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ORIGINAL ARTICLE

# Feasibility of reduced-intensity conditioning followed by unrelated cord blood transplantation for primary hemophagocytic lymphohistiocytosis: a nationwide retrospective analysis in Japan

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**Abstract** A nationwide retrospective analysis was performed on patients who received allogeneic hematopoietic stem cell transplantation for primary or familial hemophagocytic lymphohistiocytosis (HLH) in Japan. The present analysis investigated whether reduced-intensity conditioning (RIC) followed by cord blood transplantation (CBT) (RIC–CBT) is feasible, compared to the outcomes of myeloablative conditioning and bone marrow transplantation. Based on the JSHCT data, 53 patients were analyzed. The overall survival rate (OS) was $65.4 \pm 6.6$ %. RIC–CBT ($n = 13$) was not inferior to other methods. Patients with a performance status of PS 4 (ECOG scale) with HLH-associated severe organ dysfunction during the initiation of conditioning had extremely poor outcomes. The OS rate in the RIC–CBT patients, excluding those with a performance status 4, was $80.0 \pm 12.6$ %. RIC may reduce treatment-related mortality; in addition, patients with engraftment failure, which is the main adverse event following RIC–CBT, were successfully rescued with secondary CBT. Unrelated cord blood may represent an alternative source if a patient has no related donor. As a RIC regimen for CBT, 140 mg/m$^2$ melphalan with fludarabine and anti-lymphocyte globulin or anti-thymocyte globulin may be feasible, but further dosage optimization should be performed in controlled clinical trials.

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**Keywords** Primary HLH · FHL · Reduced-intensity conditioning · Cord blood transplantation

## Introduction

Primary hemophagocytic lymphohistiocytosis (HLH), also known as familial HLH (FHL), is a distinct disease entity of congenital immunodeficiencies. Primary HLH involves genetically impaired production, transfer or release of cytotoxic granules of T or NK cells [1, 2]. Patients with primary HLH exhibit complete mortality due to hypercytokinemia, hemophagocytic syndrome (HPS) or organ failure including that of the brain and liver. Further, allogeneic hematopoietic stem cell transplantation (HSCT) is the only cure [1, 3].

Reduced-intensity conditioning (RIC) and umbilical cord blood transplantation (CBT) were developed in the 2000s. Comparing to myeloablative conditioning (MAC) [4], RIC is particularly desirable in children because it is less toxic and may reduce late complications such as short stature, hypogonadism, and infertility. Cord blood (CB) has immediate availability before disease progression if there is no family donor. One of the most severe adverse events after CBT following RIC (RIC–CBT) is engraftment failure and the subsequent infection. Although results regarding bone marrow transplantation (BMT) following RIC (RIC–BMT) for primary HLH were recently reported to be encouraging [5], these included few cases of CBT following RIC (RIC–CBT). A previous study on HSCT for FHL in Japan revealed that neither RIC nor CBT was inferior. However, this was a questionnaire-based study and not a nationwide study; additionally, it included few RIC–CBT cases [6].

The present study is a nationwide retrospective analysis on the outcome of allogeneic HSCT for primary HLH in Japan. This analysis aims to clarify whether RIC–CBT is inferior to MAC or BMT. Furthermore, if RIC–CBT is feasible, this study aims to provide insights into the timing, eligibility, optimized regimen, and dosage for RIC–CBT. This study was approved by the Research Ethics Committee of Osaka Medical Center and Research Institute for Maternal and Child Health.

## Patients and methods

### Data collection

The Japan Society for Hematopoietic Cell Transplantation (JSHCT) annually collects data on HSCT in Japan using a standardized reporting form, the Transplant Registry Unified Management Program (TRUMP) system. A total of 72 HSCT cases were registered as primary/familial HLH between January 1990 and December 2009 (Fig. 1). There is no information in the registry on the affected genes. Furthermore, no autologous HSCTs were recorded, and 13 allogeneic HSCTs were excluded at data clearance including 4 due to different diagnoses and 9 due to second HSCT. We initially extracted 59 patients who underwent the first allogeneic HSCT for primary/familial HLH (Fig. 1). Subsequently, 2 patients who underwent peripheral blood (PB) stem cell transplantation were excluded because the donors were haploidentical. Further, 4 patients were excluded because of insufficient conditioning data that may represent unestablished RIC regimen other than fludarabine (Flu) and melphalan (LPAM). Therefore, 53 patients were included in the following analysis.

