Successful Hematopoietic Stem Cell Transplantation with Reduced Intensity Conditioning in Three Patients with Primary Hemophagocytic Lymphohistiocytosis: Case Report and Review of the Literature

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory clinical syndrome of uncontrolled immune response which results in hypercytokinemia due to underlying primary or secondary immune defects. HLH can be classified into familial (primary) and acquired (secondary) forms according to the underlying defect. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option in primary HLH, and the outcome of HSCT for HLH patients has improved over the last decades. However, HSCT for HLH still carries significant morbidity and mortality. Herein, we described three patients with primary HLH, including a 4.5 years old girl with Chédiak-Higashi Syndrome (CHS- LYST gene mutation), a 5.5 years old boy with Griscelli syndrome type 2 (GS2- Rab27a gene mutation), and an 8.9 years old girl with Hemophagocytic lymphohistiocytosis Syndrome type 5 (HLH 5- STXBP2 gene mutation). All three patients received allogeneic HSCT with a reduced-intensity conditioning (RIC) regimen, including Fludarabine, Melphalan, Rabbit Anti-thymocyte globulin (r-ATG), and graft versus host disease (GvHD) prophylaxis by Methylprednisolone and Cyclosporine. The outcome of HSCT for HLH patients has improved, and HSCT can provide long-term survival for familial HLH. Ongoing challenges in various aspects of HSCT remain to be elucidated, including donor selection, the timing of HSCT, the conditioning regimen, and mixed chimerism after HSCT.

KEYWORDS: Hematopoietic stem cell transplantation; Hemophagocytic lymphohistiocytosis; Reduced intensity conditioning; Inborn errors of immunity

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulation syndrome characterized by unremitting fever, cytopenias, hepatosplenomegaly, coagulopathy, and elevations in ferritin and soluble interleukin-2 receptor (sIL-2R) [1]. Also other clinical presentations including hypertriglyceridemia, liver dysfunction, coagulation disorders, and renal insufficiency .The pathognomonic feature of this syndrome is the presence of hemophagocytosis in bone marrow, lymph nodes, spleen, or liver [2] . Patients can also develop central nervous system involvement, multiorgan failure, and other complications [3].

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There are two descriptions for HLH; primary or familial HLH (fHLH) and secondary HLH. Familial HLH results from pathogenic mutations in major genes, including PRF1, UNC13D, STX11, and STXBP2, or can occur in many other genetic defects, including hypopigmentary disorders (Griscelli syndrome, Chédiak Higashi syndrome, Hermansky Pudlak syndrome), X-linked lymphoproliferative (XLP) diseases, Epstein-Barr virus (EBV) susceptibility disorders, and specific mutations in CDC42, NLRC4, FAAP24, and SLC7A7 [4, 5]. Secondary HLH refers to HLH in combination with many infectious, malignancy, and rheumatologic disorders. For instance, common pathogens include DNA viruses (EBV, cytomegalovirus, and adenovirus), intracellular pathogens (e.g., Leishmania), influenza viruses, and tuberculosis. Lymphoma and leukemia are also common malignancies associated with HLH.

Defects in perforin and granule-mediated cytotoxicity molecules underlie the pathophysiology of HLH. Granule-mediated cytotoxicity is one of the mechanisms natural killer cells (NK cells), and cytotoxic T lymphocytes use to kill virus-infected and malignant cells. First, perforin makes a pore in the target cell membrane, and then, granule-mediated cytotoxicity will be exerted on the target cell and induce apoptosis [6]. In familial HLH, this mechanism is impaired, and prolonged immunologic synapse ensues without killing the target cell. Accumulation of antigen-presenting cells and stimulated T cells results in hyperinflammation and multi-organ damage [3].

In both types of HLH, immunosuppressive agents are prescribed to dampen the hyperinflammatory state. In secondary HLH, additional antimicrobial treatment or chemotherapy is necessary due to infection and malignancy. Hematopoietic stem cell transplantation (HSCT) provides a curative option in familial HLH patients with pathologic variants in PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST, and SH2D1A and some patients with XIAP deficiency [7].

