

Unrelated Cord Blood Transplantation in Severe Combined Immunodeficiency (SCID) Patients, the First Report in Iran

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Severe combined immunodeficiency is a true pediatric emergency; children with SCID were the first patients with immunodeficiencies to be successfully transplanted with unrelated and T-cell-depleted, haploidentical bone marrow. The pattern of inheritance of SCID is X-linked and autosomal recessive (ADA def, Jak3, RAG1, RAG2, IL 7R α).

In this case report, we describe a one-year-old boy with B+T- SCID who received unrelated cord blood transplantation from the Cord Blood Bank in Germany with a 4/6 HLA antigen match. The conditioning regimen was 1mg/kg/day Busulfan and 10mg/kg/day Cyclophosphamide. Both of them were given for two days. GVHD prophylaxis was performed with Cyclosporine A and Methotrexate.

Stage III skin GVHD appeared on day 7 and gastric GVHD with a 250-300^{cc} volume appeared on day 8. On day 14, CVP, CRP, LDH and SGOT increased, blood pressure decreased and arrhythmia with T change, AV block, RBBB and bradycardia appeared. With the conclusion of Myocarditis, the patient was treated with diuretics and limitation of liquid intake, Dexamethazone, Dopamine and IVIG. The heart condition was improved gradually. During hospitalization, there was no decrease in platelet count and radiated PRBCS transfusion was performed twice. The patient was discharged on day 60. Donor cell chimerism of 60% was detected with STR-PCR, which was followed up regularly and tapered the immunosuppressive therapy.

Unrelated cord blood is a stem cell source in SCID patients and it is a curative treatment in patients without appropriate donors.

Key words: SCID, cord blood transplantation

Introduction:

The syndromes of SCID are caused by diverse genetic mutation that lead to absence of all adaptive immune function and in many cases a lack of NK cells. Patients with this group of disorders have the most severe of all of the recognized immunodeficiencies. Affected infants diarrhea, pneumonia, otitis, sepsis and cutaneous infections within the first few months of life. Growth may appear normal initially but extreme wasting usually, ensues after diarrhea and infections begin. Persistent infection with opportunistic organisms such as candida albicans, pneumocystis carini, varicella, measles, parainfluenza 3, CMV, ebstein barr virus (EBV) and bacillus calmette- guerin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for GVHD from maternal immunocompetent T cells crossing the placenta or from T lymphocyte in nonirradiated blood products or allogeneic bone marrow.

Infants with SCID have lymphopenia. This is present at birth, indicating that the condition could be diagnosed in all affected infants if routine white blood counts and manual differential counts were done on all cord bloods. They also have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro, and delayed cutaneous anergy. Patients with ADA deficiency have the lowest absolute lymphocyte counts, usually less than 500/mm³. Serum immunoglobulin concentration is diminished to absent and no antibody formation occurs after immunization. Analysis of lymphocyte population and subpopulations

demonstrate distinctive phenotypes for the various genetic forms of SCID. T cells are extremely low or absent in all types; when present, they are in most cases transplacentally derived maternal T cells.

Typically, patients with SCID have a very small thymus (<1g) that usually fails to descend from the neck, contain few thymocytes, and lacks corticomedullary distinction and Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and paracortical areas of the spleen are depleted of lymphocytes; lymph nodes, tonsils, adenoids and Peyer's patches are absent or extremely underdeveloped. Unless immunologic reconstitution is achieved through bone marrow transplantation, death usually occurs in the 1st year of life and almost invariably before the end of the 2nd year. If diagnosed at birth or within the first three months life, 95% of cases can be treated successfully with HLA-identical or T-cell depleted haploidentical bone marrow stem cells without the need for pretransplant chemoablation or post-transplant GVHD prophylaxis.