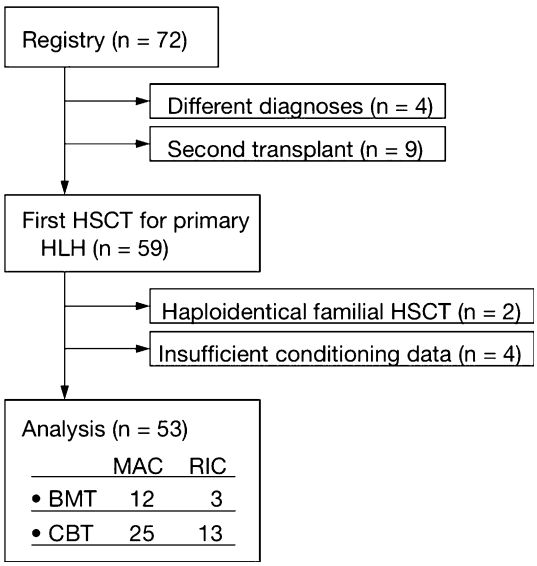


**Fig. 1** Analyzed patients selected from the registry. Different diagnoses ($n = 4$) were as follows: one patient with acute myeloid leukemia, one with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)-like disease, one with chronic inflammatory neurological cutaneous articular (CINCA)-like disease and a patient of extreme age (36 years old) for primary/familial HLH. The analysis focuses on 1st HSCT for primary HLH in non-haploidentical setting

### End points

The primary end point was the overall survival (OS), which was defined as the time from HSCT until death due to any cause. Second HSCTs were not censored in the OS. Patients alive at the last follow-up were censored. The causes of death were categorized as progression of disease (i.e., fulminant HLH) or treatment-related mortality (TRM); in turn, TRM was subcategorized into infection, graft-versus-host disease (GVHD), and organ failure as a post-HSCT adverse event or progression of pre-HSCT

morbidity due to primary disease (i.e., without fulminant HLH after HSCT). Event-free survival (EFS) was defined as the time from HSCT until any of the following events: recurrence/progression of disease, TRM, or second HSCT (due to engraftment failure or loss of donor chimerism with or without primary disease).

## Definitions

MAC and RIC were defined according to the consensus report on the intensity of conditioning regimens by Bacigalupo et al. [7]. Representative regimens were shown in Table 1. The date of neutrophil recovery was regarded as the first day of 3 consecutive days in which the absolute neutrophil count exceeded 500/μL. Engraftment failure was defined as an absolute neutrophil count <500/μL or donor chimerism <5 % in the white blood cells (WBCs) from PB on day 30 after HSCT or later. Continuous complete donor chimerism was defined as neutrophil count >500/μL and donor-type WBC >95 % in PB; mixed chimerism was defined as neutrophil count >500/μL and donor-type WBC of 5–95 % in PB on day 30 or later. The performance status (PS) of each patient was scaled at the initiation of conditioning based on the Eastern Cooperative Oncology Group (ECOG) PS scale [8].

**Table 1** Patient characteristics

| | Graft source and conditioning type | | | | MAC vs. RIC (*p*) |
|---|---|---|---|---|---|
| | BMT | | CBT | | |
| | MAC ($n = 12$) | RIC ($n = 3$) | MAC ($n = 25$) | RIC ($n = 13$) | |
| Age at HSCT (years) | | | | | |
| 0 | 4 (33 %) | 2 (67 %) | 7 (28 %) | 6 (46 %) | |
| 1–4 | 6 (50) | 0 (–) | 12 (48) | 4 (31) | >0.1 |
| >5 | 2 (17) | 1 (33) | 6 (24) | 3 (23) | |
| Sex | | | | | |
| Male | 3 (25) | 1 (33) | 12 (48) | 9 (69) | >0.1 |
| Female | 9 (75) | 2 (67) | 13 (52) | 4 (31) | |
| Conditioning regimen | | | | | |
| MAC | | | | | |
| BU + CY + Etp-based | 10 (83) | – | 13 (52) | – | |
| TBI + CY-based | 1 (8) | – | 7 (28) | – | – |
| Others | 1 (8) | – | 5 (20) | – | |
| RIC | | | | | |
| Flu + LPAM-based | – | 3 (100) | – | 13 (100) | |
| GVHD prophylaxis | | | | | |
| CsA-based | 7 (58) | 2 (67) | 16 (64) | 3 (23) | |
| Tac-based | 4 (33) | 1 (33) | 6 (24) | 10 (77) | – |
| Others | 1 (8) | 0 (–) | 3 (12) | 0 (–) | |
| HLA mm for GVH direction | | | | | |
| Related donor | | | | | |
| HLA 6/6 | 5 (42) | 2 (67) | – | – | |
| HLA 5/6 | 1 (8) | 0 (–) | – | – | |
| Unrelated donor | | | | | |
| HLA 6/6 | 6 (50) | 0 (–) | 6 (24) | 8 (62) | – |
| HLA 5/6 | 0 (-) | 1 (33) | 13 (52) | 4 (31) | |
| HLA ≤ 4/6 | – | – | 6 (24) | 1 (8) | |
| Year of HSCT | | | | | |
| 1990–1994 | 1 (8) | 0 (–) | 0 (–) | 0 (–) | |
| 1995–1999 | 5 (42) | 0 (–) | 8 (32) | 0 (–) | 0.002 |
| 2000–2004 | 3 (25) | 2 (67) | 13 (52) | 3 (23) | |
| 2005–2009 | 3 (25) | 1 (33) | 4 (16) | 10 (77) | |

