Successful haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide in a child with X-linked chronic granulomatous disease: A first report in Asia

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Abstract

Background: HLA-matched hematopoietic stem cell transplantation (HSCT) is the curative treatment for chronic granulomatous disease (CGD).

Objective: To report a case of X-linked CGD with active infection successfully treated by haploidentical HSCT with post-transplant high dose cyclophosphamide (PTCY).

Methods: A 5-year-old Thai boy with CGD was undergone for haploidentical HSCT using PTCY with correction of the phagocytic function. He presented with Chromobacterium violaceum liver abscess at the age of 9 months and experienced recurrent perianal abscess and invasive pulmonary aspergillosis even receiving antimicrobial prophylaxis. PTCY was given on day 3 and 4, after CD34+ cells infusion.

Results: The peripheral blood-nucleated cell chimerism showed 100% on day 16 and remained 100%. Dihydrorhodamine (DHR) assay on day 108 and day 214 showed normal results. Currently at 22 months post HSCT, he does not receive antibiotic and anti-fungal prophylaxis.

Conclusions: Haploidentical HSCT with PTCY could be an effective treatment option for children with CGD.

Key words: Haploidentical transplantation, Hematopoietic stem cell transplantation. Chronic granulomatous disease, Cyclophosphamide, Graft-Versus-Host Disease

Introduction

Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency caused by the genetic mutation in any of the five subunits of NADPH oxidase complex responsible for the respiratory burst in phagocytosis pathway. Patients with CGD are at increased risk of life threatening catalase-positive bacteria, Bacille Calmette-Guerin (BCG) and fungal infection, granuloma formation and inflammatory intestinal disease such as inflammatory bowel disease. Conventional treatment for patients with CGD is lifelong antibiotic and antifungal prophylaxis and immunomodulation with interferon gamma in some cases. Despite appropriate antimicrobial prophylaxis, patients with CGD have experienced infection/admission/surgery 0.71 episode per year. In addition antimicrobial prophylaxis cannot prevent inflammatory intestinal complications. Allogenic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for CGD. Children with CGD undergoing HSCT have shown to have better growth parameters and quality of life comparable to levels reported in healthy children. HSCT in children with CGD were performed using matched related donor (MRD)
or matched unrelated donor (MUD) with favorable outcome. Unfortunately, searches for the HLA-matched related donors and HLA-matched unrelated donors have greatly limited the widespread application of HSCT for CGD patients. Reports on familial haploidentical HSCT for CGD are scarce, however, haploidentical HSCT could be an option in some CGD patients for whom HLA-matched related or unrelated donors are not available. Successful haploidentical HSCT in CGD by using T-cell depletion with anti-CD3 antibodies using ex-vivo CD34+ magnetic bead selection has been reported, but the cost of these ex-vivo T-cell depletion is high and required advance technology. Herein, we report a case of X-linked CGD with active infection successfully treated by maternal haploidentical HSCT using post-transplant high dose cyclophosphamide (PTCY) with full correction of the phagocytic function.

Figure 1. The dihydrorhodamine (DHR) test results of the patient comparing before (A) and post-Haploidentical HSCT on day 108 (B) and day 214 (C).

Report of Case

A Thai boy presented with BCGitis at 4 weeks after BCG vaccination and Chromobacterium violaceum liver abscess at the age of 9 months. Dihydrorhodamine (DHR) assay was compatible with CGD (Figure 1A). Genetic analysis of all 13 coding exons of the CYBB gene has identified the mutation in exon 9 (c.905_905delTCAC). The mutation was not identified in the mother. After a prolonged course of antibiotic treatment for Chromobacterium violaceum, he was prescribed cotrimoxazole and itraconazole for the antibiotic and antifungal prophylaxis. However, he developed recurrent perianal abscess requiring prolonged intravenous antibiotics. At the age of 1 year, he was diagnosed with having pulmonary tuberculosis requiring anti-TB treatment for 1 year. One year later, he developed invasive pulmonary aspergillosis infection requiring
voriconazole treatment. He also had recurrent perianal abscess requiring intravenous antibiotics and fistulotomy. Since then he had recurrent infections even on antimicrobial prophylaxis. HSCT was discussed with parents. However, he was the only child in his family, neither matched sibling nor matched unrelated donor was available. The mother was later identified as a haploidentical donor, and the family decided to perform a haploidentical HSCT at the age of 5 years. The patient’s HLA typing was: A 33,11; B 58:01, 51:01; C 03:02, 14:02; DRB1 16:02, 14:04; DQB1 05:02, 06:01, and his mother’s HLA typing was: A 33, 11; B 44:03, 51:01; C 07, 14:02; DRB1 07:01, 14:04; DQB1 02:02, 06:01. Screening for donor-specific anti HLA antibodies was negative.

