IJHOSCR

Case Report

International Journal of Hematology-Oncology and Stem Cell Research

# Combined Haploidentical Hematopoetic Stem Cell Transplantation and Liver Transplantation in a Pediatric Patient

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Received: 01, Jul, 2022
Accepted: 21, Aug, 2023

**ABSTRACT**

Solid organ transplantation from the same donor is an established procedure for end-stage organ failure that developed after a previous hematopoietic stem cell transplantation (HSCT); however, it is rarely done in patients transplanted with unmanipulated haplo-HSCT. There are no pediatric reports regarding the long-term performance of organ transplantation after haplo-HSCT with post-transplant cyclophosphamide (PTCY).

A juvenile myelomonocytic leukemia patient, who underwent unmanipulated haplo-HSCT with PTCY from her mother at the age of 3 years, developed chronic liver graft versus host disease (GvHD) which was refractory to specific GvHD treatment. Liver transplantation (LT) from her mother (the donor of her haplo-HSCT) was decided as the next line of treatment.

LT was performed on day 540 post-HSCT, and the donor's left lateral segment was appropriately removed and attached to the recipient. The symptoms of GvHD completely regressed in a month. The patient died on day 121 after LT, because of a possible hepato-pulmonary syndrome.

Organ failure can develop after allo-HSCT secondary to GvHD and therefore performing HSCT from a haplo-donor may be superior to a matched unrelated donor in terms of subsequent organ transplantation for organ failure.

**Keywords:** Post-transplant cyclophosphamide; Liver transplantation; Hematopoetic stem cell transplantation

## INTRODUCTION

A major limitation of solid organ transplantation is the long-term need for pharmacologic immunosuppression to prevent graft rejection, which may lead to end-organ damage, infections, and secondary malignancies. Therefore, there is a growing interest in investigating platforms for achieving permanent tolerance to prevent

immunosuppression[1,2]. Combining organ transplantation with HSCT from the same donor may provide immune tolerance to the donor; however, currently, only a limited number of patients have undergone combined organ and allo-HSCT[3-5].

Availability of a matched donor is the paramount limiting factor in combined organ transplant and HSCT. Haplo-matched relatives are easier to identify and can be found frequently; therefore, combined organ transplant and HSCT from a haplo-matched relative, is becoming increasingly important[5-7]. PTCY for prophylaxis against GvHD and prevention of graft rejection, in transplant patients is gaining popularity. The time interval between organ transplantation and HSCT required for tolerance induction is one of the greatest drawbacks of the combined transplant approach. The general approach to PTCY in combined organ transplantation and HSCT includes infusion of hematopoietic stem cells (HSCs) after revascularization of the organ and, consequently, using PTCY on the 3rd and 4th day of HSC infusion with a calcineurin inhibitor and mycophenolate[6].

There is more experience with solid organ transplantation from the same donor for end-stage organ failure that developed after a previous HSCT [8]. However, there are very few studies related to solid organ transplantations performed for end-stage organ failure, developing after unmanipulated haplo-HSCT[9-12]; only two of these cases were associated with PTCY. Furthermore, there are no reports of organ transplantation long after haplo-HSCT with PTCY in pediatric patients. The objective of this clinical case report is to highlight a case where in a pediatric patient underwent unmanipulated haplo-HSCT with PTCY from her mother, and was transplanted with the same donor´s liver long after the HSCT. This raises the importance of haplo-HSCTs in terms of a need for an organ transplantation from the same donor because of an organ failure that may develop after HSCT.

