Haploidentical HCT using post-transplant cyclophosphamide (PTCy) is a readily available option in the absence of an HLA-matched donor. We conducted a retrospective single-center study on the outcome of haploidentical HCT in children with non-malignant diseases. We gathered data from 44 patients underwent HCT in the period 2015 to 2020. The indications for HCT were bone marrow failure, primary immunodeficiency, metabolic disorders, and hemoglobinopathy. Median age at HCT was 4 years (range 0.7–20). The conditioning regimens were myeloablative (n = 17) or reduced intensity (n = 27). After a median follow-up of 20 months (range 4–71), 2-year overall survival was 89% and 2-year GvHD-free relapse-free survival (GRFS) was 66%. Incidence of primary graft failure was 13.6%. Cumulative incidence of grade II–IV acute and moderate/severe chronic GvHD were 20% and 6.4%, respectively. Younger age at HCT (<4 years) and primary immunodeficiency were significantly associated with better GRFS (p < 0.05). In conclusion, haploidentical HCT using PTCy is feasible and curative in children with non-malignant diseases lacking an HLA-matched donor. Early diagnosis and referral in addition to timely treatment can further improve outcomes.

Keywords Haploidentical · Non-malignant diseases · Hematopoietic cell transplantation · HSCT · Primary immunodeficiency · Post-transplant cyclophosphamide

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is curative for a variety of non-malignant diseases, including primary immunodeficiency (PID), bone marrow failure (BMF), and metabolic disorders [1–5]. However, finding a donor can be a barrier for HCT, as many patients do not have a suitable HLA-matched related donor. Moreover, the chance of finding an HLA-matched unrelated donor for some ethnic groups remains low (http://bethematch.org) [6].

Haploidentical HCT has become an alternative donor source for patients who do not have an HLA-matched donor that is readily available for almost all patients. Nevertheless, graft failure (GF) and graft-versus-host disease (GvHD) are the main barriers for haploidentical HCT [7, 8]. In more recent years, T cell replete haploidentical HCT using post-transplant cyclophosphamide (PTCy) has emerged as a promising strategy, and is being used more frequently due to availability, safety profile, and low cost of the procedure [9]. This approach relies on cyclophosphamide to eliminate both donor and host alloreactive T cells to reduce the risk of both GF and GvHD [10, 11]. Moreover, hematopoietic stem cells are protected from the cytotoxic effects of PTCy due to higher amounts of aldehyde dehydrogenase, an enzyme responsible for metabolizing the drug [12, 13].

Over the last decade, haploidentical HCT with PTCy has been increasingly used for patients with non-malignant diseases.
diseases with variable outcomes [14–22]. This increase is attributed to improvement in diagnostic testing including genetic testing, the increased use of reduced toxicity regimens, improvement in supportive care, and donor pool expansion. Here, we describe patient and transplant characteristics and outcomes after haploidentical HCT with PTCy in 44 children with non-malignant diseases.

Patients and Methods

Patients

This retrospective study included 44 patients <21 years of age who underwent haploidentical hematopoietic cell transplantation (HCT) using post-transplant cyclophosphamide (PTCy) at our center between January 2015 and December 2020. The study was approved by the Institutional Review Board of our institution. Indications for HCT were a variety of non-malignant diseases (Table 1). All patients received mycophenolate mofetil and tacrolimus or cyclosporine A starting day +5 post-HCT as GvHD prophylaxis. All HCTs were supported with granulocyte colony-stimulating factor (G-CSF) starting from day +5 post-HCT.

