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Hematopoietic Stem Cell Transplantation in Patients with Severe Combined Immunodeficiency: A Single-Center Experience

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ABSTRACT

Objective: The aim of this study was to determine the factors affecting outcomes in patients who underwent hematopoietic stem cell transplantation (HSCT) with the diagnosis of severe combined immunodeficiency (SCID). Furthermore, our aim is to share our single-center experience of HSCT among SCID patients.

Materials and Methods: The data of patients who underwent HSCT with the diagnosis of SCID between January 2014 and January 2021 in the pediatric bone marrow transplant unit of Istanbul Medipol University were retrospectively analyzed. Demographic and clinical data, treatment regimens, donor source, type of transplantation, pre- and post-transplantation infections, and complications were evaluated.

Results: Among fifteen patients who underwent HSCT, 5 (33%) were female. The mean age at diagnosis was 3 months (1-6 months), and at transplantation 6 months (3-10 months). The mean time from diagnosis to transplantation was 3 months (2-9 months). There was a history of consanguineous marriage in thirteen (87%) and sibling death in eight (53%) cases. As donors, six (40%) were siblings and five (33%) were unrelated, while four (27%) patients underwent haploid transplantation. Four (27%) patients died during the first 100 days of transplantation. The median follow-up period was 23 months (9-61 months). Overall survival probability was calculated as 73%.

Conclusion: SCID should be considered as an emergency in pediatrics. Devastating complications, including severe organ damage, life-threatening infections, and even death, could appear in case of diagnostic delay. HSCT is a currently available curative treatment option. Subjects with a confirmed diagnosis should be referred to the appropriate bone marrow transplant center and treated as soon as possible.

Keywords: Bone marrow transplantation, children, severe combined immunodeficiency

INTRODUCTION

Primary immunodeficiencies (PID) are defined by the inherited deficiency and/or dysfunction of components of the immunity. Today, more than 430 gene disorders have been reported to cause congenital defects of the immune system (1). Severe combined immunodeficiency (SCID) represents the most severe form of PIDs. SCID is a heterogeneous disease group caused by the development disorder and dysfunction of both T and B cells. It is divided into T-B- or T-B+ groups, according to the status of B lymphocytes. The frequency of PID in the community is estimated to be between 1/50000 and 100000 (2). In a study conducted in our country, it was reported as 1/10000 (3). While the X-linked form is more frequent in western countries, the autosomal recessive form is more commonly seen in our region. More than 18 gene disorders have been reported to cause SCID, so far.

Hematopoietic stem cell transplantation is the most efficient treatment option for patients with SCID, although

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several medical treatments and gene therapies have provided significant improvements in overall survival and quality of life for PID patients. Allogeneic hematopoietic stem cell transplantation (HSCT) has been performed for about 50 years in patients with PID, and the first successful bone marrow (BM) transplant was performed in 1968 (4).

Factors affecting prognosis include transplant age, pre-transplant infections and organ damage, human leukocyte antigen (HLA) compatibility, and preparation regimen. If the diagnosis is made in a timely way and HSCT is performed from a sibling with full HLA compatibility, the survival rate is over 90% (4).

MATERIALS AND METHODS

The file data of fifteen patients who underwent HSCT transplantation with the diagnosis of SCID between January 2014 and January 2021 in the pediatric BM transplant unit of Istanbul Medipol University were retrospectively analyzed. Diagnosis of the patients was established by laboratory evaluation (complete blood count, immunoglobulin (Ig) G, A, M levels, $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocyte, $CD19^+$ B lymphocyte and $CD16/56^+$ NK cell counts by flow cytometry) and confirmed by genetic testing. Age at diagnosis, transplantation age, gender, family history, HSCT type, donor type, stem cell source, preparatory regimen treatments, engraftment time and complications (pre- and post-transplantation infections), veno-occlusive disease (VOD), and graft versus host disease (GVHD) were recorded.

The local ethics committee of the hospital approved the study (June 2020-Decision no: E10840098). Written informed consent was obtained from the parents of all individuals.

Statistical Analysis

For statistical analysis, Statistical Package for Social Sciences (SPSS) package program V28.0 was used. For mean, median standard deviation data, continuous variables were used. Categorical variables were used for the frequency and percentage data. $p<0.05$ was considered significant.

RESULTS

Characteristics of the Patients

Of fifteen patients, five (33%) were girls and ten (67%) were boys. The median age of symptom onset was 2 months (1-3 months), at diagnosis 3 months (1-6 months), and at transplantation 6 months (3-10 months). The mean time from diagnosis to transplantation was 3 months (range: 2 and 9 months). The most common presentation findings were growth retardation and lower respiratory tract infection (LRTI). There was consanguinity among parents in thirteen (87%) patients, and a history of sibling death in eight (53%) patients. Clinical findings of the patients are shown in Table 1.

