Fatih Erbey
Specialist, M.D
Pediatric Oncology
erbeyfa@gmail.com

İbrahim Bayram
Assist. Prof. M.D.
Pediatric Oncology
mrbairam@cu.edu.tr

Sema Yılmaz
Specialist. M.D.
Pediatric Oncology
semayilmaz@hotmail.com

Ercüment Ovalı
Prof. M.D.
Hematology
eovali@superonline.com

Atila Tanyeli
Prof. M.D.
Pediatric Oncology
atanyeli@cu.edu.tr

Dear editor,

Mesenchymal Stem Cell Experience in Acute Graft Versus Host Disease

(*Akut Greft Versus Host Hastalığında Mezenkimal Kök Hücre Deneyimi*)

Five-year-old boy with thalassemia major was underwent allogenic transplant from HLA full match sibling donor. Short term treatment of methotrexate was given in addition to cyclosporine-A (CsA) for graft-versus-host disease (GVHD) prophylaxis. Engraftment was provided on the 18th day of transplantation. On day 33 the patient progressively developed cognitive deficits and; anemia and trombocytopenia were determined. Plasma LDH and indirect bilirubin levels were 934 U/L and 3.7 mg/dl, respectively. Haptoglobulin level (10.8 mg/dl) was low but reticulocyte count (8%) was high. Anisocytosis, poikilocytosis and above 4% schistocytes were seen on peripheric blood smear. Direct Coombs was negative. Renal, hepatic and pulmonary function test were within normal limits. Transplantation associated microangiopathy (TAM) was diagnosed with these findings. 30 mg/kg pulse steroid was begun and plasma exchange was added to the therapy. CMV DNA was not detected in peripheral blood samples. Steroid dose was begun to decrease after 5 days. On day 54, haptoglobulin and LDH levels were 87.2 mg/dl and 379 U/L, respectively, despite to multiple transfusions, anemia and continuing trombocytopenia. Because of high reticulocyte and schistocyte counts defibrotide was begun. Tacrolimus was switched of CsA. Because Candida parapsilosis was grown in Hickman catheter and he was febrile, the catheter was removed and amphotericin B was started. On day 71, TAM was under partial remission, but the patient had diarrhea and; ALT/AST (243/163 U/L) and total bilirubin level (4.5 mg/dl) increased. Because of developing grade II acute GVHD (aGVHD), steroid was added. When the amount of stool increased to 95 ml/kg in a day, octreotide was added to therapy. The patient received daclizumab because of unresponsiveness to Steroids. We decided to isolate mesenchymal stem cells (MSC) from HLA full match sibling donor. Informed consent was taken from parents for the donation and transfusion of MSC. In follow up, clinical situation progressed to grade IV aGVHD (total bilirubin level and the amount of stool were found to be 18.8 mg/dl and 125 ml/kg/d, respectively). Cultured MSC (9.45 x 10^6/kg) was infused on day 95. No acute complication was recorded. After 48 hours of MSC infusion, total bilirubin level and the amount of stool were 10.2 mg/dl and 65 ml/kg/d respectively. The patient transferred to the intensive care unit due to multiple organ dysfunctions and was died because of massive pulmonary hemorrhage on day 99.

GVHD is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT), leading to serious morbidity and mortality. There is no effective therapy for severe steroid-refractory aGVHD.

MSC from bone marrow cause immunoregulation in vitro and in vivo. They do not induce lymphocyte proliferation when co-cultured with allogeneic lymphocytes and they are not targets for cytotoxic lypmhocytes or NK-cells. MSC may also be tolerated when transplanted across major histocompatibility complex barriers in humans. In vitro findings indicate that MSC are immunosuppressive. They also inhibit the formation of cytotoxic T-cells and NK-cells (1). Recently, Le Blanc et al (2), reported a case of grade IV therapy-resistant aGVHD of the gut and liver which showed rapid improvement after infusion of MSC. Ringden et al (3), gave MSC to 8 patients with

This study was presented at the VIth Meeting of the EBMT Paediatric Diseases Working Party and 1st Meeting of the EBMT Paediatric Nurses, Poznan/Poland, June 2-4, 2008.

Submitted : February 11, 2009
Revised : December 22, 2009
Accepted : March 22, 2010

Corresponding Author:
Dr. Fatih Erbey
Çukurova Üniversitesi Tıp Fakültesi
Pediatrik Onkoloji Anabilim Dalı
Kemik İliği Transplantasyon Ünitesi
Adana- Turkey

Phone : 90 - 322 3386060
Email : erbeyfa@gmail.com

steroid-refractory grades III-IV GVHD and one who had extensive chronic GVHD. Their survival rate was significantly better than that of 16 patients with steroid-resistant biopsy-proven gastrointestinal GVHD, not treated with MSC during the same period.

In our experience, the dose of MSC was 9.45 x 10^6 cells per kg body weight. In the literature, there is no concensus about optimal dose of MSC. Le Blanc et al (4), had administrated MSC to 55 patients with aGVHD. Their median dose of MSC was 1.4x10^6/kg and the maximum dose of MSC (9x10^6/kg) was similar like in our experience.

We used steroid and daclizumab therapies respectively in our patient who went to aGVHD. When steroid unresponsiveness occurred, MSC had been cultured. ThisÊtook a period of at least 3 weeks so while at the time of MSC infusion multiple organ dysfunctions were already developed. But a significant reduction was detected at bilirubin and diarrhea after MSC infusion. So we think if steroid resistant aGVHD occurs it is likely to give MSC immediately.

References

1.Tian Y, Deng YB, Huang YJ, Wang Y. Bone marrow derived mesenchymal stem cells decrease acute graft-versus-host disease after allogeneic hematopoietic stem cells transplantation. Immunol Invest 2008; 37:29-42.

2.Le Blanc K, Samuelsson H, Gustafsson B, et al. Transplantation of mesenchymal stem cells to enhance engraftment of hematopoietic stem cells. Leukemia 2007; 21:1733-1738.

3.Ringden O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft versus host disease. Transplantation 2006; 81:1390-1397.

4.Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008; 371:1579-1586.