Table 1 Indications for hematopoietic cell transplantation

| Indication for transplant, n (%) | N=44 (100%) |
|---------------------------------|------------|
| Primary immunodeficiency        | 16/44 (36.3%) |
| Chronic granulomatous disease   | 4/44 (9%) |
| Severe combined immunodeficiency| 3/44 (6.9%) |
| Leukocyte adhesion deficiency   | 2/44 (4.5%) |
| Severe congenital neutropenia   | 2/44 (4.5%) |
| Hyper IgM syndrome              | 2/44 (4.5%) |
| Autoimmune lymphoproliferative syndrome | 1/44 (2.2%) |
| Hyper IgE syndrome              | 1/44 (2.2%) |
| Griscelli syndrome              | 1/44 (2.2%) |
| Severe aplastic anemia          | 14/44 (32%) |
| Inherited bone marrow failure   | 8/44 (18.2%) |
| Fanconi anemia                  | 5/44 (11.1%) |
| Congenital amegakaryocytic thrombocytopenia | 3/44 (6.9%) |
| Metabolic disorder              | 4/44 (9%) |
| Cerebral adrenal leukodystrophy | 2/44 (4.5%) |
| Mucopolysaccharidosis type II   | 1/44 (2.2%) |
| Osteopetrosis                   | 1/44 (2.2%) |
| Hemoglobinopathy                | 2/44 (4.5%) |
| Beta thalassemia major          | 1/44 (2.2%) |
| Sickle cell disease             | 1/44 (2.2%) |

Definitions and Outcomes

Endpoints studied included neutrophil and platelet recovery, graft failure, acute and chronic GvHD, event-free survival (EFS), GvHD-free relapse-free survival (GRFS), and overall survival. Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) ≥0.5×10⁹/L for 3 consecutive days. Platelet recovery was defined as achieving platelets ≥20×10⁹/L, unsupported for 7 days. The diagnosis and grading of acute and chronic GVHD were based on international standard criteria [23, 24]. Graft failure (GF) was defined as either failure to show neutrophil recovery or whole blood donor chimerism <5% beyond day 30 after HCT (primary GF) or complete loss of donor cells (<5% donor cells) after initial engraftment (secondary GF). Preparative regimens were classified as myeloablative (MAC) or reduced intensity (RIC) if the dose of alkylating agents or TBI is reduced by at least 30% from a MAC approach [25, 26]. Regimens containing one of the following were classified as MAC: TBI at a total dose of ≥8 Gy, busulfan at a dose of ≥12 mg/kg. Other regimens were classified as RIC including fludarabine and melphalan regimen and Fanconi anemia regimen (fludarabine, TBI 2 Gy).

Statistical Analysis

Kaplan–Meier curves were plotted for overall survival (OS), GvHD-free relapse-free survival (GRFS), and event-free survival (EFS), and p values were obtained for Mantel-Cox log-rank tests performed using R version 4.0.3. Values of p<0.05 were considered statistically significant. EFS was calculated as the time from first HCT until the first occurrence of GF or death. GRFS was calculated as the time from first HCT until the first occurrence of any of the following events: GF, disease relapse (poor graft function/graft failure with disease relapse requiring repeat transplant), death, grade 3–4 aGvHD, or moderate/severe cGvHD. Univariate analysis was performed with the Kaplan–Meier method using R version 4.0.3. Variables tested included age at HCT (<4 years versus ≥4 years), conditioning regimen intensity (MAC versus RIC), serotherapy use, thiotepa use, CD34 stem cell dose, CD3 cell dose, type of disease (PID versus others), stem cell source (bone marrow versus peripheral blood), ABO matching, gender matching, and donor age. The cumulative incidence of GvHD was also calculated using competing risk analysis, using R version 4.0.3.
Results

Patient and Transplant Characteristics

The characteristics of 44 patients studied including transplant characteristics are depicted in Table 2. Median age at HCT was 4 years (range 0.7–20). MAC regimens were used in 17/44 (39%) patients and RIC in 27/44 (61%) patients. Fludarabine, cyclophosphamide, and TBI 2–4 Gy with or without thiotepa +/− antithymocyte globulin (ATG) were the predominant regimens in 18 patients (41%). Bone marrow was used as stem cell source in 18/44 (41%) patients and peripheral blood in 26/44 (59%) patients. Serotherapy

