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

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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 567 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) was 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), being 79% and 81%, respectively. HCT from unrelated cord blood (URCB), accounting for 27% 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, hematologic recovery, or retransplantation incidence. Multivariate analyses of data on those receiving HCT during the 2006–2016 period revealed that respiratory impairment at HCT was associated with poor OS (hazard ratio [HR], 2.3; P = 0.01) and that URCB (HR, 2.7; P = 0.003) and related donor other than MSD (HR, 2.7; P = 0.02) were associated with poor EFS.

Conclusions

We present the 1985–2016 status of HCT for non-SCID IEI in Japan with sufficient statistical power, highlighting the potential of URBM as an alternative donor and the substantial applicability of URCB. Detailed evaluation is needed for optimizing the HCT strategy for each IEI.

Introduction

Inborn errors of immunity (IEI) consist of 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, such as susceptibility to serious 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 firstly 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 for those with severe defects or dysregulation in cellular immunity. Unrelated cord blood (URCB) is commonly used in Japan and accounted for 33% of all allogenic HCTs during the period 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 to 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

Event-free survival (EFS), defined as the period from HCT to death or retransplantation, was calculated to assess survival without graft failure. The diseases were classified into the following categories: combined immunodeficiency (CID; CD40 ligand deficiency, DOCK8 deficiency, ZAP-70 deficiency, bare lymphocyte syndrome, and unspecified CID), Wiskott–Aldrich syndrome (WAS), hemophagocytic syndrome (familial hemophagocytic lymphohistiocytosis (FHL), Chediak–Higashi syndrome, and X-linked lymphoproliferative disease), phagocytic disorder (chronic granulomatous disease [CGD], severe congenital neutropenia [SCN], leukocyte adhesion deficiency, Shwachman–Diamond syndrome, and GATA2 deficiency), and others (see Tables 1 and S1). The conditioning regimens were classified into myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC). Regimens containing one of the following were classified as MAC; total-body irradiation at a total dose of ≥ 800 cGy, busulfan at a total dose of ≥12 mg/kg, or melphalan at a total dose of ≥150 mg/m^2, according to the Center for International Blood and Marrow Transplant Research criteria [8] and previous studies [9,10]. Other regimens were classified as RIC, including those in which the patient 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 and who lacked the HLA-C loci data, especially among patients from the initial years. The donor type was defined as follows: matched sibling donor (MSD), other related donor (ORD), URCB, and unrelated bone marrow (URBM). Neutrophil recovery was defined as the achievement of an absolute neutrophil count of ≥0.5×10^9/L for 3 consecutive days. Platelet recovery was

defined as the achievement of an absolute platelet count of ≥50×10^9/L for 3 consecutive days, unsupported by transfusion for 7 days. 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).

Statistical Analysis

OS and EFS were calculated using the Kaplan–Meier estimates, and Cox proportional hazard models were used to evaluate the impact of the independent risk factors on OS and EFS. 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 as a competing event for retransplantation. Death and retransplantation were considered as 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 for the comparisons of cumulative incidence, and the Fine–Gray model was used for evaluating the impact of independent risk factors on the cumulative incidence of retransplantation. For final models of multivariate analysis, respiratory impairment at HCT, donor type, and disease category were used as variables for OS and EFS, and donor type and disease category were used for the incidence of retransplantation because these factors showed significance according to respective univariate analyses. We limited the patients to those who received HCT from 2006 onwards for multivariate analysis of OS and EFS, because during this period, the respiratory impairment at HCT was documented for most of the cases. 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. Data are presented as the median and range unless otherwise specified. All values enclosed in brackets represent 95% CI.

Results

Patient Characteristics

A total of 567 patients with non-SCID IEI comprising 452 (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). The characteristics of the participants are shown in Table 1a, and the precise diagnoses are shown in Table 1b. The patients with CGD (126; 22%), WAS (118; 21%), FHL (101; 18%), and SCN (60; 11%) were commonly underwent HCT. The patients received HCT at the age of 4 years (0–64 years) and the time from diagnosis to HCT was 1.7 years (0–36.8 years). There was a significant difference in the interval between diagnosis and HCT according to disease category (hemophagocytic syndrome, 159 days [15 days–14.9 years]; WAS, 313 days [29 days–21.1 years]; CID, 750 days [33 days–18.8 years]; phagocytic disorder, 5.5 years [18 days–36.8 years]; P <0.001; Fig S1). Additionally, differences in various factors were observed between the disease categories (Table S1).

The HCT from MSD accounted for 117 (21%) cases. Among 376 (66%) cases of HCT from unrelated donors, 157 (28%) were URCB and 219 (39%) were URBM. All URCBTs were a single unit. Among 61 (11%) cases of HCT from ORD, 2 patients (CGD and CTLA4 deficiency) received post-transplant cyclophosphamide, and none received $TCR\alpha\beta^{+}/CD19^{+}$ depletion. The presence of respiratory impairment at HCT was observed in 41 (9%) cases whereas active bacterial or fungal infection at HCT was noted in 95 (21%) cases. There was a strong correlation between respiratory impairment and bacterial or fungal infection at HCT ($P < 0.001$).