*HLA mm* serological mismatch in HLA-A, B and DR for graft-versus-host (GVH) direction, *HSCT* hematopoietic stem cell transplantation, *BMT* bone marrow transplantation, *CBT* cord blood transplantation, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *BU* busulfan, *CY* cyclophosphamide, *Etp* etoposide, *Flu* fludarabine, *GVHD* GVH disease, *CsA* cyclosporin A, *Tac* tacrolimus

### Statistics

Statistical analyses were performed using SPSS version 14 (SPSS Inc., Chicago, IL, USA). Survival rate was estimated by the Kaplan–Meier method and assessed with the log-rank test. The $\chi^2$ test was used for univariate analysis.

## Results

The characteristics of the 53 patients are shown in Table 1. Remarkably, more than half of the patients were treated with RIC–CBT since 2005. The 2-year EFS (median ± standard error) and OS rates were 57.6 ± 6.9 % and 65.4 ± 6.6 %, respectively. The EFS and OS rates with respect to the conditioning regimen and graft source are shown in Fig. 2. The number of patients after RIC–BMT was very small for statistical analysis ($n = 3$). The EFS rates of the patients after MAC–BMT, MAC–CBT, and RIC–CBT were 65.6 ± 14.0 % ($n = 12$), 59.1 ± 10.0 % ($n = 25$), and 46.2 ± 13.8 % ($n = 13$), respectively, and there was no statistical difference ($p = 0.35$). The OS rates of the patients after MAC–BMT, MAC–CBT, and RIC–CBT were 74.1 ± 12.9 %, 63.1 ± 9.8 %, and 61.5 ± 13.5 %, respectively, and there was no statistical difference ($p = 0.66$).

### Causes of death

Out of 53 patients, 2 died of disease progression, and 16 patients experienced TRM: 6 deaths were attributed to bacterial infection, 2 to viral infection [1 cytomegalovirus (CMV) pneumonitis, 1 post-transplant lymphoproliferative disease (PTLD)], 1 to chronic GVHD, and 7 to organ failure.

In general, there were no significant differences between the MAC–BMT, MAC–UCB, and RIC–CBT groups with respect to cause of death (Table 2). However, the ratio of organ failure was high in the CBT groups. In the MAC–CBT group, organ failure occurred after HSCT in 4 cases, i.e., 2 cases of interstitial pneumonitis, 1 case of acute respiratory distress syndrome, and 1 case of thrombotic microangiopathy. However, in the RIC–CBT group, 3 patients had a PS of 4 during the initiation of conditioning; all of them suffered from HLH-associated severe organ dysfunction [the lungs, 2 patients; the liver and central nervous system (CNS), 1 patient] and died due to progression of organ failure without fulminant HLH after HSCT. Therefore, the EFS and OS rates of the RIC–CBT group, excluding those with PS of 4, were 60.0 ± 15.5 % and 80.0 ± 12.6 %, respectively.

### Conditioning regimen and engraftment in the RIC–CBT group

In the patients who lived 30 days or more after HSCT, 5/6, 2/2, 15/22, and 4/10 patients in the MAC–BMT, RIC–BMT, MAC–CBT, and RIC–CBT groups, respectively, achieved complete donor chimerism. In the RIC–CBT and MAC–CBT groups who did not achieve neutrophil recovery, 4 out of 5 patients underwent a second HSCT (Table 2); 3 achieved complete donor chimerism, while the others did not achieve neutrophil recovery and died of a bacterial infection. Conversely, a low ratio of donor chimerism might be able to control the primary disease [9].