### Table 2 Summary of patients and transplant characteristics

|                         | All patients/all HCT procedures | Died | Graft failure |
|-------------------------|---------------------------------|------|---------------|
| Number of patients      | 44                              | 5    | 8             |
| Number of HCT/procedures| 47                              |      |               |
| Median age at HCT, years (range) | 4 (0.7–20)                    | 9 (0.75–17) | 4 (0.75–13) |
| M:F                     | 1.6:1                            | 0.66:1 | 1.6:1         |
| Underlying disease      |                                 |      |               |
| Primary immunodeficiency| 16/44 (36%)                      |      |               |
| Severe aplastic anemia  | 14/44 (32%)                      | 3/14 (21%) | 5/14 (36%) |
| Inherited bone marrow failure | 8/44 (18%)                 | 1/8 (12.5%) | 1/8 (12.5%) |
| Metabolic disorder      | 4/44 (9%)                        | 1/4 (25%) | 2/4 (50%)     |
| Hemoglobinopathy        | 2/44 (5%)                        |      |               |
| Donor relationship      |                                 |      |               |
| Parent                  | 33/44 (75%)                      | 3/33 (9%) | 6/33 (18%) |
| Sibling                 | 11/44 (25%)                      | 2/11 (18%) | 2/11 (18%) |
| Median donor age (y) (range) | 25.5 (3–55)                  | 20 (13–42) | 31.5 (3–50) |
| ABO compatibility       |                                 |      |               |
| Yes                     | 29/44 (66%)                      | 5/29 (17%) | 6/29 (20%) |
| No                      | 15/44 (34%)                      | 2/15 (13%) |               |
| Stem cell source        |                                 |      |               |
| PB                      | 26/44 (59%)                      | 4/26 (15%) | 4/26 (15%) |
| BM                      | 18/44 (41%)                      | 1/18 (6%) | 4/18 (22%)   |
| Median CD34+ cell dose *10⁶/kg (n = 44) (range) | 10.3 (3.8–24.3) | 10 (7–15.9) | 11.9 (7–15.9) |
| Conditioning regimen    |                                 |      |               |
| Flu–Mel                 | 2/44 (5%)                        |      |               |
| Flu–Mel–TBI             | 10/44 (23%)                      |      |               |
| Flu–Mel–TT              | 2/44 (5%)                        |      |               |
| Flu–TBI                 | 5/44 (11%)                       | 1/5 (20%) |               |
| Flu–Cy–TBI              | 9/44 (20%)                       | 1/9 (11%) | 4/9 (44%)    |
| Flu–Cy–TT–TBI           | 9/44 (20%)                       | 2/9 (22%) | 1/9 (11%)    |
| Flu–Bu                  | 1/44 (2%)                        |      |               |
| Flu–Bu–TT               | 6/44 (14%)                       | 1/6 (17%) | 1/6 (16%)    |
| Serotherapy             |                                 |      |               |
| ATG                     | 35/44 (80%)                      | 3/35 (9%) | 7/35 (20%) |
| Alemtuzumab             | 2/44 (5%)                        |      |               |
| None                    | 7/44 (15%)                       | 2/7 (29%) | 1/7 (14%)   |
| Sex matching            |                                 |      |               |
| Match sex               | 27/44 (61%)                      | 2/27 (7%) | 4/27 (15%) |
| M–F                     | 8/44 (18%)                       | 1/8 (13%) | 2/8 (25%)   |
| F–M                     | 9/44 (21%)                       | 2/9 (22%) | 2/9 (22%)   |

ATG antithymocyte globulin; BM bone marrow; Bu busulfan; Cy cyclophosphamide; F female; Flu fludarabine; HCT hematopoietic stem cell transplantation; M male; Mel melphalan; PB peripheral blood; TBI total body irradiation; TT thiotepa
was used in 37/44 (84%) patients (35 patients received rabbit ATG and 2 received alemtuzumab). ATG was administered on days 9, 8, and 7 prior to transplant with a total dose of 7.5 mg/kg. The median follow-up in surviving patients was 20 months (range 4–71).