Notably, more patients received RIC, tacrolimus, and URBM as a donor source than the others, and patients with phagocytic disorder received HCT more frequently than the other categories in the later period (Table S2).

Overall Survival and Event-free Survival

The summary of the transplant outcomes over the entire period is shown in Table 2. The OS and the EFS for 10 years were 74% [69–78%] and 64% [60–69%], respectively. We did not observe any significant difference over time in OS or EFS (Fig. 1a, b).

There were significant differences in 10-year OS because of respiratory impairment at HCT (61% [41%–75%] for patients with respiratory impairment vs. 78% [73–83%] for those without, Fig. 1c, $P = 0.01$), but not because of bacterial or fungal infection at HCT, or because of conditioning (Fig. 1d, e). The 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, $P < 0.001$). The HCT from MSD (81% [72–87%]) and URBM (79% [71%–85%]) 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, $P < 0.001$, Fig. 1g). The patients with hemophagocytic syndrome (65% [55–73%]) had worse OS than those with other disease categories (Fig. 1h). We did not observe any statistical difference in OS according to HLA disparities in URBM, as well as in URCB (Fig. S2a, b). Additional survival curves in each disease category are shown in Fig S3 a-f. A similar OS was observed after HCT from MSD, URBM, and URCB in patients with WAS and phagocytic disorder, whereas a tendency for superior OS in the HCT from MSD was observed in patients with hemophagocytic syndrome. The intensity of the conditioning regimen did not show a significant difference in OS for any of the disease categories.

Multivariate analyses of data from the patients who received HCT from 2006 onwards (Table 3) revealed that respiratory impairment at HCT was associated with poor OS (HR: 2.3 [1.2–4.2]; $P = 0.01$). URCB (HR: 2.7 [1.4–5.2]; $P = 0.003$) and ORD (HR: 2.7 [1.2–6.1]; $P = 0.02$) were associated with poor EFS, but not with poor OS. Compared to the patients with WAS, those with hemophagocytic syndrome were associated with worse OS (HR: 3.1 [1.3–7.7]; $P = 0.01$) and showed a weaker association with EFS. Patients with phagocytic disorder showed poor EFS (HR: 2.1 [1.04–4.4]; P = 0.04). As in univariate analyses, URBM did not show significant difference in impact for OS or EFS between MSD.

Hematologic Recovery and Retransplantation

Retransplantation was performed in 61 (11%) cases with an interval of 177 days (20–2,945 days) from the first HCT. Only one patient with FHL and one with hyper IgE syndrome survived without retransplantation

even though they did not achieve donor engraftment.

The HCT from MSD and URBM was associated with faster hematologic recovery than that from ORD or URCB (neutrophil recovery at day 60: 96% [90–98%] for MSD vs. 98% [94–99%] for URBM vs. 88% [76–94%] for ORD vs. 82% [75–87%] for URCB; Fig 2a; $P < 0.001$; platelet recovery at day 60: 85% [76–90%] for MSD vs. 77% [70–82%] for URBM vs. 59% [43–72%] for ORD vs. 51% [43–58%] for URCB; $P < 0.001$; Fig. 2b). The incidence of retransplantation was low for HCT from MSD or URBM (10-year: 11% [5–18%] for MSD vs. 6% [3–10%] for URBM vs. 20% [10–31%] for ORD vs. 21% [14–29%] for URCB; $P < 0.001$; Fig. S4a). 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; 15% [5–30%] for ≥ 2mis URBM; $P = 0.04$; Fig. S2c). The HLA disparities in URCBT were associated with a tendency for higher incidence of retransplantation (Fig. S2d). Patients with hemophagocytic syndrome had slower hematologic recovery than those with other diseases (neutrophil recovery at day 60: 87% [79–92%]; $P = 0.06$; Fig. 2c; platelet recovery at day 60: 63% [54–71%]; $P < 0.001$; Fig. 2d); however, they did not show any significant difference in the cumulative incidence of retransplantation (Fig. S4b). Platelet recovery was faster in the patients who received RIC conditioning, although retransplantation was not correlated with the intensity of conditioning (Fig. 2f, and Fig. S4c). We added the analyses for retransplantation in each disease category (Fig. S3 g-l), and found that URCBT was associated with a higher incidence of retransplantation in patients with hemophagocytic syndrome ($P = 0.03$) or phagocytic disorder ($P < 0.001$), but not in those with WAS. The intensity of conditioning regimen was not associated with any significant difference in the incidence of retransplantation in each of the disease categories.