**Case presentation**

The patient was diagnosed with juvenile myelomonocytic leukemia and was admitted to our center at the age of 3 years for a second HSCT. The first HSCT, attempted at another center when she was 9 months old, was performed with 9/10 matched unrelated donor with a myeloablative conditioning regimen, and was unsuccessful. The patient had previously undergone splenectomy due to massive splenomegaly and her platelet count was over one million/ $mm^3$, leukocyte count was approximately 40,000/ $mm^3$, and she was followed-up with mercaptopurine, without any other complaints. The second HSCT was performed in our center from a 10/10 matched unrelated donor with a conditioning regimen of busulfan, cyclophosphamide, and melphalan, and GVHD prophylaxis with methotrexate and tacrolimus; however, this HSCT also resulted in graft rejection. We decided to perform unmanipulated haplo-HSCT from her mother with PTCY, when the patient was 4 years old. The following drugs were administered in the conditioning regimen: 160 mg/$m^2$ fludarabine on days –6 to –3, 42 g/$m^2$ treosulfan on days –5 to –3, and 10 mg/kg thiotepa on day –2. Stem cells harvested from donor bone marrow and peripheral blood cells on day 0, were infused with 17 × $10^6$/kg CD34+ stem cells. GvHD prophylaxis comprised tacrolimus and mycophenolate (MMF), which began on day +5 and PTCY (50 mg/kg/day) on days +3 and +5. Neutrophil and thrombocyte engraftments occurred at days 10 and 19, respectively. On day 16, a cranial MRI was performed due to the emergence of visual disturbances; based on the results of the MRI scan, a diagnosis of posterior reversible encephalopathy syndrome (PRES) was made. Due to PRES, tacrolimus was discontinued; however, skin rash and diarrhea developed after one day, which was diagnosed as acute GvHD after differential diagnosis. Methylprednisolone was prescribed along with the ongoing MMF; however, rash and diarrhea worsened to gastrointestinal bleeding in the next 3 days. Therefore, treatment was initiated with ruxolitinib on day 19. The rash was ameliorated; but hemorrhagic diarrhea continued; in addition, cholestasis developed on day 41. Extracorporeal photopheresis (ECP) was initiated on day 49 because of high-grade GvHD. Treatment with steroids, ruxolitinib, and mycophenolate was discontinued because of side effects but these drugs were administered again from time to time, while ECP was ongoing. She had mild aspergillosis with a waxing and waning pattern in the lung; therefore, she was

administered voriconazole for months. In the 3rd month of HSCT, her hemorrhagic diarrhea resolved and she was administered medication including MMF, steroids, and ECP, only for cholestatic jaundice. Conjugated bilirubin level was 15 mg/dl on the day of discharge (day 176). The patient was followed up for 9 months thereafter for hyperbilirubinemia with a fat-soluble vitamin supplement. On day 308, ECP was discontinued due to non-responsiveness, and further treatment was done with MMF and steroids only. The patient was frequently admitted to the hospital for upper GI bleeding; therefore, we decided to evaluate her for possible cirrhosis with portal hypertension, but the procedure was delayed due to her unstable general condition. On day 492, the patient experienced convulsions, which were attributed to possible PRES due to steroids. Despite supportive and medical treatment, an increase of conjugated bilirubin over 20 mg/dl and frequent upper GI bleeding were recorded; liver biopsy results revealed a fibrotic liver. Based on these findings, liver transplantation (LT) from her mother (the donor of her haplo-HSCT), was decided as the next line of treatment. Following a multidisciplinary discussion regarding optimization of the patient's clinical condition, LT was performed on day 540 post-HSCT. The recipient and donor were operated simultaneously, and the donor's left lateral segment was appropriately removed and attached to the recipient. The operation was completed without complications. Methylprednisolone (250 mg) was administered intraoperatively in the anhepatic phase and then tapered post transplant, to 125 mg, 60 mg, 30 mg, 15 mg, 5 mg, and 2.5 mg per day, respectively. The maintenance methylprednisolone dosage was 2.5 mg. Treatment with cyclosporin A (CsA) was started after LT for prophylaxis of liver rejection despite the history of PRES, because there were no reports of convulsions since months. No complications were detected in the postoperative clinical follow-ups, and the patient was discharged on the 12th postoperative day. PRES symptoms (convulsion and hypertension) developed again a month after the start of treatment with CsA; therefore, CsA was replaced with MMF. Cranial MRI was indistinct for PRES and infarction in the brain, and we decided to start administration of enoxaparin. The patient's hyperbilirubinemia normalized in 3 weeks and no GI bleeding was observed after LT. On day 579 (+39 post-LT), everolimus was added to MMF with prednisolone (2.5 mg/day) as a precautionary measure for graft rejection. However, the possibility of voriconazole-related hepatotoxicity could not be ruled out. Following normalization of liver function tests, everolimus was discontinued and the patient was treated with MMF and prednisolone (2.5 mg/day) on day 603 (+63 post-LT). It was decided that the dosage would be tapered and eventually completely stopped over a period of 3 months.