**Engraftment and Graft Failure**

Median time to neutrophil engraftment was on day +12 (range 10–26) and for platelet engraftment was on day +18 (range 12–52). Full donor chimerism was confirmed in 36/42 evaluable patients (86%). Two patients died before chimerism evaluation (SAA × 1, and osteopetrosis × 1). Primary graft failure (GF) was observed in 6 patients (13.6%) and secondary GF in 2 patients. Five of the 8 patients with GF had severe aplastic anemia (SAA) and 3 out of these (60%) had strong donor-specific antibodies. Four of the 8 patients with GF underwent a second HCT. All surviving patients had full donor chimerism at last follow-up except for 5 patients with mixed donor chimerism (SCID × 3, CGD × 1, and thalassemia × 1) and all five are free of disease.

**Overall Survival, Event-Free Survival, and GvHD-Free Relapse-Free Survival**

After a median follow-up of 20 months (range 4–71), 39 of the 44 patients are alive and disease-free. The causes of death for the 5 patients (11%) were sepsis in 3 patients, intracranial hemorrhage in 1 patient, and diffuse alveolar hemorrhage in another patient. Three of the 5 deaths were related to primary GF. The 2-year overall survival for the whole cohort was 89%, the 2-year EFS was 77%, and the 2-year GRFS was 66% (Fig. 1a). The analysis of factors associated with GRFS showed that younger age at HCT (< 4 years, \( p = 0.034 \)) and primary immunodeficiency (\( p = 0.048 \)) were associated with less events. Univariate analysis of factors associated with EFS showed a trend toward improved EFS for PID patients compared to other non-malignant diseases (\( p = 0.05 \)). There was a trend toward improved OS for patients with PID (\( p = 0.075 \)) but did not reach statistical significance (Fig. 2 and Table 3). Transplant characteristics and outcomes per disease group are represented in Table 4.

**Post-transplant Complications**

Four patients (9%) developed moderate hepatic sinusoidal obstruction syndrome (SOS) and all were treated successfully with defibrotide. There was no severe SOS. Acute GvHD grade 2–4 was observed in 9/44 (20%) patients. Most cases of aGvHD were mild (grade 2, \( n = 7 \); grade 3, \( n = 2 \)) and most of these were skin aGvHD except for the 2 patients with grade 3 aGvHD in skin and gut (Fig. 1b). Chronic GvHD was observed in 10/44 (22%) patients. cGvHD was mild in 8 patients, moderate in 1, and severe in 1 patient (Fig. 1b). The cumulative incidences of systemic CMV reactivation, BK hemorrhagic cystitis, and EBV viremia were 55%, 20%, and 16%, respectively. All infections were treated successfully with no long-term complications. There was no CMV disease. Only 2 of 7 patients with EBV viremia required antiviral therapy and none required rituximab. No patients had developed EBV-related lymphoproliferative disease (PTLD).

**Discussion**

We show here that haploidentical HCT using PTCy is feasible and effective in treating non-malignant diseases, after a median follow-up of 20 months (range 4–71). The 2-year
Fig. 2 Kaplan–Meier survival curve analysis representing: A overall survival (OS) by age (<4 years vs >4 years); B event-free survival (EFS) by age; C GvHD-free relapse-free survival (GRFS) by age; D OS by indication for HCT (PID versus others); E EFS by indication of HCT; F GRFS by indication for HCT