The most important prognostic factor contributing to the post-transplantation survival of primary HLH patients is disease remission at the time of HSCT, regardless of the underlying genetic defect [8]. HSCs possess the ability of both multipotency and self-renewal [9]. HSCs are using to treat of various diseases include: cancers(leukemia, lymphoma), immunodeficiency, auto-immune diseases, metabolic or other genetic disorders [10, 11]. Therefore, it is very important to minimize the time for diagnosis and treatment of HLH disorders.

In this regard, we tend to report three patients with familial HLH who had allogeneic HSCTs.

CASE PRESENTATION

CASE 1

The first patient was 4.5 years old female. Her parents were consanguineous (first cousins). The family history was noncontributory. She had received complete vaccinations and had typical developmental milestones. She had a history of episodic fevers since she was 1.5 years old and was admitted four times, but the fever workup had been inconclusive. In her last admission, she complained of prolonged fever (for two weeks), which was nonresponsive to antipyretics and was accompanied by productive coughs (for five days). In the laboratory evaluation, leukopenia (white blood cell: 2300 cells/mm^3), anemia (Hb: 9 gr/dL), thrombocytopenia (Platelet: 28000 cells/mm^3), and slightly elevated inflammatory markers (erythrocyte sedimentation rate: 30, C-reactive protein: +1) were detected.

The hematologic malignancy was ruled out by normal bone marrow aspiration (BMA). She was treated with antibiotic therapy and supportive care but showed no improvement. She presented to Mofid Children's Hospital at 4.5 years of age with complaints of persistent fever. In physical examination, she had blond hair and a Hepatosplenomegaly. In laboratory results, pancytopenia, hypertriglyceridemia (=409 mg/dl), hyperferritinemia (=441mg/dl),

Table 1: Summary of hematopoietic stem cell transplant details in patients with primary hemophagocytic lymphohistiocytosis.

Variables	CASE 1	CASE 2	CASE 3
Sex	Female	Male	Female
Age P (years)	4.5	5.5	8.9
Initial Blood Index	Hb: 9, WBC: 2300, Plt: 28000, C-reactive protein: +1 erythrocyte sedimentation rate: 30, TG: 409, ferritin: 441, fibrinogen: 242 AST: 150, ALT: 94, BG: B+	BG: A+	Ferritin> 800, AST: 512, ALT: 225, BG: B+
Age D (years), Method	1.5, WES	1, WES	5, WES
Age (years) at HSCT	3	2.5	8.9
Donor Characteristic	MRD (aunt), fully matched, BG: A+	partially matched (5/6) unrelated, BG: O+	MSD (brother), fully matched, BG: B+
Cond.	Fludarabine, Melphalan, rATG	Fludarabine, Melphalan, rATG	Fludarabine, Melphalan, rATG
GVHD Pro.	Cyclosporine, Methyl prednisone, GCSF	Cyclosporine, Methyl prednisone	Cyclosporine, Methyl prednisone
TNC, $\times 10^8$ cells/kg	5.95	0.36	8.1
CD34, $\times 10^6$ cells/kg	5.15	____	3.04
Neutrophil Engraftment, day	+18	+14	+16
Latest Chimerism, % donor	60%	Failure	95%
GVHD, organ (grade)	Acute skin GVHD (St 2)	____	Skin GVHD (St 2-3)
Other Complication	CMV reactivation, PRES, hemorrhagic cystitis (due to the BK virus)	fever, NHL, hepatosplenomegaly	CMV reactivation, intermittent cyanosis, decrease oxygen saturation, methemoglobinemia
Follow-Up	Died after 3 years	Died after 4 months	Well on 5 years follow-up

Abbreviations: Age D, age at diagnosis; Age P, age at presentation; BG, blood group; CMV, cytomegalovirus; Cond, conditioning; F, female; GCSF, Granulocyte-Colony Stimulating Factor; GVHD, graft-versus-host disease; Hb, hemoglobin; M, male; MRD, matched related donor; MSD, matched sibling donor; NHL, non-Hodgkin Lymphoma; PRES, posterior reversible encephalopathy syndrome; Pro, prophylaxis; rATG, rabbit antithymocyte globulin;WES, whole-exome sequencing; S, sex; St, stage; TNC, total nucleated cell

and high level of aspartate aminotransferase (AST) (=150 u/l) and alanine aminotransferase (ALT) (=94 u/l), with normal fibrinogen (242 mg/dl) were found. Abdominal sonography showed hepatosplenomegaly (liver: 112 mm, spleen: 133 mm). The flowcytometry of lymphocyte subsets was normal. In

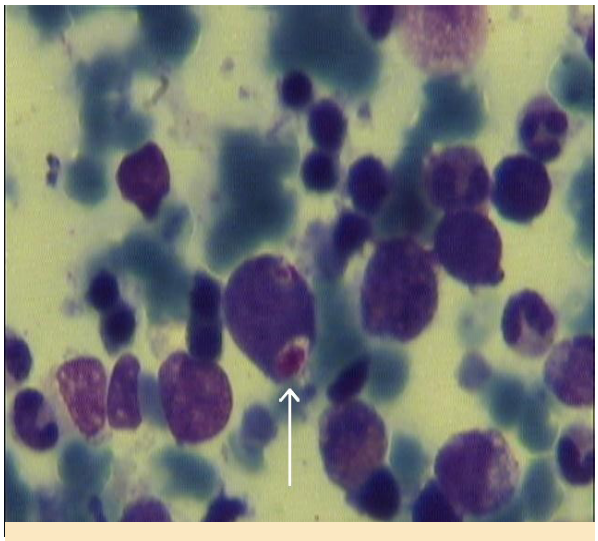

Figure 1: Giant granules in neutrophils. The laboratory bone marrow sample observation of patient 1 demonstrates giant granules in neutrophils (flash mark) representative of Chédiak Higashi syndrome.

Figure 2: Hair shaft examination of patient 2 by light microscope. Abnormal big melanin granules observed regarding Griscelli syndrome.

BMA, normal cellularity of megakaryocytes, erythroid hyperplasia, three hemophagocytic cells, and abnormal giant granules in the myeloid series were reported (Fig 1). Due to her blond hair, hepatosplenomegaly, and giant granules in BMA, the Chédiak Higashi syndrome (CHS) was suspected, and the hair shaft was sent for microscopy (Fig 2). Diffuse evenly distributed large melanin granules were seen in hair shaft direct microscopy examination. The Epstein–Barr virus (EBV) and Cytomegalovirus (CMV) polymerase chain reaction (PCR) tests were negative. The brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis were normal. She received HLH treatment based on the 2004 protocol. The diagnosis of CHS was further confirmed by the identification of a homozygous pathogenic variant in the LYST gene by whole-exome sequencing.

Eight months later, she received allogeneic HSCT from her 10/10 matched related donor (Aunt). Reduced-intensity conditioning (RIC) regimen with Fludarabine 30mg/ m^2/ day x 5 days, Melphalan 70mg / m^2/ day x 2 days, Rabbit Anti-thymocyte globulin (r-ATG) 2.5mg /kg/day x 3 days, and GvHD prophylaxis with Cyclosporine 3mg/kg /day/IV infusion divided dose BID since day -1 and Methyl prednisone 2mg/ kg /day/divided dose BID since day +1 and Granulocyte-Colony Stimulating Factor (GCSF) since day +5 were applied. The recipient and donor were CMV IgG-positive. The blood group of the recipient and donor were B-positive and A-positive, respectively. On day zero, stem cell infusion with total nucleated cell count (TNC) of 5.95×10^8 cells/Kg and CD34 of 5.15×10^6 cells/Kg was done. The engraftment was achieved on day +18. The chimerism was full donor chimerism (>95%).

After HSCT, she was complicated with acute GvHD (skin-stage II), CMV reactivation, hemorrhagic cystitis (due to the BK virus), and posterior reversible encephalopathy syndrome (PRES). All complications were treated and improved. During follow-up after several months, she progressed to mixed donor chimerism about 60%. After 3 years, despite being under control for chronic GvHD with 80% chimerism , she died because of entropathy and electrolyte imblanace.

CASE 2

The second patient was a 5.5 years old male, an only child of non-consanguineous parents with no familial history of HLH. At the age of

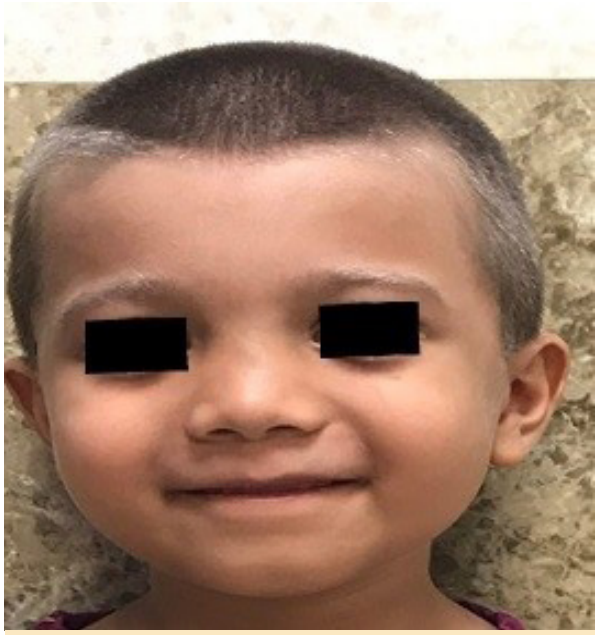

Figure 3: Oculocutaneous hypopigmentation and silvery gray hair, including eyebrows and eyelashes, in physical examination of the patient with Griscelli syndrome (GS).

one year, he developed pancytopenia and hepatosplenomegaly. He had oculocutaneous hypopigmentation and silvery hair (Fig 3). The genetic study showed RAB27A genetic mutation, and Griscelli syndrome type II diagnosis was established. While in remission, he was referred to our hospital for transplantation. The pre-HSCT evaluation showed a normal BMA and a normal polymorphic pattern in the flow cytometry. MRI study and CSF analysis were normal. The EBV and CMV PCR assays were negative. After complete evaluation for allogeneic HSCT, he received a reduced-intensity conditioning (RIC) regimen with Fludarabine, Melphalan, r-ATG, and GvHD prophylaxis with Cyclosporine and Methyl prednisone (The same as patient 1).

On day -3, after starting Melphalan, he presented acute dyspnea and vomiting. Therefore, Melphalan administration was held, and treatment with an O2 supply, diphenhydramine, and hydrocortisone was done. After two days with the desensitization protocol by immunology consult, Melphalan infusion was done, and the patient tolerated Melphalan without a problem.

He underwent allogeneic HSCT from partially matched (5/6) unrelated cord blood HSCT (TNC: 3.6×10^7 cells/Kg). The recipient's blood group was A positive, and the donor's blood group was O positive. He was engrafted on day +14, but his chimerism evaluation showed primary graft failure (GF). During follow-up four months after HSCT, he presented with fever, massive cervical lymphadenopathy, hepatosplenomegaly, and EBV titers above 50000. BMA was normal, with no hemophagocytosis, but the result of cervical lymph node biopsy was compatible with B cell non-Hodgkin Lymphoma (NHL). He did not have response to chemotherapy and died.

CASE 3

The third patient was 8.9 years old female born to consanguineous (first cousins) parents. She had multiple episodes of gastroenteritis, fever, and pancytopenia since she was 5 years old. She also suffered from chronic hepatitis, diagnosed by elevated liver function tests (LFT) and evidence of active hepatitis on the liver biopsy. She was further complicated with generalized edema, ascites, bleeding disorders, and splenomegaly. Also, she had a cleft palate, mild developmental delay, and a history of seizures. On MRI, ventriculomegaly and brain atrophy were detected. CSF analysis was normal without hemophagocytosis. Lymphocyte flowcytometry, BMA, and Bone marrow biopsy (BMB) were normal.

She had normal serum triglyceride, a high ferritin level (>800 mg/dl), and high liver enzymes (AST: 512 u/l, ALT: 225 u/l). Neurologic consultation was performed, and treatment with Topiramate, Levetiracetam, and Clobazam was continued. She was diagnosed as type-V familial HLH with mutated STXBP2. Due to HLH criteria, she received HLH 2004 protocol. EBV and CMV PCR assays were negative. After a complete evaluation similar to other previously described patients, she prepared for HSCT. Then she was admitted to the HSCT ward. Reduced-intensity conditioning (RIC) regimen; Fludarabine, Melphalan, and r-ATG and GvHD prophylaxis with Cyclosporine and Methyl prednisone was administered

(The same as patients 1 and 2).

She received allogeneic HSCT from peripheral blood (PBSC; peripheral blood stem cells) from her fully matched 3-year-old brother (MSD; matched sibling donor). Hematopoietic stem cells were harvested two times, and TNC of 8.1×10^8 cells/Kg and CD34 of 3.04×10^6 cells/Kg were infused. The blood group of the recipient and donor were both B-positive. She engrafted on day +16 post-transplant. The chimerism study was 95%. Despite the good result of chimerism about 10-14 days after engraftment, she developed persistent progressive pancytopenia and severe hypocellular bone marrow. Therefore, after multiple work-up and evaluations, no response to supportive care, and persistent full donor chimerism (95%), booster stem cell infusion from MSD was made on days +91 and +134. She had a good response to treatment with CBC recovery. The other important complication was intermittent cyanosis and decrease oxygen saturation (85%), with a diagnosis of methemoglobinemia due to using Dapsone instead of cotrimoxazole, which improved after discontinuing the drug. Also, CMV reactivation and skin GVHD stage 2-3 occurred and were controlled by Ganciclovir, Corticosteroids, and Tacrolimus, respectively. After 5 yaers, she is well with mixed 55% chimerism.

DISCUSSION

Diagnosis, chemoimmunotherapy, and hematopoietic stem cell transplantation (HSCT) play a prominent role in familial HLH. In this study, we aimed to report the clinical status of our patients and describe the transplantation procedures we applied.

In 1939, HLH was first described by Ronald Bodley Scott and Robb-Smith AHT, who reported isolated cases of children with fever, fatal systemic inflammation, and bone marrow or tissue specimens evaluation. In 1952, Farquhar JW and Claireaux AE suggested genetic disposition in some HLH cases (fHLH). During more than two last decades, several clinical trials related to HLH disorders, including the HLH-2004 protocol, were published to facilitate the diagnosis and management of HLH [12]. Then Several studies have investigated the outcome of HSCT, as a curative treatment for familial HLH. In a French report, 48 patients with primary HLH went through HSCT Between May 1982 and March 2004, with a median follow-up of 5.8 years extending to 20 years. The median age was 3 years old (range 1 day-18 years old). Pre-transplant treatment of 15 (31%) children between 1982 and 1991 was a chemotherapy regimen based on VP-16 combined with Corticosteroids, Cyclosporine A, and intrathecal (IT) Methotrexate. Other 33 (69%) children, from 1991 to 2004, had received an immunotherapy regimen consisting of Corticosteroids and Cyclosporine A associated with or without ATG and intrathecal Methotrexate. 14 (30%) patients received an HSCT from a matched sibling donor (in 1 case, later recognized that the donor also had familial HLH). Four patients received the transplant from a fully matched unrelated donor, 1 from a 2-antigen mismatched unrelated donor, and 29 (60%) patients from a haploidentical family donor. 12 out of 48 patients required second transplantation. The source of hematopoietic stem cells was bone marrow in 53 (88%) and peripheral blood stem cells in 7 patients. 20 out of 48 patients died, 4 early after HSCT and 16 later. The overall event-free survival rate was 58.5%, and of all 60 transplants, engraftment occurred in 42, failure in 14, and was not assessable in 4 patients due to early death [13]. Another cohort study from the USA investigated 46 patients with HLH and other primary immunodeficiencies over 45 years. Overall, 34 patients had HLH, including 25 familial HLH. All 46 patients underwent HSCT with a median age of 2.3 years old (range 5 months-28 years old), and 34 patients (74% of all transplanted patients) were less than 10 years old. Twenty-five patients received bone marrow from an HLA-matched unrelated donor, 13 from 1 HLA-locus mismatched unrelated donor, 7 from an HLA-matched sibling, and one from a mismatched related donor. The median chimerism with sustained engraftment at one year was 99% for all patients and 92.9% for familial HLH (range 23%-100%). In 1 year and

18 months, total deaths were reported in 14 patients; therefore, the overall survival rate for the whole cohort was 66.7%, and for familial HLH was 82.4% [14].

From 2000 to 2014, an Italian study was performed on 109 patients with HLH. The median age at the diagnosis was 1 year old (range 27 days to 18 years old), whereas the median age at first transplantation was 2 years (range 4 months to 20 years), and the genetic abnormality related to HLH was found in 80% of subjects. Ninety-five patients received one transplant procedure, while 14 received more episodes (12 patients 2 procedures, one patient 3 procedures, one patient 4 procedures) due to rejection in 8 and disease relapse in 6 subjects. The conditioning regimen was Busulfan-based for 61 patients, Treosulfan-based for 21 patients, Fludarabine-based for 26 patients, and Melphalan-Etoposide for one patient. Transplantation sources were bone marrow for 70, peripheral blood stem cells for 18, and umbilical cord blood for 21 subjects. The donor for the first transplant was an HLA-matched sibling donor for 25, an unrelated donor using high-resolution HLA typing for 73, and an HLA-partially-matched family donor for 11 patients. Totally 31 patients died, 26 patients due to transplant-related complications (Veno-occlusive disease, lung Aspergillosis, and mainly for multiorgan failure). The median observation time for surviving patients was 5.2 years (range 9 to 14.9), with an overall survival rate of 71% for the whole study population [15]. In another study on 25 HLH patients (involving 23 fHLH) from June 2009 to June 2019, successful outcomes were observed. All subjects underwent HSCT with a reduced-intensity conditioning protocol comprised of targeted sub-myeloablative Busulfan, Fludarabine, and Serotherapy comprising Alemtuzumab (0.5-0.8 mg/kg) for unrelated donors and Rabbit anti–T-cell globulin for related-donor transplants. The transplantation source for 17 subjects was bone marrow (15, 10/10-HLA–matched and 2, 9/10-HLA–matched from an unrelated donor), 6 subjects from peripheral blood stem cells, and 2 from the umbilical cord. The median neutrophil and platelet engraftment time was 20 days and 28 days, respectively. After 36 months of median follow-up, the median donor CD15+ neutrophil chimerism was 99.5%, the median donor CD3+ T-cell chimerism was 97%, and the median donor CD56+ NK cell chimerism was 97.5%. At the last follow-up, all patients were alive and disease-free [16]. In China, a study including 38 patients with familial HLH was performed from November 2015 until June 2019. All patients had been treated by the HLH-94 or HLH-2004 protocol. Two patients responded poorly, so they received additional therapy by DEP (Doxorubicin-Etoposide-Methyl prednisolone). One of them partially responded, while another one showed no improvement and was a candidate for the HSCT. Fifteen patients underwent HSCT in the median age of 2.7 years (range 0.7–12.3 years). 10 (66.6%) patients received transplants from partially HLA-matched family donors, and five (33.4%) from matched donors. Busulfan-based pre-conditioning regimens, including Busulfan (1.1 mg/kg), Fludarabine (35 mg/m2), Cyclophosphamide (50 mg/kg), and Anti-thymocyte globulin (2.5–3.5 mg/kg) were used in 8 patients. The other type of preconditioning regimen used in 7 patients was total body irradiation (TBI)-based preconditioning, namely, TBI (3 Gy), Fludarabine (35 mg/m2), Cyclophosphamide (50 mg/kg), and Anti-thymocyte globulin (2.5–3.5 mg/kg). The 3-year overall survival rate of patients treated by HSCT was 71.1%. After 36 months of all patients' follow-up, 30 patients were alive, and 8 patients died following multiorgan failure, infections, and GVHD. The median survival time was 23 months [17]. Recently, a large international prospective study on 187 HLH children, with 134 having familial HLH, demonstrated promising results. Two hundred nine transplantations were done for all patients from 1 January 2004 to 31 December 2012; the last day of data entry was 31 December 2017. 78 (58%) familial HLH patients aged 1 year old at transplantation and only 10 (8%) aged ≥ 6 years. The median age was 103 days at the start of the treatment and 309 days at HSCT. The median time to transplantation was 129 days. Known conditioning regimens were Busulfan-based in 69, Fludarabine-based in 26, and Treosulfan-based in 18 patients with

familial HLH. As of 31 December 2017, a total of 120 children (64%) were alive, with a follow-up of ≥3 years in 107, ≥4 years in 96, and ≥5 years in 81 patients from the first HSCT. The 5-year overall survival post-HSCT was 66% and event-free survival was 60%; whereas, these numbers were 71% and 62% respectively for fHLH patients, significantly higher than children without verified fHLH [18].

A study on 261 patients with HLH who were transplanted between 2005 and 2018 was done in the USA to compare HSCT conditioning regimens. Bone marrow for 128, peripheral blood stem cells for 21, and umbilical cord blood for 112 patients were the source of transplantations. Twenty-six patients received transplantation from HLA-matched sibling donors, 85 from HLA-matched unrelated donors, and 150 from HLA-mismatched unrelated donors. There were four groups of regimen study; (1) Fludarabine (Flu) and Melphalan (Mel) in 123 subjects; (2) Flu, Mel, and Thiotepa (TT) in 28 subjects; (3) Flu and Busulfan (Bu) in 14 subjects; and (4) Bu and Cyclophosphamide (CY) in 96 subjects. Alemtuzumab was most likely to be provided with the Flu/Mel and Flu/Mel/TT regimens, and Antithymocyte globulin was more likely to be provided with the Bu/Cy and Flu/Bu regimens. The 5-year probability of event-free survival (EFS) was 44%, 70%, 79%, and 61% after the Flu/Mel, Flu/Mel/TT, Flu/Bu, and Bu/Cy regimens with the lowest rate in patients who received the Flu/Mel regimen. The 5-year incidence of graft failure was 42%, 15%, 7%, and 18% after the Flu/Mel, Flu/Mel/TT, Flu/Bu, and Bu/Cy regimens, respectively, where the highest risk of graft failure was in Flu/Mel regimen.

The day 100 probability of grade II-IV acute GVHD was 24%, 21%, 21%, and 30% after the Flu/Mel, Flu/Mel/TT, and Bu/Cy regimens, respectively. However, chronic GVHD risks were higher with the Flu/Mel/TT, Flu/Bu, and Bu/Cy regimens compared to the Flu/Mel regimen [19].

In the current study, we applied a reduced-intensity conditioning regimen for all three patients. After engraftment, the result of the chimerism study in patients 1 and 3 was compatible with full donor chimerism, but Patient 1 gradually showed a decrease of chimerism to about 60% several months after HSCT with stable clinical status and no more treatment. Patient 3, at all times, had full donor chimerism of about 95-100% despite pancytopenia after HSCT, and patient 2 had primary graft failure (GF). RIC has improved post-HSCT survival for HLH with less morbidity and mortality at the cost of more frequent mixed chimerism. The minimum level of donor chimerism required to prevent HLH reactivation in humans remains to be determined. Most studies reported that donor chimerism >20%-30% is protective against late reactivation. Lower levels do not, however, inescapably result in recurrences [20].

In Summary, allogenic HSCT could be a lifelong treatment for familial HLH patients, but further studies are required to elucidate some challenges related to HSCT in familial HLH regarding the timing of transplantation, donor selection, conditioning regimen, mixed chimerism, and other post-HSCT complications in familial HLH.

CONFLICTS OF INTEREST: None declared.

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