Multivariate analysis revealed that URCB (HR: 3.8 [1.8–7.9]; $P < 0.001$), ORD (HR: 3.0 [1.3–6.9]; $P = 0.01$), and phagocytic disorder (HR: 2.5 [1.2–5.1]; $P = 0.02$), compared to WAS, were associated with an increased incidence of retransplantation (Table S3), as observed in the multivariate analysis for EFS.

Chimerism

More robust donor chimerism was achieved in patients who received HCT from MSD or URBM than in those who received HCT from ORD or URCB (Fig. S5a). The donor dominance in chimerism was not significantly different between MAC and RIC regimens (Fig. S5b). 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. 2g), 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. 2h). 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 the incidence of GVHD (Fig. S2e-h).

Other HCT-related complications are shown in Table 4. Among the patients evaluated, viral and fungal infection was observed in 21% and 12%, respectively. URCBT was significantly associated with a higher incidence of post-HCT bacterial infection ($P = 0.03$), but not with post-HCT viral infection (Table S4). In terms of long-term toxicities, 14 (3%) patients developed malignancy, most of which were associated with post-transplant lymphoproliferation. Short stature was most commonly seen, occurring in 19% of the patients. We did not observe statistical association of MAC regimens and the incidence of these complications (data not shown).

Cause of Death

Death from infection was the most common, accounting for 43 (33%) cases (Table 5). Among the patients who died, MAC regimen was commonly associated with death from infection ($P = 0.0496$, Table S5). The donor type or disease category was not correlated 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]).

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, low retransplantation incidence, and sufficient donor chimerism. The preparation for HCT from URBM takes several months in Japan and is not suitable for urgent transplantation, but our analysis reconfirms that URBM can be considered as 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, high retransplantation incidence, and low donor chimerism. Furthermore, multivariate analyses demonstrated that URCB was an independent risk for poor EFS and retransplantation. Although URCBT for SCID patients in Japan showed excellent outcome, including OS, hematologic recovery, and stable engraftment [submitted], the disadvantage for engraftment is well known in the HCT for hematologic disorders other than SCID [16-20]. 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, we observed a poor OS/EFS, as well as poor engraftment and a high incidence of cGVHD. In our cohort, post-transplant cyclophosphamide or $TCR\alpha\beta^{+}/CD19^{+}$ depletion,

which are beginning to be adopted in haploidentical HCTs for IEIs worldwide [21-26] as well as in Japan [27], was not used in most of the cases. The introduction of these novel techniques can expectedly help exploit more available donors and also improve the outcome of HCT from ORD in the coming decades. Furthermore, gene therapy (GT) for numerous IEIs, including SCID, WAS, CGD, and leukocyte adhesion deficiency, is being developed [28]. 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. The OS, retransplantation incidence, and donor chimerism for RIC regimens were not significantly different from those for MAC regimens, indicating sufficient efficacy of RIC regimens. This was also true in the analysis for each disease category. Although we did not observe a difference in HCT-related complications between the two regimens, MAC regimens were more commonly associated with death from infection; and we speculate that strong tissue injury associated with MAC, such as mucosal damage, probably contributed to it. RIC regimens potentially reduce short- and/or long-term conditioning-related toxicities and are considered suitable in HCT for IEI.

We also demonstrate that respiratory impairment at HCT was an independent risk for OS. The strong association between respiratory impairment and infection implied that the infection was responsible for dyspnea in most of the patients. Unlike for SCID patients in western countries [10,12] and Japan [submitted], the presence of infection alone was not associated with poor survival, but infection and subsequent pulmonary damage could be a risk. The management of non-infectious manifestations is equally important as the control of infectious events before HCT. For instance, it is well known that the remission status of hemophagocytic syndrome is associated with good survival after HCT [29,30]. Several targeted therapies have been developed for IEI in recent years, such as anti-interferon-γ antibody for hemophagocytic lymphohistiocytosis [31], JAK inhibitor for hemophagocytic lymphohistiocytosis [32], or STAT1 or STAT3 gain-of-function [33], CTLA4-Fc fusion protein for CTLA4 haploinsufficiency [34] or LRBA deficiency [35], and PI3K inhibitor for activated PI3Kδ syndrome [36]. 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 and each disorder is associated with a different background of the patients (Fig. S1 and Table S1) or outcome of HCT (Fig. S3). In patients with WAS, the similar outcomes for URBM and MSD confirmed that URBM was preferable as an alternative donor. We also show that OS or incidence of retransplantation after URCBT for WAS patients was not different from that for HCT from MSD, suggesting the potential of URCB as a candidate donor as well. The availability of URCB for WAS patients was consistent with the finding from studies from western countries [37,38]. Busulfan-based RIC regimen is effective for WAS patients in terms of survival and donor engraftment [37], and our results are consistent with this finding.