Two weeks prior to HSCT, he developed a high fever with active perianal abscess requiring an intravenous antibiotic. Subsequently his fever was resolved and then he received the conditioning regimen consisted of rabbit anti-thymocyte globulin (ATG; Thymoglobulin, Sanoﬁ, Quebec, Canada) 1.5 mg/kg/day for 3 days (day −12 to day −10), fludarabine (Flu) 35 mg/m²/day for 6 days (day −7 to day −2) and busulfan 120 mg/m²/day for 4 days (day −7 to day −4). Peripheral blood stem cells (PBSC; 10 × 10⁶ CD34+ cells/kg) were transfused on day 0. GVHD prophylaxis consisted of cyclophosphamide (50 mg/kg/day) given on day +3 and +4 and together with tacrolimus (TAC) and mycophenolate mofetil (MMF) starting on day +5 (Figure 2). MMF was discontinued on day +60. There were no toxic effects from the conditioning regimen aside from fever in conjunction with the ATG administration and the PBSC infusion. Antifungal therapy and acyclovir were continued through the transplant and GCSF was given during neutropenia. Neutrophil engraftment was noted on day +13 and platelet engraftment was noted on day +30. The peripheral blood-nucleated cell chimerism showed 100% on day 16 and remained 100% at the time of the report. DHR analysis showed the normal result on day +108 and day +214. (Figure 1B and 1C, respectively). His infectious complications post HSCT was cytomegalovirus (CMV) colitis on day +15 (plasma CMV viral load; 1,070 copies/mL and CMV PCR positive from stool). However, he was successfully treated with intravenous ganciclovir. He also developed BK virus hemorrhagic cystitis on day +30 and it resolved after supportive care. At the present time, 22 months post HSCT, he is well engrafted and shows no sign of infection or GVHD. His growth parameters have improved but still lower than those in healthy, age-matched children have.

Discussion

We have recently reported a successful haploidentical peripheral blood stem cell transplantation using post-transplant cyclophosphamide (PTCY) in a Thai child with Wiskott Aldrich syndrome. Post-transplant high dose cyclophosphamide (PTCY) was proposed to have the ability to selectively deplete the alloreactive donor T cells which are responsible for GVHD and graft rejection. It also can preserve non-alloreactive memory T cells and blood stem cells enhancing successful engraftment. Our patient had a rapid neutrophil engraftment on day +13 and rapid complete the peripheral blood-nucleated cell chimerism on day +16 which is more rapid than in previous reports of non-PTCY CGD allogeneic HSCT. The successfulness of haploidentical HSCT using PTCY in CGD was reported in 2 cases of X-linked CGD from USA and Spain: 12-year-old boy with active pericardial infection with Scedosporium apiospermum and 11-year-old boy with active inflammatory bowel disease. Among reported cases of haploidentical HSCT using PTCY in CGD, there are different in conditioning regimen. Parta et al. used non-myeloablative conditioning with busulfan, fludarabine, cyclophosphamide and total body irradiation, while Regueiro-Garcia et al. used reduced intensity conditioning regimen and GVHD prophylaxis.

**Figure 2. Time course for conditioning regimen and GVHD prophylaxis.**
### Table 1. Summary of reported cases of X-linked chronic granulomatous disease successfully treated with haploidentical HSCT with Post-transplant cyclophosphamide.

<table>
<thead>
<tr>
<th>Age at transplantation (year)</th>
<th>Reported complications</th>
<th>Type of stem cells</th>
<th>Conditioning regimen</th>
<th>Complications</th>
<th>GVHD prophylaxis</th>
<th>Donor</th>
<th>Conditioning regimen</th>
<th>Day of neutrophil engraftment after transplantation</th>
<th>Day of platelet engraftment after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Recurrent perianal abscess, invasive pulmonary aspergillosis</td>
<td>Peripheral blood stem cells</td>
<td>Fludarabine, busulfan, treosulfan</td>
<td>Fludarabine, busulfan, cyclophosphamide, sirolimus</td>
<td>Fludarabine</td>
<td>Father</td>
<td>Treosulfan</td>
<td>Day 14</td>
<td>Day 17</td>
</tr>
</tbody>
</table>

In conclusion, we have reported the first and youngest haploidentical HSCT using PTCY in CGD in Asia. Haploidentical HSCT using PTCY could be a treatment option in those pediatric CGD patients who HLA-matched related or unrelated donors are not available leading to an improvement in the quality of life.

**Conflict of interest**

The authors declare no conflict of interest

**Acknowledgments**

The authors wish to thank the inpatient and outpatient nursing and other staff in the pediatric unit at Ramathibodi Hospital for their outstanding care of our patients. This work has been supported by Ramathibodi Foundation and Mahidol University Research Grant.

**Author contribution**

- Acquisition of data and manuscript preparation: All authors
- Final approval: All authors

**References**