Successful Allogeneic Hematopoietic Stem Cell Transplantation for a Patient with Very Severe Aplastic Anemia During Active Invasive Fungal Infection

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Allogeneic hematopoietic stem cell transplantation (HSCT) may not be considered feasible in a patient with active fungal infection due to transplant-related mortality. We report a case of HSCT performed on a 6-month-old girl, who was diagnosed with very severe aplastic anemia (vSAA) at the age of 2 months, during active invasive pulmonary aspergillosis (IPA). Despite receiving continuous antifungal treatment and multiple granulocyte infusions, her IPA was aggravated. She underwent allogeneic HSCT from a matched sibling donor using conditioning regimen of fludarabine, reduced dose of cyclophosphamide, and anti-thymocyte globulin (ATG) during IPA. After neutrophil engraftment, fever subsided and IPA improved. She was continued on voriconazole for 7 months after HSCT. She is alive with normal hematopoiesis 4 years post-transplant. Our report suggests that allogeneic HSCT using conditioning regimen of fludarabine, reduced dose of cyclophosphamide, and ATG can be a feasible option for the patients with vSAA even during active fungal infection.

Key Words: Aplastic anemia, Hematopoietic stem cell transplantation, Invasive pulmonary aspergillosis

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for severe aplastic anemia (SAA). Active fungal infection is considered as a contraindication for allogeneic HSCT due to high transplant-related mortality. However, patients with SAA (especially, very severe aplastic anemia [vSAA]), who have active fungal infection, are difficult to be salvaged with anti-fungal treatment alone, and allogeneic HSCT can be the only treatment option for them. Here, we report a patient who underwent successful allogeneic HSCT during severe active invasive pulmonary aspergillosis (IPA) using conditioning regimen of fludarabine, reduced dose of cyclophosphamide, and anti-thymocyte globulin (ATG).
Case Report

A 2-month-old girl presented with tachypnea. Complete blood count (CBC) showed pancytopenia with a hemoglobin (Hb) level of 5.0 g/dL, a reticulocyte count of 7,195/µL, a white blood cell (WBC) count of 2,000/µL, an absolute neutrophil count (ANC) of 90/µL and a platelet count of 4,000/µL. The peripheral blood smear revealed leukopenia, neutropenia, normocytic normochromic anemia with anisopoikilocytosis and thrombocytopenia. She had no organomegaly, hypo- or hyperpigmentation, facial anomaly or skeletal deformity. Her height and weight were 52.8 cm (5 percentile), 3.3 kg (3 percentile), respectively. Bone marrow aspirates and trephine biopsy specimen confirmed severe hypocellularity (<10%) without dysplasia or infiltrates, which was consistent with SAA. Marrow cytogenetics was normal, and there was no evidence of paroxysmal nocturnal hemoglobinuria clone or chromosome fragility. Echocardiography revealed that she had perimembranous ventricular septal defects (VSD) and patent foramen ovale. After diagnosis of SAA, she developed five episodes of neutropenic fever, which were resolved with empirical antibiotics.

At 6 month of age, she was admitted due to neutropenic fever. The laboratory findings were as follows: WBC 400/µL; ANC 12/µL; Hb 9.3 g/dL; platelet 23,000/µL; C-reactive protein 18.37 mg/dL; galactomannan >10.0 S/C ratio (Signal to Cutoff ratio, normal <0.5). Chest computed tomography (CT) scan revealed the consolidation in the lingual division of upper lobe of left lung and pleural effusion in the left hemithorax, which suggested invasive fungal pneumonia. There were no abnormal findings on abdominal CT. Because IPA was suspected, she was started on amphotericin B (AmB), along with teicoplanin and meropenem as an empirical treatment. After 3 days, AmB was switched to liposomal AmB because of a sustained fever. Because fever did not subside and pulmonary lesions were aggravated, liposomal AmB was switched to voriconazole. In addition, she received 8 courses of granulocyte infusions. During granulocyte infusion, fever subsided transiently without significant improvement of pulmonary lesions. Caspofungin was added to previous medication. However, fever persisted and dyspnea developed, causing her to be dependent on oxygen supply. Chest CT scan showed that pulmonary lesions were aggravated with cavitary lesion, multiple ground-glass opacity, atelectasis, and pleural effusion (Fig. 1). Because her condition did not improve despite receiving multiple courses of granulocyte infusions, and continuous antifungal treatment, she proceeded to undergo allogeneic HSCT from an HLA full matched sibling donor during her active invasive fungal infection. The conditioning regimen was composed of cyclophosphamide (60 mg/kg once daily i.v. on days −8, and −7), fludarabine (30 mg/m² once daily i.v. on days −6, −5, −4, −3, and −2), and rabbit-antithymocyte globulin (Thymoglobulin®, r-ATG, 2.5 mg/kg once daily i.v. on days −4, −3, and −2). The infused cell dose of CD34 positive cells was...
2.23×10⁶/kg. For graft-versus-host disease (GVHD) prophylaxis, cyclosporine and methotrexate (10 mg/m² on days 1, 3, and 6) were used, Alprostadil (Eglandin®) was used to prevent veno-occlusive disease (VOD), Telocplanin and meropenem were continued during transplant because of a sustained neutropenic fever. For viral prophylaxis, acyclovir was used. Monitoring for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) was performed weekly using a pp65 antigenemia test (CMV) and real-time polymerase chain reaction (CMV, EBV) once weekly in the first 3 months and monthly thereafter until 6 months post-transplant. The recovery of the ANC to more than 500/μL occurred at 10 days after stem cell infusion. Fever subsided after WBC engraftment. We stopped administration of caspofungin and continued her on voriconazole. After HSCT, her galactomannan titer was gradually decreased. On day 28, a bone marrow examination revealed normocellular marrow with bilineage regeneration and short tandem repeat (STR) revealed a complete donor chimerism. After HSCT, her galactomannan titer was gradually decreased. On day 28, a bone marrow examination revealed normocellular marrow with bilineage regeneration and short tandem repeat (STR) revealed a complete donor chimerism. Acute GVHD, VOD, CMV reactivation as well as regimen related toxicity including hemorrhagic cystitis did not occur. Chest CT scan at 4 months after HSCT showed that pulmonary lesions were nearly resolved (Fig. 1). She was continued on voriconazole until 7 months after HSCT. The patient is alive for 4 years after HSCT with normal hematopoiesis and without evidence of any infection and chronic GVHD.

**Discussion**

Although supportive cares such as transfusion, G-CSF use, and prophylactic antibiotics use have been introduced, SAA has a high mortality rate with supportive care alone [1]. HSCT from an HLA full matched sibling donor is the treatment of choice for SAA. Because invasive fungal infections (IFI) are likely to be reactivated during conditioning for HSCT and can be fatal, patients with active IFI have been excluded from transplant programs. Indeed, tissue damage resulting from IFI or its therapy can increase transplantation mortality rates [2,3]. However, HSCT may be necessary to provide the best chance for early neutrophil recovery to some patients [4]. For this reason, HSCT can be considered for the patients with an active IFI. Several authors have reported successful outcomes for HSCT in patients with active IFI [3,5-7].

In the report by Martino et al, three patients had undergone HSCT during active IFI while receiving AmB treatment [6]. All of them died of progressive fungal infection. In the report by Avivi et al, five patients had undergone HSCT with active IFI [8]. Their patients were continued on AmB or liposomal AmB. Four of five patients did not survive the transplant. Two of these patients died of fulminant fungal infection. In the report by Aki et al., however, seven of thirteen patients with active IFI died of fungal infection related causes after the transplantation [5]. Four patients survived and remained free of infection and relapse with median follow up of 306 days. In their cohort, five of thirteen patients treated with a combination of new antifungal drugs: liposomal AmB±caspofungin or voriconazole, caspofungin+voriconazole. Three of the five patients who had received a combination therapy survived. Aki et al. claimed that remarkable improvements in survival rates are due to a new generation of antifungal drugs: liposomal AmB±caspofungin or voriconazole, caspofungin+voriconazole. Our case also received a combination of voriconazole and caspofungin as antifungal agents. Our report suggests that these more effective and/or less toxic antifungal agents contributed to successful transplantation during active IFI.

Introduction of effective conditioning regimen without increasing toxicity has been reported as another factor for successful outcomes after HSCT with active IFI [7,9-11]. One of the most important factors influencing the recurrence of the invasive fungal infection is duration of profound neutropenia [9,12,13]. Cyclophosphamide (200 mg/kg) and ATG have been commonly used as the conditioning regimen for allogeneic HSCT from a matched sibling donor. In our case, we used the conditioning regimen composed of cyclophosphamide (120 mg/kg), fludarabine (150 mg/m²), and r-ATG (7.5 mg/kg) to decrease the risk of cardiotoxicity associated with high-dose cyclophosphamide, because the patient had large VSDs. Fludarabine has been successfully incorporated into conditioning regimen for unrelated HSCT for SAA [14]. With the addition of fludarabine and reduction of cyclophosphamide dose, we could achieve the same degree of immunosuppressive effect and en-
graftment without graft failure, which is considered a significant problem in HSCT in SAA patients.

In conclusion, our report suggests that allogeneic HSCT using conditioning regimen of fludarabine, reduced dose of cyclophosphamide, and r-ATG can be a feasible option for the patients with SAA even during active fungal infection.

References