The interval between diagnosis and HCT was the shortest for patients with hemophagocytic syndrome 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 URCBT was 58%, which was similar to that reported from Europe [39] and Japan [40]; however, it was not satisfactorily

compared to the 10-year OS for HCT from MSD (79%), and the incidence of retransplantation was higher in URCBT than for HCT from MSD. Further approaches, including optimal conditioning regimen, exploring indication of haplo-HCT with post-transplant cyclophosphamide [41], or better pre-HCT disease control using molecular-targeted therapies [31,32], would be necessary for improving the management of HCT in the coming decades.

In patients with phagocytic disorder, the outcome for HCT from URBM and MSD was equivalent. Moreover, this disease category showed a risk for retransplantation as well as poor EFS, and URCBT for these diseases showed a significant risk for 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 URCBT. URCBT for CGD patients is reported to have poor engraftment in studies from Japan [42] and European countries [43], which is consistent with our results. Because the time between diagnosis and HCT was relatively long and urgent HCT is considered rare, URCB may be used for these diseases only on limited occasions. We also observed the non-inferiority of the RIC regimen to MAC regimen for phagocytic disorders. Recently, the prospective clinical trials have shown that a fludarabine/busulfan-based RIC regimen is effective in CGD patients [44,45]. To reduce regimen-related toxicity, especially in recipients with concomitant infection, RIC is recommended for these diseases.

We provided some insights for preferred management of HCT for some disease categories. To establish a better disease-specific management, it is important to conduct a precise evaluation for each disease through retrospective analyses, or possibly through prospective studies. Moreover, novel therapeutic modalities including GVHD prophylaxis, GT, or molecular targeted approaches are being established with a sufficient number of patients, requiring revision of the current strategies for each IEI.

Our study has several limitations. First, some important information, such as precise genotype of the diseases was not available in the TRUMP registry for the patients who received HCT in the earlier period, which might have reduced the sample size and affected the analyses. Second, the TRUMP registry was not oriented for the HCT for IEI; some disease-specific complications that might affect the outcome of HCT were missing (e.g., colitis for WAS, CGD, or XIAP deficiency, and autoimmunity for WAS or CTLA4 haploinsufficiency). The data of immunologic reconstitution after HCT, such as lineage specific chimerism or discontinuation of immunoglobulin were also unavailable. Third, a precise analysis of each disease was not performed. For further detailed analysis, we have already published retrospective studies for each IEI from Japan [42,46,47] and will also 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 backgrounds and outcome 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 has 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.

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 Graft-versus-host disease

GT Gene therapy

HCT Hematopoietic cell transplantation

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

RIC Reduced-intensity conditioning

SCID Severe combined immunodeficiency

SCN Severe congenital neutropenia

TRUMP Transplant Registry Unified Management Program

URBM Unrelated bone marrow

URCB Unrelated cord blood

URCBT Unrelated cord blood transplantation

WAS Wiskott–Aldrich syndrome

Declarations

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Conflicts of interest/Competing interests: All authors declare that there are no conflicts of interest to disclose concerning this study.

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.

Availability of data and material: 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/.

Code availability: All statistical analyses were performed using the Stata software v16.1 and EZR 1.42.

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AUTHOR CONTRIBUTION

SM designed the research, analyzed the data, and wrote the manuscript. KU, MYan, AI, YS, HY, and KK revised 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.

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Tables

Table 1a: Details of the characteristics of the patients

Characteristics (Number of patients evaluated)			
Patient sex (n=567)		**Conditioning (n=543)**	
Male	452 (80%)	MAC	222 (41%)
Female	115 (20%)	RIC	321 (59%)
Age at Diagnosis (n=552)		No conditioning (included in RIC)	4 (0.7%)[a]
0 years	315 (57%)	**GVHD prophylaxis (n=565)**	
1~4 years	144 (26%)	Cyclosporine	213 (38%)
5~9 years	49 (9%)	Tacrolimus	329 (58%)
10~19 years	36 (7%)	None	6 (1%)
20~ years	8 (1%)	Other	17 (3%)
Median years old (range)	0 (0-64)	**Donor Type (n=567)**	
Age at HCT (n=567)		Bone marrow	382 (67%)
0 years	100 (18%)	MSD	116 (21%)
1~4 years	205 (36%)	MORD	7 (1%)
5~9 years	89 (16%)	mMORD	40 (7%)
10~19 years	115 (20%)	URBM	219 (39%)
20~ years	58 (10%)	Cord blood	160 (28%)
Median years old (range)	4 (0-69)	URCB	157 (28%)
Time from diagnosis to HCT (n=552)		MSD	2 (0.4%)
~1 year	223 (40%)	mMORD	1 (0.2%)
1~3 years	112 (20%)	Peripheral blood	22 (4%)
3~6 years	76 (14%)	MSD	10 (2%)
6~10years	42 (8%)	mMORD	12 (2%)