Patient introduction:

Clinical Characteristics: A one-year-old boy, a known case of B+T-SCID who was referred to the Children's Medical Center of Tehran university of Medical Sciences. He was the second child of his family. The first child of the family died from diffuse infection after BCG vaccination. The diagnosis was confirmed by family history, flow-cytometry and the consideration of immunoglobulin levels when he was two

months old. He was not vaccinated with live attenuated vaccines, and received monthly immunoglobulin 400mg/kg/IV and co-trimoxazole. The patient did not lose any weight and growth indices remained normal. He did not have any history of pulmonary infection. In a clinical examination, the anterior fontanel was open (2×1cm), the heart and lungs were normal and there was no organomegaly. In the inguinal region, mild Candidiasis lesions were detected. In an X-Ray, the chest and wrists were normal. Biochemistry findings were normal and his blood group was O⁺.

Cord blood transplantation:

The patient received an unrelated transplant with 4/6 HLA antigen matches from the Cord Blood Bank. The conditioning regimen was Busulfan 1mg/kg/day and Cyclophosphamide 10mg/kg/day for 2 days. Transplantation was performed by the injection of cord blood from a female donor with B⁺ blood group, CD34(1.77x10⁶), MNC 87%(2.73x10⁷/kg), WBC(3.14x10⁷/kg) Viability 70%. Cyclosporine A and Methotrexate were administered for GVHD prophylaxis. Cefazidime and Vancomycin were dispensed at the onset of the fever on day 3 after transplantation. Methylprednisolone was administered with the by the appearance of stage III skin GVHD on day 7 and 8. Intestinal GVHD appeared as 250-300ml-volume diarrhea. Blood, urine and stool cultures were negative. As a consequence of uncontrolled intestinal GVHD, Methylprednisolone was increased to 2mg/kg/day, and it was controlled. On +14 his blood pressure decreased and CVP increased (19-20 cm H₂O). Arrhythmia and Bradycardia, T changes, left axis deviation, AV block, and RBBB was found in ECG. CPK, LDH and SGOT increased. Heart size mildly increased. With the conclusion of myocarditis, the patient was treated with diuretics and a limitation of liquid intake, Dopamine, Dexamethazone, IVIG. Therefore, CVP decreased and arrhythmia was treated within 10 days. AS a result of platelet count decrease, radiated packed cell transfusion was performed twice. The patient was discharged on day 60, and a 60% donor cell chimerism was detected with STR-PCR, being followed up regularly and tapering the immunosuppressive therapy that consisted of Cyclosporine and oral Prednisolone.

Discussion:

X-linked SCID (XSCID) is the most common form of SCID in the United States, accounting for approximately 47% of cases. Clinically, immunologically, and histopathologically, affected individuals appear similar to those with other forms of SCID except for having uniformly low percentages of T and NK cells and an elevated percentage of B cells (T-, B+, NK -), a characteristic feature they share only with janus kinase 3 (jak3)-deficient patients with SCID. The abnormal gene in XSCID was mapped to Xq13, cloned, and found to encode the common γ (γ c) chain for several cytokine receptors, including IL- 2 , IL- 4, IL-7, IL-9,

and IL-15. The shared γ c chain functions both to increase the affinity of the receptors for the respective cytokine and to enable the receptors to mediate intracellular signaling. Carriers can be detected by demonstrating nonrandom X-chromosome inactivation or the deleterious mutations in their T, B, or NK lymphocyte. Unless donor B or NK cells develop, patients with SCID have very poor B- and NK- cell function after nonablated bone marrow cell transplantation because of the many cytokine receptor defects, despite excellent reconstitution of T-cell function by donor-derived T cells.

Autosomal recessive SCID; this pattern of inheritance of SCID is less common in the United States than in Europe. Mutated genes on autosomal chromosomes have been identified in four forms of SCID: ADA deficiency, jak3 deficiency, IL-7 receptor α chain (IL-7R α) deficiency, and RAG1 or RAG2 deficiency; other causes are likely to be discovered.