We analyzed the conditioning regimens and engraftment in patients who lived 30 days or more after RIC–CBT ($n = 10$) in further detail (Table 3). Higher doses of LPAM (>120 mg/m$^2$ in total) with Flu and anti-lymphocyte globulin or anti-thymocyte globulin (ALG/ATG)

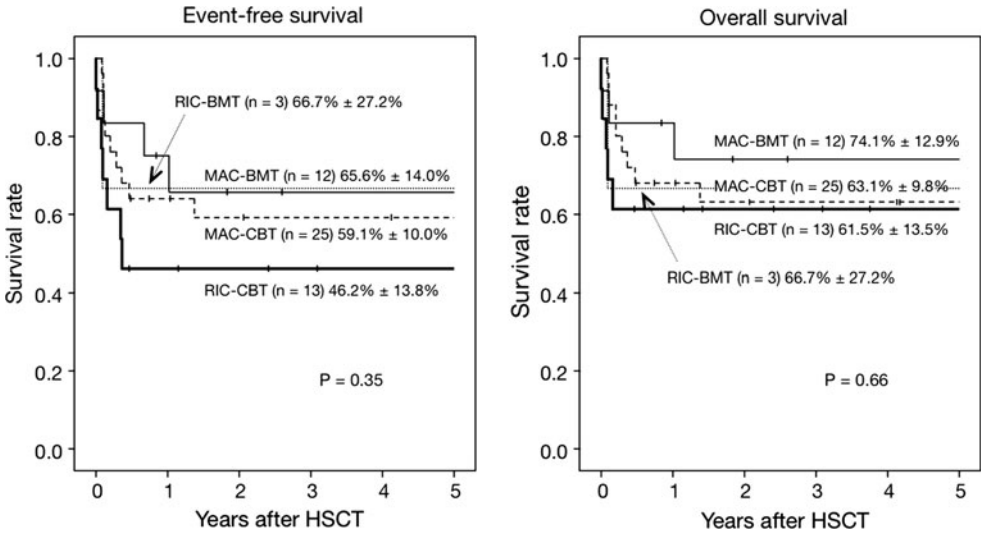


**Fig. 2** Survival rates after HSCT. In total ($n = 53$), the 2-year event-free survival (EFS) and overall survival (OS) rates (median ± standard error %) were 57.6 ± 6.9 % and 65.4 ± 6.6 %, respectively. The EFS and OS according to the conditioning regimen and graft source are shown. The number of RIC–BMT was too small ($n = 3$) for further statistical analysis. There were no statistical differences in EFS and OS between MAC–BMT, MAC–CBT and RIC–CBT. *Solid line* MAC–BMT, *dotted line* RIC–BMT, *broken line* MAC–CBT, *bold line* RIC–CBT

**Table 2** HSCT type and causes of death

| Conditioning-source | (n=) | Persistent neutropenia and 2nd HSCT | | | Cause of death | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Persistent neutropenia | 2nd HSCT | Subsequent neutropenia | Progression of fulminant primary HLH | TRM | | | | |
| | | | | | | Bacterial infection | Viral infection | Chronic GVHD | Organ failure | |
| MAC-BMT | (12) | 0 | | | 1 | 1 | 0 | 1 | 0 | |
| RIC-BMT | ( 3 ) | 0 | | | 0 | 1 | 0 | 0 | 0 | |
| MAC-CBT | (25) | 3 | → 2 | → 1[a] | 1 | 2[a] | 2 | 0 | 4[b] | 0.12 |
| RIC-CBT | (13) | 2 | → 2 | → 0 | 0 | 2 | 0 | 0 | 3[c] | |

Persistent and subsequent neutropenia: neutrophil count did not exceed 500/uL at day 30 after HSCT or later. Second HSCT was all CBT

*TRM* treatment-related mortality

[a] One patient died of bacterial infection for persistent/subsequent neutropenia

[b] Three non-infectious lung complications (2 interstitial pneumonitis and 1 acute respiratory distress syndrome) and one thrombotic micro-angiopathy (TMA)

[c] Progression of pre-HSCT organ failure due to primary HLH (i.e., without fulminant HLH after HSCT)

resulted in better engraftment. Continuous complete donor chimerism was observed at 100 days after RIC–CBT in all the patients who had once achieved complete donor chimerism at the time of engraftment. Lower doses of LPAM with Flu and ALG adversely affected the engraftment even when concomitant with cyclophosphamide 50–60 mg/kg. Regarding the influence of total body irradiation (TBI), HLA incompatibility to host-versus-graft direction, and infused-cell number on engraftment, we cannot draw any conclusion, because our study contained very small number of patients.