10 years~	99 (18%)	Bone marrow + cord blood (MSD)	1 (0.2%)
Median years (range)	1.7 (0-36.8)	Peripheral blood + cord blood (MSD)	1 (0.2%)
Year of HCT (n=567)		Bone marrow + peripheral blood (mMORD)	1 (0.2%)
1985~2005	200 (35%)	**Disease category[b] (n=567)**	
2006~2016	367 (65%)	Combined immunodeficiency	48 (8%)
Respiratory impairment at HCT (n=443)		Wiskott-Aldrich syndrome	118 (21%)
Yes	41 (9%)	Hemophagocytic syndrome	129 (23%)
No	402 (91%)	Phagocytic cell disorder	201 (35%)
Bacterial or Fungal Infection at HCT (n=443)		others	71 (13%)
Yes	95 (21%)		
No	348 (79%)		

[a]A patient with CHARGE syndrome and 3 patients with Di-George syndrome received unconditioned HCT.

[b]The details of diagnosis are shown in table S1.

HCT, Hematopoietic cell transplantation; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; GVHD, graft-versus-host-disease; MSD, matched sibling donor; MORD, matched other related donor; mMORD, mismatched other related donor; URBM, unrelated bone marrow; URCB, unrelated cord blood

Table 1b: Details of the diagnosis of the patients according to IUIS 2019 classification

Patient diagnosis	N (%)	No. of survivors (%)			No. of survivors (%)
I. Immunodeficiencies affecting cellular and humoral immunity[a]	47 (8%)	37 (79%)	**IV. Diseases of immune dysregulation**	133 (23%)	91 (68%)
CD40 ligand def. / X-linked hyper IgM syndrome	39 (7%)	34 (87%)	Familial hemophagocytic lymphohistiocytosis[d]	101 (18%)	64 (63%)
DOCK8 def.	1 (0.2%)	1 (100%)	Chediak-Higashi syndrome[d]	7 (1%)	5 (71%)
ZAP-70 def.	1 (0.2%)	0 (0%)	XLP1[d]	1 (0.2%)	1 (100%)
Bare lymphocyte syndrome	1 (0.2%)	1 (0%)	XLP2[d]	10 (2%)	8 (80%)
Unspecified CID	5 (0.9%)	1 (20%)	Unspecified XLP[d]	10 (2%)	9 (90%)
II. CID with associated or syndromic features	136 (24%)	106 (78%)	IPEX syndrome[c]	2 (0.4%)	2 (100%)
Wiskott-Aldrich syndrome / X-linked thrombocytopenia[b]	118 (21%)	97 (82%)	CTLA4 def.[c]	1 (0.2%)	1 (100%)
Hyper IgE syndrome[c]	4 (0.7%)	3 (75%)	IL-10 receptor def.[c]	1 (0.2%)	1 (100%)
DiGeorge syndrome[c]	4 (0.7%)	2 (50%)	**V. Congenital defects of phagocyte number, function, or both**	201 (35%)	168 (84%)
CHARGE syndrome[c]	2 (0.4%)	0 (0%)	Chronic granulomatous disease[e]	126 (22%)	100 (79%)
NEMO def.[c]	3 (0.5%)	2 (67%)	Severe congenital neutropenia[e]	60 (11%)	55 (92%)
EDA-ID due to IKBA GOF mutation[c]	2 (0.4%)	0 (0%)	Leukocyte adhesion deficiency[e]	6 (1%)	6 (100%)
Unspecified EDA-ID[c]	2 (0.4%)	2 (100%)	Shwachman-Diamond syndrome[e]	5 (0.9%)	3 (60%)
Purine nucleoside phosphorylase def.[c]	1 (0.2%)	0 (0%)	MonoMAC syndrome / GATA2 def.[e]	4 (0.7%)	4 (100%)
III. Predominantly antibody deficiencies	21 (4%)	16 (76%)	**VI. Defects in intrinsic and innate immunity**	7 (1%)	3 (43%)
Common variable immunodeficiency[c]	13 (2%)	10 (77%)	Chronic mucocutaneous candidiasis[c]	4 (0.7%)	0 (0%)

Hyper IgM syndrome other than CD40L def.[c]	4 (0.7%)	4 (100%)	WHIM syndrome[c]	3 (0.5%)	3 (100%)
Activated PI3K delta syndrome[c]	3 (0.5%)	2 (67%)	**IX. Bone marrow failure**	22 (4%)	16 (73%)
X-linked agammaglobulinemia[c]	1 (0.2%)	0 (100%)	Dyskeratosis congenita[c]	22 (4%)	16 (73%)

[a]These diseases were classified as “combined immunodeficiency” in this study.

[b]Two patients were registered as “X-linked thrombocytopenia” in the TRUMP and classified as “WAS” in this study.

[c]These diseases were classified as “others” in this study.

[d]These diseases were classified as “hemophagocytic syndrome” in this study.

[e]These diseases were classified as “phagocytic cell disorder” in this study.

No., number; def., deficiency; CID, combined immunodeficiency; XLP, X-linked lymphoproliferative disease; EDA-ID, Anhidrotic ectodermal dysplasia with Immunodeficiency; GOF, gain of function

Table 2: Transplant outcomes over the whole period

Outcome (Number of patients evaluated)	Overall
Overall survival (%) (n=567)	
1 year (95% CI)	84 (80–87)
5 year (95% CI)	77 (73–81)
10 year (95% CI)	74 (69–78)
25 year (95% CI)	72 (66–76)
Event-free survival (%) (n=567)	
1 year (95% CI)	79 (75–82)
5 year (95% CI)	70 (65–73)
10 year (95% CI)	64 (60–69)
25 year (95% CI)	62 (57–67)
Neutrophil recovery (n=554)	
Cumulative incidence (%) at 30 days (95% CI)	88 (85–91)
Cumulative incidence (%) at 60 days (95% CI)	92 (89–94)
Median days of recovery (range)	17 (0–130)
Platelet recovery (n=527)	
Cumulative incidence (%) at 30 days (95% CI)	37 (33–41)
Cumulative incidence (%) at 60 days (95% CI)	69 (65–73)
Median days of recovery (range)	32 (0–356)
Retransplantation (n=567)	
Cumulative incidence (%) at 10 years (95% CI)	13 (10–17)
Median days of retransplantation (range)	177 (20-2,945)
Acute GVHD grade II–IV (n=556)	
Cumulative incidence (%) at 1 year (95% CI)	26 (22–29)
Chronic GVHD (n=491)	
Cumulative incidence (%) at 2 years (95% CI)	20 (16–23)

[a]Logrank test; [b]Gray's test

CI, confidence interval; NA, not applicable; GVHD, graft-versus-host disease

Table 3: Factors affecting overall survival and event-free survival 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			0.046				< 0.001		
MSD	70	84% (72–91%)		1		81% (69–89%)		1	
URCB	104	71% (61–79%)		1.8 (0.8–3.8)	0.13	56% (45–65%)		2.7 (1.4–5.2)	0.003
ORD	26	68% (42–84%)		1.7 (0.7–4.7)	0.27	53% (31–71%)		2.7 (1.2–6.1)	0.02
URBM	167	83% (76–89%)		1.1 (0.5–2.2)	0.87	77% (69–83%)		1.1 (0.6–2.1)	0.72
Respiratory impairment at HCT			0.005				0.05		
No	326	81% (76–85%)		1		72% (66–77%)		1	
Yes	36	64% (45–78%)		2.3 (1.2–4.2)	0.01	58% (39–73%)		1.5 (0.8–2.6)	0.18
Disease category			0.003				0.07		
Wiskott-Aldrich syndrome	58	89% (77–95%)		1		82% (69–90%)		1	
Combined immunodeficiency	28	84% (63–94%)		1.4 (0.4–5.0)	0.6	73% (51–86%)		1.5 (0.6–4.0)	0.39
Hemophagocytic syndrome	82	70% (59–79%)		3.1 (1.3–7.7)	0.01	63% (50–73%)		2.1 (0.9997–4.3)	0.05
Phagocytic disorder	147	82% (73–88%)		1.7 (0.7–4.3)	0.26	70% (60–77%)		2.1 (1.04–4.4)	0.04
Others	52	70%		2.7	0.049	64%		2.4 (1.1–	0.03

	(54–81%)	(1.0–7.3)	(48–76%)	5.4)

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.

Table 4: Transplant-associated complications

Infection	n (%)	Number of patients evaluated	Non-Infection	n (%)	Number of patients evaluated
CMV antigenemia	125 (29%)	436	Central nervous system disorder	28 (5%)	542
CMV infection	25 (6%)[a]	453	Hemorrhage	27 (5%)	542
Pneumonia	6 (1%)[a]	453	Thrombotic microangiopathy	27 (5%)	542
Hepatitis	3 (0.7%)[a]	453	Veno-occlusive disease	20 (4%)	542
Enterocolitis	9 (2%)[a]	453	Interstitial pneumonitis (Non-Infectious)	14 (3%)	542
Retinitis	2 (0.4%)[a]	453	ARDS	12 (2%)	542
Urinary tract infection	2 (0.4%)[a]	453	Post-HCT HLH	11 (2%)	542
Meningitis	1 (0.2%)[a,b]	453	BO	6 (1%)	542
Other viral infection	84 (19%)[a]	449	BOOP	2 (0.4%)	542
EBV	33 (7%)[a]	449	Cardiac failure	6 (1%)	542
Human polyomavirus 1 (BK virus)	18 (4%)[a]	449	Hemolytic anemia	5 (0.9%)	542
VZV	15 (3%)[a]	449	Pancreatitis	4 (0.7%)	542
HHV6	9 (2%)[a]	449	Malignancy	14 (3%)	545
Norovirus	6 (1%)[a]	449	PTLD	12 (2%)	545
HSV	3 (0.7%)[a]	449	DLBCL	1 (0.2%)	545
Adenovirus	3 (0.7%)[a]	449	Osteosarcoma	1 (0.2%)	545
Human polyomavirus 2 (JC virus)	2 (0.4%)[a]	449	Short stature (≤ −2SD)	74 (19%)	381
Influenza A virus / RSV	1	449	Gonadal dysfunction	20	168