Table 1. Demographic and HSCT characteristics of the patients.

Patient No	Age at diagnosis (months)	Age at HSCT (months)	Sex	Consanguinity	SCID phenotype	Mutation	HSCT type	HLA compatibility	Stem cell source	Preparation regimen
1	2	5	M	Yes	T-B-NK+	*RAG1*	MSD	10/10	BM	None
2	3	6	F	Yes	T-B-NK-	*ADA*	MSD	10/10	BM	FLU/BU/ATG
3	1	3	M	Yes	T-B+NK-	*JAK3*	HAPLO	5/10	BM	FLU/BU/ATG
4	3	5	F	Yes	T-B-NK+	*RAG1*	HAPLO	5/10	BM	FLU/BU/ATG
5	6	9	F	Yes	T-B-NK+	*RAG1*	MUD	10/10	PBSC	None
6	5	9	M	Yes	T-B-NK-	*ADA*	MUD	10/10	BM	TREO/FLU/ATG
7	2	5	M	Yes	T-B-NK+	*RAG1*	MUD	10/10	UCB	None
8	1	3	M	Yes	T-B-NK-	*ADA*	HAPLO	5/10	PBSC	TREO/FLU/ATG
9	2	3	F	Yes	T-B-NK+	Unknown	MSD	10/10	BM	None
10	4	6	M	Yes	T-B+NK-	*FOXN1*	MSD	10/10	PBSC	TREO/FLU/ATG
11	3	7	M	No	T-B-NK+	Unknown	MUD	10/10	PBSC	TREO/FLU/ATG
12	5	9	F	Yes	T-B-NK+	Unknown	MUD	10/10	PBSC	TREO/FLU/ATG
13	4	10	M	No	T-B+NK-	*IL2RG*	MSD	10/10	BM	FLU/BU/ATG
14	2	6	M	Yes	T-B+NK+	Unknown	HAPLO	10/10	BM	TREO/FLU/ATG
15	4	8	M	Yes	T-B-NK-	*ADA*	MSD	10/10	BM	TREO/FLU/ATG

ADA: Adenosine-deaminase, ATG: Antithymocyte globulin, B: B cell, BM: Bone marrow, BU: Busulfan, F: Female, FLU: Fludarabine, FOXN1: Forkhead box protein N1 (FOXN1), HLA: Human leukocyte antigen, HSCT: Hematopoietic stem cell transplantation, IL2RG: Interleukin-2 receptor gamma, JAK3: Janus kinase 3 (JAK3), M: Male, MSD: Matched sibling donor, Haplo: Haploidentical, MUD: Matched unrelated donor, NK: Natural killer cell, PBSC: Peripheral blood stem cell, RAG1: Recombination activating gene 1, SCID: Severe combined immunodeficiency, T: T cell, Treo: Treosulfan, UCB: Umbilical cord blood.

Genetic analysis was performed in all the patients, and mutation was detected in eleven of them. There was no registered mutation in four patients. Adenosine-deaminase (*ADA*) mutations were found in four cases and recombination activating gene 1 (*RAG1*) mutations were registered in four cases. Interleukin-2 receptor gamma (*IL2RG*), forkhead box protein N1 (*FOXN1*), and janus kinase 3 (*JAK3*) mutations were recorded in one case.

Transplantation

As a donor source, six (40%) patients were transplanted from a fully matched sibling donor (MSD), five (33%) from a matched unrelated donor (MUD), and four (27%) from a haploidentical donor. BM samples were used in nine (60%) patients, while peripheral blood stem cell (PBSC) was used in five (33%) and cord blood in one patient as stem cell source.

While eleven (73%) cases were treated with reduced intensity conditioning (RIC) (intravenous treosulfan 14g/m^2/day, fludarabin 30 mg/m^2/day, busulfan 3.5 mg/kg/day, anti-thymocyte globulin 10 mg/kg/day), and prophylaxis for GVHD (cyclosporine A 3 mg/kg/day, methotrexate 10 mg/m^2), no regimen treatment was applied in four (27%) cases. Before transplantation, six (40%) cases had Cytomegalovirus (CMV) infection and four of them were intubated in the intensive care unit (ICU). Stem cells were applied to these cases in the ICU without regimen treatment. While three patients died during the first 28 days after transplantation, one patient died on the 45th day from sepsis and organ failure. The common features of deceased patients were poor general condition before transplantation and disseminated CMV infection. Bacillus Calmette–Guérin (BCG)

Table 2. Complications related to HSCT.

Patient No	Clinical features	BCG vaccination	BCG activation	Pre-HSCT infection	Pre-HSCT general condition	Acute GVHH	Outcome
1	Pneumonia, growth retardation	No	No	CMV	Poor, intubated	No	Fatal
2	Pneumonia, growth retardation	Yes	No		Good	No	Alive
3	Growth retardation, moniliasis	No	No		Good	Yes	Alive
4	Pneumonia, growth retardation	Yes	No		Good	Yes	Alive
5	Pneumonia, growth retardation, diarrhea	Yes	No	CMV	Poor, intubated	No	Fatal
6	Growth retardation, moniliasis	Yes	No		Good	No	Alive
7	Pneumonia, growth retardation, eczema	No	No	CMV	Poor, intubated	No	Fatal
8	Pneumonia, growth retardation, eczema	No	No		Good	Yes	Alive
9	Pneumonia	Yes	No	CMV	Poor, intubated	No	Fatal
10	Fever, diarrhea	Yes	Yes		Good	No	Alive
11	Growth retardation, moniliasis	No	No		Good	No	Alive
12	Pneumonia, growth retardation	No	No		Good	No	Alive
13	Pneumonia, growth retardation	Yes	No		Good	No	Alive
14	Pneumonia, growth retardation, eczema, moniliasis	No	No	CMV	Poor	Yes	Alive
15	Pneumonia, eczema	Yes	Yes	CMV	Good	No	Alive

BCG: Bacillus Calmette–Guérin, CMV: Cytomegalovirus, GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation

vaccine was administered in seven (47%) cases. Anti-tuberculosis prophylaxis was applied to these cases during the transplantation process. BCG reaction developed only in one case.

While acute GVHD was developed in four (27%) patients who underwent transplantation from a haploidentical donor, chronic GVHD with chronic skin involvement developed in one patient. Lymphoproliferative disease and VOD did not develop in any patient. No patient required intravenous immunoglobulin (IVIG) infusion.

Engraftment took place in all patients, except for three patients who died during the first 28 days after transplantation. Eleven (73%) surviving cases are still being followed up in our clinic as fully chimeric. The overall survival probability was calculated as 73%.

DISCUSSION

SCID represents an urgent condition with fatal outcome in case of diagnostic and treatment delay. HSCT is the only available option for treatment of SCID patients (5,6). The aim of our study was to understand the factors affecting survival and mortality at the time of diagnosis in SCID patients who were treated with HSCT.

Early diagnosis significantly affects the survival of patients with SCID (7,8). Diagnosis is delayed in countries where newborn screening tests are not applied. Patients with suspected SCID should be referred to immunology specialists as soon as possible. If the diagnosis and treatment is delayed, severe organ damage and/or death can occur.

In some cases of partial SCID, such as Omenn's syndrome, immunologic laboratory markers could be observed in the range of normal values due to maternal engraftment, resulting in diagnostic delay (9,10). Two of our cases with Omenn syndrome (*RAG1* mutations) were late-diagnosed because the total lymphocyte count, lymphocyte subgroup, and immunoglobulin levels were found to be normal. CD45RO (memory T cell) marker should be checked in terms of maternal engraftment in patients with suspected SCID, with normal first-line immunological tests.

In general, positive family history leads to timely diagnosis. In a previous study, it was reported that patients with PID who were diagnosed at birth due to a positive family history were diagnosed earlier than their family members (11). In our study, 53% (n=8) of cases had a history of sibling death, and consequently they were diagnosed earlier than the patients without a family history.

One of the most important factors affecting survival in HSCT is early transplantation. Patients transplanted during the neonatal period (first 28 days of life) had better survival rates than those transplanted later (95% vs 76%; respectively) (12). T cell development was reported to be significantly improved in patients with HSCT in the first 3.5 months (13). The mean age of transplantation of our patients was six months.

Selection of a suitable donor for transplantation in patients is of critical importance. In general, stem cell source, conditioning treatment, and GVHD prophylaxis depend on the type of donor (14). HLA typing to evaluate potential donors should be performed in all family members immediately with the diagnosis of SCID. A sibling or related donor that is perfectly matched with HLA is preferred. When the patient does not have a suitable relative, an unrelated matched donor or haploidentical donor may be selected.

RIC therapy should be preferred in the pre-transplant regimen treatment. It is less toxic when compared to full myeloablative regimens. In one study, survival four years after HSCT was 94% in the RIC group versus 58% in the myeloablative conditioning group (15). A full myeloablative regimen was applied in none of our patients. Therefore, no side effects related to regimen therapy were observed.