Table 3 Univariate analysis

| Variable                     | Number of patients (n = 44) | 2-yr OS (95% CI) | 2-yr EFS (95% CI) | 2-yr GRFS (95% CI) |
|-----------------------------|-----------------------------|------------------|-------------------|--------------------|
| Age                         |                             |                  |                   |                    |
| <4                          | 23                          | 0.96 (0.88–1)    | 0.83 (0.68–0.99)  | 0.83 (0.68–0.99)   |
| ≥4                          | 21                          | 0.81 (0.65–0.99) | 0.71 (0.55–0.94)  | 0.5 (0.31–0.78)    |
| p value                     |                             | 0.13             | 0.34              | 0.034              |
| Conditioning regimen        |                             |                  |                   |                    |
| MAC                         | 17                          | 0.88 (0.73–1)    | 0.82 (0.66–1)     | 0.76 (0.57–0.99)   |
| RIC                         | 27                          | 0.89 (0.78–1)    | 0.74 (0.59–0.93)  | 0.6 (0.44–0.84)    |
| p value                     |                             | 1                | 0.52              | 0.34               |
| Stem cell source            |                             |                  |                   |                    |
| BM                          | 18                          | 0.94 (0.84–1)    | 0.72 (0.54–0.96)  | 0.67 (0.48–0.92)   |
| PB                          | 26                          | 0.84 (0.72–0.99) | 0.8 (0.67–0.97)   | 0.65 (0.47–0.9)    |
| p value                     |                             | 0.35             | 0.55              | 0.8                |

Results are highlighted in bold according to the definition of significance; p value < 0.05

BM bone marrow; MAC myeloablative conditioning; PB peripheral blood; RIC reduced intensity conditioning
OS for patients with a variety of non-malignant diseases, including PID, inherited BMF syndromes, SAA, metabolic disorders, and hemoglobinopathy, was 89%. The 2-year EFS and GRFS in our cohort of 44 patients were 77% and 66%, respectively.

Our data compares favorably to the published literature on haploidentical HCT for children with non-malignant diseases. There are 4 relatively recent publications with more than 10 patients describing outcomes of haploidentical HCT in children with a variety of non-malignant diseases. Uppuluri and colleagues have reported the results of 16 patients with PID who received haploidentical HCT; OS was 62.5% and grade II–IV aGvHD was 50% at a median follow-up of 23.3 months [20]. Benedicte et al. have reported the outcomes of haploidentical HCT for 27 patients with OS of 77% and grade II–IV aGvHD of 46% at a median follow-up of 25.6 months [19]. Mallhi and colleagues have reported the results of 23 patients using haploidentical HCT. After a median follow-up of 2.5 years, OS and EFS were 91% and 78%, respectively. Grade II–IV aGvHD was 78% [21]. Olaya M et al. have reported outcomes of 47 patients with inborn errors of immunity using different donors. Nineteen patients underwent haploidentical HCT with an OS of 72% [15].

In univariate analysis model (Table 3), the only factors associated with a better GRFS were transplantation at an age younger than 4 years and PID as an indication for HCT [27]. This could reflect that early recognition and diagnosis of these diseases leads to less severe post-HCT complications with better survival outcomes. Active infections at the time of HCT have been known to be associated with poor survival in patients with PID. Moreover, we show that particularly patients with PID had 100% overall survival compared to other non-malignant diseases in our cohort. Although we did not find a significant improvement in survival over time, this could relate to allowing patients with more severe diseases to have access to transplant.

Eight patients developed GF. Four of the 8 patients proceeded to second HCT and are alive. Only age at HCT (after 4 years) showed a significant association with higher incidence of graft failure. Most patients with GF were transplanted for SAA ($n=5$). This could be attributed to the risk of transfusion-induced sensitization to the HLA-haploidentical grafts [28, 29]. Interestingly, 3 out the 5 patients with SAA and GF had strong donor-specific antibodies and despite desensitization with intravenous immunoglobulins (IVIG), rituximab and plasmapheresis, they succumbed to GF. Since successful engraftment was a major concern in SAA patients, in 2018, we elected to modify conditioning regimen to include thiotepa (10 mg/kg) and increased the dose of TBI from 2 to 4 Gy. Since this modification in conditioning, we have only seen 1 GF out of 8 SAA patients transplanted. The limited sample size does not allow us to derive definitive recommendation on transplant conditioning regimen. In view of the relatively higher graft failure rates in SAA patients with strong donor-specific antibodies in our cohort, we recommend adding thiotepa and/or increasing the TBI dose in this subset of patients. The desire to lower toxicity and end organ damage is highly desirable when HCT is offered to children with non-malignant diseases. We did not show that RIC is associated with more GF. Hence, using RIC in patients with certain non-malignant diseases such as PID should be further investigated in prospective manner.

We had three patients with SCID in our cohort, and all had T-B-NK+ phenotype and received fludarabine and melphalan for conditioning. Medina age at HCT was 0.8 years (0.5–1). All three patients are alive and free of disease with no infections and mixed chimerism but near total T cell chimerism.

### Table 4: Transplant characteristics and outcomes per disease group

| Variable                  | PID        | SAA        | IBMFS      | Metabolic   | Hemoglobinopathy | Overall |
|---------------------------|------------|------------|------------|-------------|------------------|---------|
| Age (y), median (IQR)     | 3.0 (6.0)  | 6.5 (7.0)  | 5.0 (5.2)  | 3.5 (6.3)   | 11.5 (8.5)       | 4.0 (7.0) |
| Conditioning regimen      |            |            |            |             |                  |         |
| MAC                       | 8 (50.0)   | 1 (7.1)    | 3 (37.5)   | 4 (100.0)   | 1 (50.0)         | 17 (38.6)|
| RIC                       | 8 (50.0)   | 13 (92.9)  | 5 (62.5)   | 0 (0.0)     | 1 (50.0)         | 27 (61.4)|
| Stem cell source          |            |            |            |             |                  |         |
| BM                        | 6 (37.5)   | 6 (42.9)   | 4 (50.0)   | 1 (25.0)    | 1 (50.0)         | 26 (59.1)|
| PB                        | 10 (62.5)  | 8 (57.1)   | 4 (50.0)   | 3 (75.0)    | 1 (50.0)         | 18 (40.9)|
| 2-yr OS (%)               | 100        | 79         | 88         | 75          | 100              | 89      |
| 2-yr EFS (%)              | 94         | 57         | 88         | 50          | 100              | 77      |
| 2-yr GRFS (%)             | 88         | 43         | 60         | 50          | 100              | 66      |
| Follow-up (m), median     | 20         | 14         | 27         | 9           | 22               | 20      |

BM bone marrow; IBMFS inherited bone marrow failure syndrome; m month; MAC myeloablative conditioning; PB peripheral blood; PID primary immunodeficiency; RIC reduced intensity conditioning; SAA severe aplastic anemia; y year
There is a general agreement that the rates of acute and chronic GvHD must be kept to a minimum for HCT for non-malignant diseases. We observed an acceptable rate of GvHD as most of the patients had only grade 1 aGvHD and mild chronic GvHD. Haploidentical HCT using PTCy along with using serotherapy contributed to the low rates of GvHD in our cohort with no mortality from viral infections.

One limitation of our study is the retrospective design. Second, non-malignant diseases are a heterogeneous group with a diverse pathophysiology, making it difficult to select the best conditioning regimen for each disease.

In conclusion, our data show that in resource limited settings, and when HLA identical donors are not available, haploidentical HCT using PTCy is feasible and effective in curing children with various non-malignant diseases with acceptable rates of GvHD. GF remains an obstacle especially when anti-HLA antibodies are strongly present due to transfusion-induced sensitization, despite using desensitization techniques. With the expansion of HCT in children to transfusion-induced sensitization, despite using desensitization techniques, with the expansion of HCT in children to transfusion-induced sensitization, despite using desensitization techniques, the best conditioning regimen for each disease.

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