/ parainfluenza virus / Coxsackievirus	(0.2%)[a,b]			(12%)	
Fungal infection	62 (12%)[a]	525	Hypothyroidism	11 (4%)	285
Candidiasis	4 (0.8%)[a]	525			
Aspergillosis (definitive)	30 (6%)[a]	525			
Aspergillosis (suspected)	20 (4%)[a]	525			
Unspecified fungal infection	11 (2%)[a]	525			
Bacterial infection	172 (38%)[a]	452			

[a]The patients whose infection was diagnosed before and after transplantation are included.

[b]The number (and the percentage) of each item is shown.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella zoster virus; HHV6, human herpesvirus 6; HSV, herpes simplex virus; RSV, respiratory syncytial virus; ARDS, acute respiratory distress syndrome; HCT, hematopoietic cell transplantation; HLH, hemophagocytic lymphohistiocytosis; BO, bronchiolitis obliterans; BOOP, bronchiolitis obliterans organizing pneumonia; PTLD, post-transplant lymphoproliferative disorder; DLBCL, diffuse large B-cell lymphoma; SD, standard deviation

Table 5: Causes of death

Cause of death	n (%)
Infection	43 (33%)
Non-Infection	88 (67%)
Pulmonary (non-infection)	33 (25%)
Others (non-infection)	55 (42%)
Hemorrhage	8 (6%)
Multi-organ failure	8 (6%)
Liver failure	5 (4%)
Cardiac failure / cardiomyopathy	4 (3%)
Thrombotic microangiopathy	4 (3%)
Acute GVHD	4 (3%)
Chronic GVHD	4 (3%)
Secondary malignancy	3 (2%)
Renal failure	2 (2%)
CNS dysfunction	2 (2%)
Veno-occlusive disease	2 (2%)
Hemophagocytic syndrome	2 (2%)
EBV-LPD	1 (1%)
Pancreatitis	1 (1%)
Unknown	5 (4%)
Total	131

GVHD, graft-versus-host disease; CNS, central nervus system; EBV-LPD, Epstein Barr virus associated lymphoproliferative disorder.

