 1-1-20 Daiko Minami, Higashi-ku, Nagoya, Aichi, Japan
3 Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto, Japan
4 Japanese Data Center for Hematopoietic Cell Transplantation, 1-1-20 Daiko Minami, Higashi-ku, Nagoya, Aichi, Japan
5 Division of Hematology/Oncology, Kanagawa Children’s Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama, Kanagawa, Japan
6 Department of Pediatrics, Hokkaido University Hospital, North 14, West 5, Kita-Ku, Sapporo, Hokkaido, Japan
7 Department of Pediatrics, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi, Japan
8 Department of Pediatric Hematology/Oncology, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima-ku, Osaka, Japan
9 Department of Pediatrics, Tokai University School of Medicine, 143 Shimokosuaya, Isehara, Kanagawa, Japan
10 Department of Pediatrics, Yokohama City University Hospital, 3-9 Fukaura, Kanazawa-ku, Yokohama, Kanagawa, Japan
11 Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan
12 Department of Pediatrics, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, North 15 West 7, Kita-ku, Sapporo, Hokkaido, Japan
13 Department of Hematology/Oncology, Osaka Women’s and Children’s Hospital, 840 Murodocho, Izumi, Osaka, Japan
14 Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumaicho, Showa-ku, Nagoya, Aichi, Japan

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
15 Center for Transfusion Medicine and Cell Therapy, Medical Hospital, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan
16 Department of Pediatrics, Hiroshima University Graduate School of Biomedical & Health Sciences, Kasumi 1-2-3 Minami-ku, Hiroshima, Japan
17 Department of Cancer Immunotherapy, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Osaka 2-15, Japan
18 Department of Innovative Medical Science, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, Japan
19 Central Japan Cord Blood Bank, 539-3 Minami-Yamaguchi-cho, Aichi Red Cross Blood Center 4F, Seto, Aichi, Japan
20 Department of Healthcare Administration, Nagoya University Graduate School of Medicine, 65 Tsurumaicho, Showa-ku, Nagoya, Aichi, Japan
21 Department of Community Pediatrics, Perinatal, and Maternal Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan