Use of MSCs to Modulate Immune Suppression and Immune Reconstruction in a Patient with Aplastic Anemia Complicated by Invasive Sino-Orbital Aspergillosis

Hakan Özdoğan, Mahmut Yeral, Can Boğa, İlknur Kozanoğlu
Başkent University Adana Adult Bone Marrow Transplantation & Stem Cell Therapy Center Department of Physiology, Adana, Turkey

Abstract:
Cultured human bone marrow mesenchymal cells (MSCs) have immunomodulatory and tissue regenerative properties. This report summarizes the result of post-transplant treatment with MSCs of a 26-year-old patient with aplastic anemia complicated by invasive sino-orbital aspergillosis. The patient was treated with MSCs to benefit from the dual effects of MSCs in immune reconstitution: suppression against alloreactive T cells and facilitation of the re-engraftment process. The patient did not develop acute or chronic graft-versus-host disease. The Aspergillus infection healed completely. The engraftment failure was also ended without any complications. During his last visit in his fourth year after transplantation, the patient was in hematological remission. Human bone marrow-derived MSCs seem to have an important role in preventing or overcoming immunological complications in patients who undergo stem cell transplantation.

Key Words: xx, xx, xx

Özet:

Anahtar Sözcükler: xx, xx, xx
The infectious complications and immune dysfunction after human hematopoietic stem cell transplantation (HSCT) can activate acute graft-versus-host disease (GvHD) among patients undergoing HSCT [1]. The restoration of immune function is critical in effective treatment of invasive fungal infection and prevention of acute GvHD in these patients [2]. Mesenchymal stem cells (MSCs) are capable of regulating immune function and supporting marrow stroma [1,2,3,4,5].

Here we present a patient with very severe aplastic anemia and invasive aspergillosis who was successfully treated with hematopoietic stem cells from a sibling donor and MSCs from original and third-party donors.

Case Presentation

A 26-year-old male patient with aplastic anemia was admitted to our center with fever, periorbital swelling, periorbital pain, and bloody nasal discharge. The patient had been diagnosed with severe aplastic anemia 10 days before, when the bone marrow examination (aspiration and biopsy) was compatible with severe idiopathic aplastic anemia (bone marrow cellularity of <10%). Empirical ceftazidime initiated for infection control was ineffective. Nasal and right periorbital erythema had developed 3 days before admission. On physical examination, fever of 38.5 °C, nasal and right periorbital erythema, and right periorbital swelling were detected. Ecchymosis and petechial lesions over the lower limbs were also present. Examination of the eyes was normal and no neurological abnormalities were detected. His hematological test revealed pancytopenia (WBC: 0.33x10^9/L, Hb: 7 g/dL, Plt: 19x10^9/L). The percentages of lymphocytes, neutrophils, and eosinophils in the peripheral blood were 91%, 1.9%, and 2.4% of total nuclear cells, respectively. The percentage of reticulocytes in the peripheral blood was 0.13% of erythrocytes. Peripheral blood smear revealed normochromic and normocytic erythrocytes and decreased leukocytes (mostly lymphocytes) and platelets. Serologic tests for antibodies to hepatitis B and C virus, cytomegalovirus, Epstein–Barr virus, and human immunodeficiency viruses 1 and 2; serological tests for antinuclear antibodies; and a direct Coombs’ test were all negative. Biochemical tests revealed normal vitamin B12, folic acid, and serum iron. Computed tomography of the paranasal sinuses demonstrated a space-occupying lesion of the right maxillary and ethmoid sinus region. Histopathology showed numerous PAS-stained Aspergillus hyphae without tissue invasion. Tissue culture revealed Aspergillus fumigatus.

The patient was a student. At the time of admission, he reported that he had not used any drugs or been exposed to any known chemicals recently.

Voriconazole administration was started with limited clinical benefit (12 mg/kg/day). However, 20 days later, the patient developed fever and flare of nasal discharge.

The First Transplant

A human leukocyte antigen (HLA)-compatible sibling bone marrow donor was available for transplantation. Hence, the patient underwent non-myeloablative allogeneic peripheral HSCT with a conditioning regimen including antithymocyte globulin (5 mg/kg/day for 3 days) and cyclophosphamide (50 mg/kg/day for 4 days). Five million cells per kilogram of CD34 cells were infused from the HLA-matched sibling donor. Prophylaxis against GvHD was given with cyclosporine and methotrexate. Naturally, the patient was at high risk of GvHD because of the active fungal infection. For use prior to the possible onset of acute GvHD, human bone marrow MSCs, cultured ex vivo, were obtained from his original donor under good manufacturing practice conditions (ATI Technology Co., Trabzon, Turkey).

Following peripheral HSCT, neutrophil engraftment occurred on day +16. However, platelet recovery was not complete until day +32. Culture-expanded MSCs were infused on day +32 to the patient for hematopoietic support and their immunosuppressive effect to prevent acute GvHD. The MSC dose used was 1x10^6/kg. Platelets engrafted within 10 days following MSC infusion. On day +60, complete peripheral blood count revealed the following: Hb, 8 g/dL; WBC, 2.2x10^9/L (30% neutrophils, 68% lymphocytes, 2% monocytes); Plt, 70x10^9/L. A chimerism study revealed 100% donor T-cell chimerism in the peripheral blood. He had no cytopenia or evidence of acute GvHD on days +90 and +180. No early or late adverse events were demonstrated after MSC infusion. There was no improvement of the patient’s fungal infection after MSC infusion.

Second Transplant

The patient developed late donor-type engraftment failure in the eighth month. The use of immunosuppressive therapy including corticosteroids and cyclosporine for control of engraftment failure was ineffective. The patient therefore underwent a second transplant from the original donor using the same conditioning protocol. Human MSCs were obtained from an HLA-mismatched unrelated donor. This time, to promote engraftment, MSCs were given 4 h before stem cell infusion. The doses of MSCs and CD34 cells were 0.8x10^6/kg and 6.43x10^6/kg, respectively. No lymphocyte depletion was performed because of absence of GvHD. Times to reach an absolute neutrophil count greater than 0.5x10^9/L and a platelet count greater than 50x10^9/L
immunosuppressive treatment, in the eighth month. Bone marrow cells, unresponsive to filgrastim and efficient HSCT [7]. We observed severe destruction of engrafted rejection unresponsive to immunosuppressive therapy after aplastic anemia patients with no engraftment or graft patient recovered quickly. Engraftment occurred as we wanted, with no GVHD, and the infusion on day +32 in order to at least prevent acute GVHD. To prevent delay in infusion of MSCs, bone marrow MSCs from an HLA-mismatched unrelated donor were used based on the literature knowledge on this issue [9,10]. Successful and sustained engraftment occurred without any complications.

Although a definitive conclusion cannot be made for MSCs’ usage, we think that MSCs allowed us to obtain a positive outcome from the point of view of the literature knowledge as discussed below. It has been reported that MSC infusion together with allogeneic hematopoietic stem cells resulted in fast engraftment of neutrophils and platelets [11]. Further support for the enhancement of hematopoietic recovery was presented by Le Blanc et al. [8]. They showed that MSCs promoted donor cell engraftment in patients with primary or secondary graft failure. It was also reported that MSC treatment suppressed acute GVHD in transplanted patients, who had better overall survival than patients in the control group [12]. Other investigators supported this observation [9,10].

MSCs seem to be a promising treatment option for stem cell recipients who need fast hematopoietic recovery owing to co-morbidity.

Conflict of interest
The authors declare no conflict of interest.

References