## Discussion

Primary HLH, also called FHL, is currently understood to involve genetically impaired machinery of cytotoxic granules in the T or NK cells. Primary HLH is diagnosed based on the affected proteins as follows: perforin, FHL2; Munc13-4, FHL3; syntaxin11, FHL4; and Munc18-2, FHL5 [10, 11]. Secondary HLH accompanied by Epstein–Barr virus (EBV) infection, malignancies, and autoimmune diseases was excluded from the present analysis [10]. However, there was no information on affected proteins in the JSHCT database or TRUMP system. There are borderline HLH as well as some rare well-defined syndromes (with a known impaired protein that also affects somatic cells other than T or NK cells) such as Griscelli syndrome type 2 (Rab27a), Hermansky–Pudlak syndrome type 2 (AP3β-1 subunit) and Chediak–Higashi syndrome (CHS). Moreover, it is possible that some rare congenital metabolic disorders accompanied by HPS in secondary HLH were not excluded, such as galactosialidosis and cobalamin C disease.

Our data regarding HSCT, including CBT, are similar to those of other reports [3]; however, in our series, the survival rate after CBT was slightly, but not significantly, worse than after BMT. However, all CBTs were performed under unrelated settings. The OS rate after unrelated BMT (6 MAC and 1 RIC) was no more than 42.9 ± 18.7 %, which was worse than MAC–CBT and RIC–CBT, although the difference was not significant. Unrelated CB may be an alternative source if the patient has no related donor. However, our analysis was not based on the controlled randomized prospective study, and there were some confounding factors between the groups. More than 70 % of MAC–BMT and MAC–CBT were done before 2004, and more than 70 % of RIC–CBT was done since 2005. Patients who underwent MAC might have been treated with HLH-94-based protocol [3], and patients who underwent RIC–CBT might have been treated with HLH-2004-based protocol [2]. Supportive care has also made advances during the latest decade.

Some persisting HPS activity from the primary disease did not automatically preclude HSCT [12]. However, all of the 3 patients at PS 4 for severe organ dysfunction of the liver, lungs, and/or CNS attributed to the primary disease had extremely poor outcomes in the present study. RIC–CBT might be chosen for such patients because of its safety and emergent accessibility; however, even if the primary disease was controlled after HSCT, their organ failure was irreversible and fatal during the peri-transplant period. To

**Table 3** RIC–CBT regimen and engraftment

| Pt# | Age at | | Sex | Conditioning regimen | | | Neutrophil recovery | Chimerism (engraftment) | Infused cells | | HLA mm for | | GVHD prophylaxis | Acute GVHD | 2nd HSCT | Outcome (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Diag | HSCT | | Flu | LPAM | Others | | | ANC | CD34+ | GVH | HVG | | | | |
| 1 | 5 months | 7 months | F | 125 (low) | 180 (high) | ALG45 | + | Donor | 10.4 | 4.6 | 0 | 0 | CsA/MTX | 0 | – | 420 + alive |
| 2 | 12 years | 15 years | F | 120 (low) | 140 (high) | ALG40 | + | Donor | 3.3 | nd | 1 | 1 | Tac/MTX | III | – | 1834 + alive |
| 3 | 4 years | 4 years | F | 120 (low) | 140 (high) | ALG40 | + | Donor | 4.5 | 1.1 | 0 | 0 | Tac/MTX | II | – | 2276 + alive |
| 4 | 2 months | 7 months | M | 100 (low) | 120 (high) | ATG8 | + | Donor | nd | nd | 0 | 0 | Tac/MTX | I | – | 168 + alive |
| 5 | 1 month | 4 months | M | 180 (high) | 140 (high) | CY60 | + | Mix | nd | 2.5 | 0 | 0 | CsA/MTX | 0 | – | 879 + alive |
| 6 | 0 month | 5 months | M | 180 (high) | 140 (high) | – | + | Failure[a] | 6.8 | 2.0 | 1 | 1 | CsA/MTX | 0 | No | 1127 + alive |
| 7 | 3 years | 4 years | F | 125 (low) | 80 (low) | TBI (4 Gy) | – | Failure | 4.3 | nd | 0 | 0 | Tac/MTX | 0 | Yes | 1367 + alive |
| 8 | 4 years | 5 years | M | 180 (high) | 70 (low) | CY60, ALG20 | – | Failure | 3.8 | 3.2 | 1 | 2 | Tac/MTX | 0 | Yes | 515 + alive |
| 9 | 2 months | 6 months | M | 180 (high) | 70 (low) | CY50, ALG20, Etp200 | + | Failure[a] | 23.8 | nd | 0 | 0 | Tac/MTX | 0 | No | 54 TRM[b] |
| 10 | 0 month | 1 year | M | 180 (high) | 70 (low) | CY50, ALG20, Etp200 | + | Mix | 19.0 | nd | 0 | 0 | Tac | II | – | 30 TRM[b] |

The patients who lived 30 days or more after RIC–CBT are shown ($n = 10$). HLA mm: serological mismatch in HLA-A, B and DR for graft-versus-host (GVH) or host-versus-graft (HVG) direction, chimerism: donor, complete donor chimerism (donor-type WBC > 95 %) in PB; mix, mixed chimerism with 5–95 % of donor-derived WBC; failure, engraftment failure <5 %. Neutrophil recovery was defined as absolute neutrophil count <500/uL at day 30 after HSCT

*Flu* fludarabine, *Etp* LPAM and etoposide (mg/m$^2$), *ALG/ATG* anti-lymphocyte/thymocyte globulin, *CY* cyclophosphamide (mg/kg), *Pt#* patient number, *Diag* diagnosis, *nd* no data, *TBI* total body irradiation, *TRM* treatment-related mortality

[a] Gradual reduction of donor cell ratio (finally <5 %)

[b] Progression of pre-HSCT organ failure due to primary HLH (i.e., without fulminant HLH after HSCT)

improve survival, when the HPS would be resistant to the chemotherapy and immunosuppressants, patients should be treated with HSCT as early as possible before disease progression; and in such cases, unrelated CBT is superior to unrelated BMT because CB is immediately available.

In RIC–CBT group, the rate of TRM due to post-HSCT organ failure was low while that of incomplete engraftment was high compared to the MAC–CBT. Unlike TRM, patients without neutrophil recovery or donor chimerism could be rescued with a second HSCT. Incomplete donor chimerism is a major adverse event of RIC even after BMT [5]. The present study suggests that LPAM 140 mg/m$^2$ with Flu and ALG/ATG might be sufficiently intense for complete donor cell engraftment and that RIC–CBT might be feasible. However, these findings are limited because of the small number of patients, variable dosages, and retrospective nature of the present study. Nevertheless, our analysis warrants a prospective study for further dosage optimization. Low-dose TBI instead of ALG/ATG might also result in complete engraftment; however, there is a concern that higher rates of subsequent primary neoplasms may occur with low-dose TBI, although this has not been reported thus far. Low-dose TBI might also have some influence on fertility. For example, it is predicted that the fractionated radiation dose of 3 and 6 Gy at the age of 0–4 years results in early ovarian failure at the age of 35.1–35.6 $\pm$ 3.9 years and 22.6–24.0 $\pm$ 3.9 years, respectively [13]. In this point of view, RIC regimen for children should not include busulfan either, because busulfan is also known to cause ovarian failure [14]. Our recommended RIC of Flu, LPAM, and ALG/ATG preserved ovarian function in adolescents and young adults [15]. Therefore, it is worthwhile to investigate whether this regimen preserves children's growth and fertility potentials. ALG/ATG usage is reported to be a risk factor for the development of viral diseases such as EBV-associated PTLD [16, 17]. Furthermore, ALG has already been commercially unavailable. Therefore, optimized dosages of ATG and Flu should be investigated. Researchers in Japan recently began a regional (i.e., not nationwide) trial of RIC with Flu, LPAM, and low-dose TBI for patients undergoing CBT [18]. Some of our patients (#1, #2, #5, #6, and #8 in Table 3) will be control patients in that regional trial, and patient #7 (Table 3) will be study patient [18].

In conclusion, the eligibility criteria for allogeneic HSCT for the treatment of primary/familial HLH should not include patients with a PS of 4 and severe organ dysfunction due to a primary disease. Unrelated RIC–CBT may be an alternative HSCT if a patient has no related donor. Patients should undergo HSCT as early as possible with a well-controlled status of primary HLH after diagnosis before the disease progresses. LPAM 140 mg/m$^2$ with Flu and ATG/ALG might be feasible, but further dosage optimization should be performed in controlled clinical trials.

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