Figures

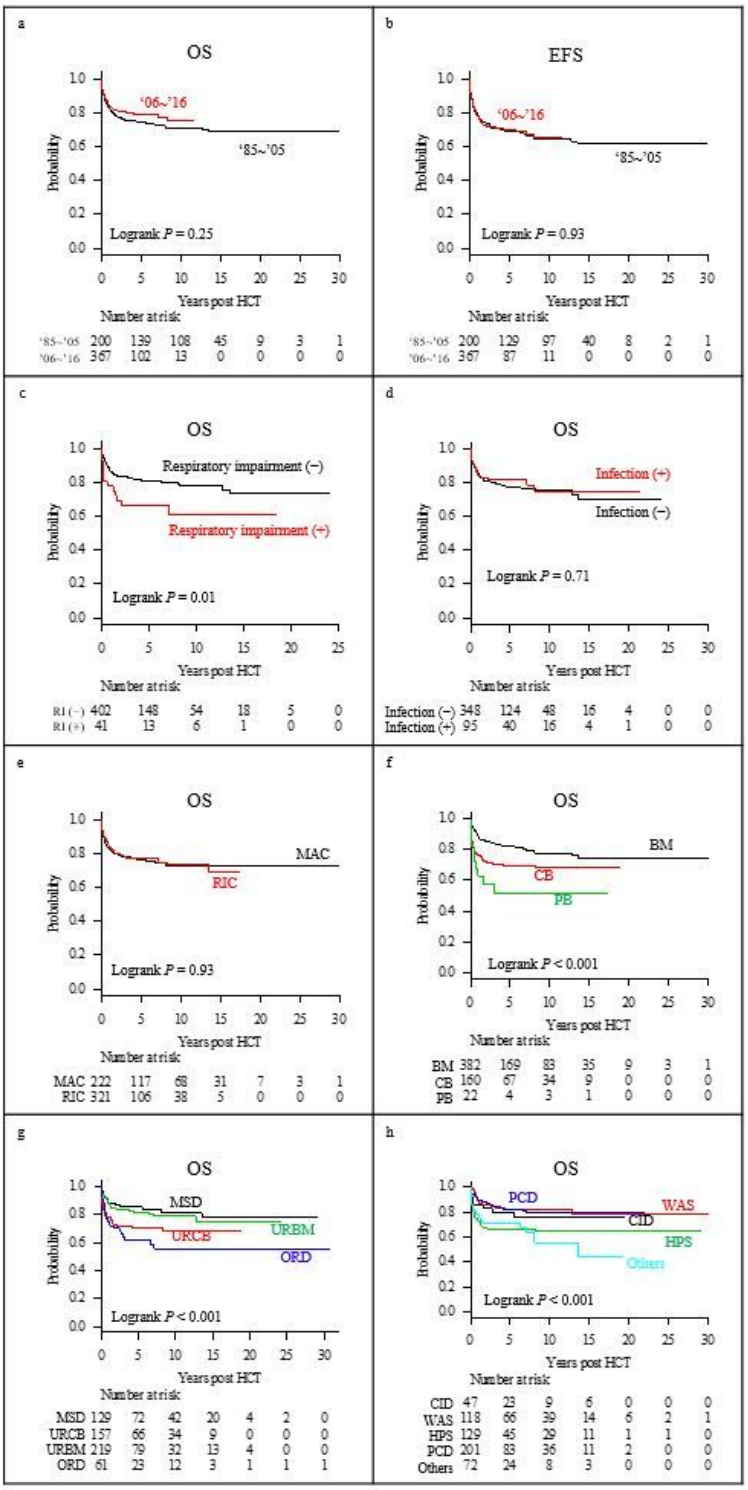

Figure 1

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 the 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; CID, combined immunodeficiency; WAS, Wiskott–Aldrich syndrome; HPS, hemophagocytic syndrome; PCD, phagocytic disorder.

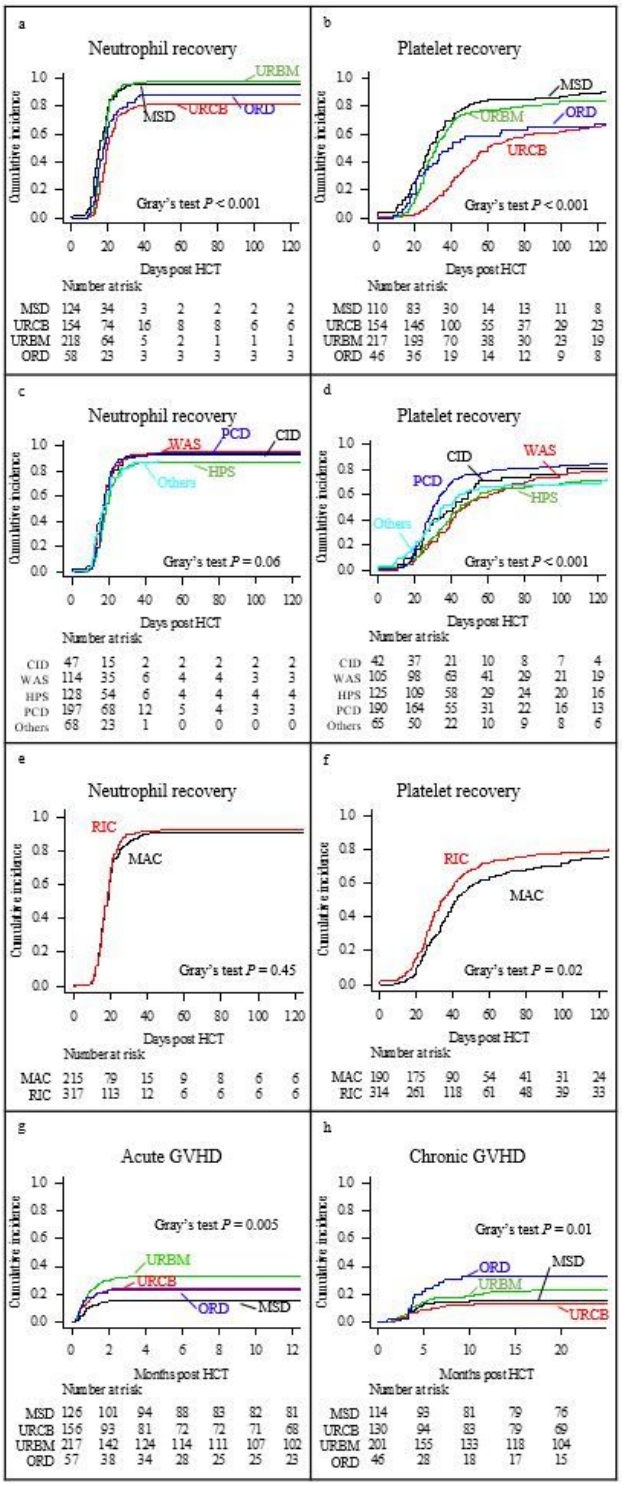

Figure 2

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; CID, combined immunodeficiency; WAS, Wiskott–Aldrich syndrome; HPS, hemophagocytic syndrome; PCD, phagocytic disorder; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease.

Supplementary Files

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