The patient developed hypoxia without respiratory distress on day 601 (+61 post-LT), which was ameloriated with minimal oxygen support. A thorax computed tomography (CT) scan revealed a decrease in the number of lesions than the previously reported aspergillosis; therefore tests were carried out to determine the condition that may cause intracardiac or pulmonary right-to-left shunt. An echocardiogram ruled out the possibility of an intracardiac shunt. Mild signs of pulmonary hypertension were observed. Agitated saline contrast echocardiography (SCE) was planned for the differential diagnosis of hepato-pulmonary syndrome (HPS) which is a pulmonary complication of liver disease characterized with intrapulmonary vascular dilatations, and abnormal gas exchange ; however, the patient developed a refractory convulsive state that required intensive care unit support. She died on day 661 (+121 post-LT) because of cardiopulmonary insufficiency. No GvHD was observed after LT and chimerism analysis had always been reported as full donor chimerism after the last HSCT. Her bilirubin levels were normal, hepatic enzymes were at the upper levels of the normal, and she had not experienced any GI-related bleeding post LT.

**DISCUSSION**

To the best of our knowledge, this is the first pediatric case of LT performed with the same donor, long after unmanipulated haplo-HSCT with PTCY. The patient´s liver disease was secondary to liver GvHD and ameloriated a few weeks after the LT, which was performed 1.5 years after HSCT. A mild possible

rejection risk was observed a month after LT and at the last follow-up, on day 121 post-LT, the patient´s liver function was satisfactory. Based on these findings, we planned to discontinue the administration of immunosuppressants in a few months. The patient died because of a respiratory event that was not associated solely with lung parenchymal disease. We evaluated the patient for a differential diagnosis of pulmonary right-to-left shunt; however, she died after a refractory convulsive event. Therefore, we were not able to carry out the agitated SCE to rule out a possible HPS. It is likely that the patient had mild HPS before LT and the symptoms deteriorated after the transplant. Although LT is curative in HPS, severe post-transplant hypoxemia occurs in 6%–21% of patients with HPS[13]. One approach to eliminate long-term immunosuppression in organ transplantation is to perform organ transplantation together with HSCT from the same donor, although this approach is still in the nascent stage[3-5]. However, in patients who have previously received HSCT from a relative donor, if an organ transplant is to be performed long after HSCT for reasons such as liver insufficiency resulting from high-grade liver GvHD, it is reasonable to perform LT from the same living donor. Combined organ transplant and HSCT from the same donor is beneficial as there is possibility of development of permanent tolerance, which prevents the requirement of immunosuppression. Although there are reports of HSCT and subsequent organ transplantation from the same HLA-matched relatives reflecting this situation[14], there are few reports of subsequent organ transplantation performed after unmanipulated haplo-HSCT[9-12], two of which were successfully treated with PTCY. To our knowledge, this is the first reported case of organ transplantation performed long after unmanipulated haplo-HSCT with PTCY in a pediatric patient. It seems that the establishment of chimerism with replacement of all host cells with donor hematopoietic and immune cells in haplo-HSCT with PTCY is sufficient for the maintenance of organic functions of transplanted organs. The transplanted organ can be considered to be an “autograft” to the immunocompetent cells in the patient.

In recent years, haploidentical HSCTs have been compared with matched unrelated HSCTs, and their advantages and disadvantages have been discussed[15, 16]. As solid organ failure after allo-HSCT occurs in up to 5% cases[17-19], it seems that performing HSCT from a haplo-donor may be superior to a matched unrelated donor in terms of subsequent organ transplantation for organ failure. Organ failure can develop after allo-HSCT secondary to transplant-related exposures and GvHD; however, conservative therapeutic strategies are only partially effective in these patients, and it is reasonable to decide earlier to perform organ transplantation from the same donor, which makes haplo-HSCT more advantageous.

**CONFLICT OF INTEREST**

None to declare.

**Abbreviations**

| | |
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| HSCT: | Hematopoetic stem cell transplantion |
| GVHD: | Graft-versus-host disease |
| PTCY: | Post-transplant cyclophosphamide |
| MMF: | Mycophenolate |
| ECP: | Extracorporeal photopheresis |
| CsA: | Cyclosporin A (CsA) |

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