Disseminated CMV infection was present in five (33%) cases before transplantation, and four of them died. Infections are responsible for most of the deaths that occur before or shortly after transplantation. While 5-year survival is 50% in infants with active infection, it is 82% in infants without infection (16). The most frequently detected organisms are CMV, Epstein-Barr virus (EBV), and adenovirus (17). Other important viral pathogens include respiratory syncytial virus, parainfluenza, enteroviruses, hepatitis viruses, and herpes simplex viruses (18). Administration of live vaccines to patients with SCID could cause severe infection (19). The live attenuated BCG vaccine causes disseminated mycobacterium infection. It is recommended to give anti-tuberculosis prophylaxis during the transplantation process to patients who have received the BCG vaccine. Live vaccines should not be administered in cases with a positive family history or suspected SCID (20). The polymerase chain reaction (PCR) method should be used in the diagnosis and follow-up of viral infections. Serological tests should not be used in the diagnosis because patients with SCID cannot form antibody responses and may have positive IgG titers reflecting maternal or exogenously administered IgG (21).

CONCLUSION

When the diagnosis and treatment of SCID is delayed, severe organ damage develops, or the patient dies from infections. Early diagnosis and transplantation in the early period have a significant positive effect on the survival rate. Patients should be screened for appropriate donors as soon as they are diagnosed and referred to an experienced transplant center for transplantation.

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REFERENCES

1. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015; 136: 1186. [CrossRef]
2. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020; 40: 24. [CrossRef]
3. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalences and patient characteristics of primary immunodeficiency diseases in Turkey-two centers study. J Clin Immunol 2013; 33(1): 74-83. [CrossRef]
4. Cowan MJ, Neven B, Cavazanna-Calvo M, Fischer A, Puck J. Hematopoietic stem cell transplantation for severe combined immunodeficiency diseases. Biol Blood Marrow Transplant 2008; 14(1 Suppl 1): 73-5. [CrossRef]
5. Lankester AC, Albert MH, Booth C, Gennery AR, Güngör T, Hönig M, et al. EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity. Bone Marrow Transplant 2021; 56(9): 2052-62. [CrossRef]
6. Wahlstrom JT, Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for severe combined immunodeficiency. Curr Pediatr Rep 2015; 3: 1. [CrossRef]
7. Miyamoto S, Umeda K, Kurata M, Yanagimachi M, Iguchi A, Sasahara Y, et al. Hematopoietic cell transplantation for severe combined immunodeficiency patients: a Japanese retrospective study. J Clin Immunol 2021; 41(8): 1865-77. [CrossRef]
8. Neven B, Leroy S, Decaluwe H, Le Deist F, Picard C, Moshous D, et.al. Long-term outcome after hematopoietic stem cell transplantation of a single-center cohort of 90 patients with severe combined immunodeficiency. Blood 2009; 113(17): 4114-24. [CrossRef]
9. Muller SM, Ege M, Pottharst A, Schulz AS, Schwarz K, Friedrich W. Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients. Blood 2001; 98: 1847-51. [CrossRef]
10. Lev A, Simon AJ, Trakhtenbrot L, Goldstein I, Nagar M, Stepensky P, et al. Characterizing T cells in SCID patients presenting with reactive or residual T lymphocytes. Clin Dev Immunol 2012; 2012: 261470. [CrossRef]
11. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood 2011; 117: 3243. [CrossRef]
12. Griffith LM, Cowan MJ, Notarangelo LD, Kohn DB, Puck JM, Pai SY, et.al. Primary Immune Deficiency Treatment Consortium (PIDTC) report. J Allergy Clin Immunol 2014; 133(2): 335-47.
13. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood 2002; 99: 872. [CrossRef]
14. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. J Pediatr 2009; 155: 834. [CrossRef]
15. Dvorak CC, Hassan A, Slatter MA, Hönig M, Lankester AC, Buckley RH, et al. Comparison of outcomes of hematopoietic stem cell transplantation without chemotherapy conditioning by using matched sibling and unrelated donors for treatment of severe combined immunodeficiency. J Allergy Clin Immunol 2014; 134: 935. [CrossRef]
16. King D, Davies GE, Gaspar HB, Veys PA. Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen. Blood 2005; 105(2): 879-85. [CrossRef]
17. Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood 2017; 130: 2718. [CrossRef]
18. Brown LK, Clark I, Brown JR, Breuer J, Lowe DM.. Norovirus infection in primary immune deficiency. Rev Med Virol 2017; 27: e1926. [CrossRef]
19. Patel NC, Hertel PM, Estes MK, de la Morena M, Petru AM, Noroski LM, et al. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med 2010; 362: 314. [CrossRef]
20. Canessa C, Romano F, Lippi F, Bianchi L, Kashef S, Rezaei N, et al. Bcgitis and vaccine-derived poliovirus infection in a patient with a novel deletion in RAG1 binding site. Int J Immunopathol Pharmacol 2013; 26: 511. [CrossRef]
21. Dvorak CC, Puck JM, TePas E. Hematopoietic cell transplantation for severe combined immunodeficiencies. (Available from [updated 06/02/2022.;cited2022January].https://www.uptodate.com/contents/search/hematopoietic-cell-transplantation-for-severe-combined-immunodeficienciese).