Transplantation in SCID:

The transplantation of histocompatible bone marrow has reproducibly resulted in patients developing normal numbers of donor-derived T lymphocytes with normal antigen-specific immune function. However, the patients have had variable correction of their ability to make a specific antibody, and many patients have continued to require monthly intravenous immunoglobulin (IVIG) administrations because of their inability to produce protective antibodies. After transplantation, all T lymphocytes are of donor origin, whereas in most patients, the B lymphocyte continues to be of recipient origin. Thus, the B lymphocytes with a defective IL-4 receptor are still unable to undergo immunoglobulin class switching even though normal numbers of functional donor-derived T lymphocytes are present. For reasons that are still unknown (possibly the nature of the primary γ c defect), a minority of patients develop some donor-derived B lymphocytes. Such patients can generate protective immunoglobulin G (IgG) antibodies and do not require immunoglobulin replacement therapy.

Gatti et al. (1968) first reported the successful correction of SCID by allogeneic BMT. Results have gradually improved due to earlier diagnosis, prevention of life-threatening complications such as transfusion – induced graft-versus-host disease (GVHD) , and the availability of more effective antibiotics. In Europe, the cure rate has exceeded 90% since 1983. The most remarkable features of HLA-identical sibling marrow transplantation for SCID are the lack of an absolute requirement for conditioning, the rarity of acute and chronic GVHD, and the rapid development of T and B-cell functions posttransplantat. In most cases, only lymphocytes of donor origin develop. A minority (<10%) of SCID patients who undergo HLA-identical sibling BMT are supplemented with intravenous immunoglobulin in the long term. Only approximately

20% to 30% of SCID patients (as other potential HST transplant recipients) have an HLA-identical sibling. From the literature, it appears that at least 600 patients with SCID syndromes received a T-cell-depleted marrow from a related donor, usually a parent. About 60% are alive with development of immune function. Some single centers reported success rates above 70% (Buckley et al; 1986, 1993). Overall 2-year survival in Europe is now 60%. Analyses have been performed to delineate prognostic factors for the success of these transplants. It appeared that neither the syndrome nor the T-cell depletion method used had any influence on outcome. Major factors were age, the time of transplant (the two variables are not independent), use of a protective environment, and since 1986, use of a conditioning regimen. A recent European survey showed that the outcome of T-cell-depleted, HLA-nonidentical BMT in B-SCID was worse than that in B+ SCID. This was in part related to a lower rate of engraftment, possibly caused by the ability of patient NK cells to reject donor marrow. Results of HLA-nonidentical, T-cell-depleted transplants for SCID syndromes in Europe differ significantly from those of HLA-identical transplants ($p < 0.01$). It has been recognized that a combination of favorable factors (a protective environment, optimal donor, and use of a conditioning regimen) gives a 76% survival rate compared to 42% for all other patients.

In the absence of a conditioning regimen, failure of engraftment occurred in 50% of patients, while the use of Busulfan (8 mg/kg) and Cyclophosphamide (20 mg/kg) led to a 95% engraftment rate. It also appears that a conditioning regimen promotes the rate of development of immune function, and that T- and B-cell function both recover more frequently. The latter observation seems to be corrected with the pattern of chimerism. In the absence of a conditioning regimen, engraftment of donor B (and myeloid) cell lineages occurs in 30% or less, while it is present in 75% of conditioned patients. A high dose conditioning regimen, however, may be detrimental in profoundly immune deficient patients. Thus, Busulfan 16 mg/kg and Cyclophosphamide is associated with significantly poorer survival compared to Busulfan 8 mg/kg and Cyclophosphamide (54.5% vs. 69.5% 2-year cumulative survival rate, $p < 0.05$). A European retrospective survey of 116 patients showed that in addition to GVHD, B-SCID was an adverse factor for the development of T-cell function (Haddad, et al 1998).

As no proper donor was found for this case, 4/6 HLA antigen matched cord blood was used. Busulfan 1mg/kg/day and 10mg/kg/day Cyclophosphamide 10mg/kg/day were supplemented for 2 days, to achieve more successful engraftment. After transplantation the patient contracted myocarditis. The diagnosis of myocarditis often is difficult to establish, but should be suspected in any infant or child who presents unexplained congestive heart failure. Fever is a

common occurrence in children. A sinus tachycardia out of proportion to the level of fever, associated with a quiet precardium and a gallop rhythm should strongly suggest the diagnosis.

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