RESEARCH PAPER

Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Metabolism: Single Center Experience Over Two Decades

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Objective: We present outcome data on hematopoietic stem cell transplantation (HSCT) in children with inborn errors of metabolism (IEM). **Methods**: We retrospectively analyzed data on children up to 18 years of age, diagnosed with IEM, who underwent HSCT between January, 2002 and December, 2020. **Results**: 24 children, (mucopolysaccharidosis – 13, Gaucher disease – 4, X-linked adrenoleukodystrophy – 4, metachromatic leukodystrophy – 2, Krabbe disease – 1) were included. Donors were matched family donors in 24%, matched unrelated donors in 34%, and haploidentical fathers in 42% of the transplants, with engraftment in 91% of children. Overall survival was 72% (55-100%) with a median follow-up of 76.5 (10-120) months, and progression-free survival of 68% (MPS-76%, X-ALD - 60%, Gaucher disease – 50%, and 100% in MLD and Krabbe disease). **Conclusion**: HSCT is an available curative option, and early age at HSCT prevents end-organ damage.

Keywords: *Alternate donor HSCT, Gaucher disease, Leukodystrophy, Mucopolysaccharidosis.*

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Inborn errors of metabolism (IEM) are a unique group of diseases in children with disordered lysosomal and peroxisomal function resulting in multiple organ damage. Enzyme replacement therapy (ERT) is feasible; however, it has its disadvantage [1]. Hematopoietic stem cell transplantation (HSCT) is the standard of care in Hurler syndrome, metachromatic leukodystrophy (MLD) (late infantile and adult-onset), late-onset globoid leukodystrophy (Krabbe disease), and peroxisomal disorders like the cerebral form of X- linked adrenoleukodystrophy (X-ALD) [2]. The principle of HSCT in metabolic disorders is cross correction, where the engrafted leukocytes secrete the enzymes that are deficient in the host [3].

Accessibility to ERT can be challenging, particularly in developing countries, due to social and financial constraints and lack of local production [4]. We present our experience in HSCT in children with IEM in India, and aim to analyze variables that impact the outcome.

METHODS

This review of hospital records was conducted in the pediatric blood and marrow transplantation unit at a tertiary care referral center in Southern India. Inclusion criteria were all children up to 18 year of age, diagnosed with an IEM, who underwent HSCT between January, 2002 and December, 2020. Exclusion criteria included children diagnosed to have inborn errors of immunity other than those included in the definition of IEM.

In children suspected of having an IEM, the diagnosis was confirmed either by quantitative enzyme analysis or identifying the underlying gene mutation. All children were evaluated by pediatric cardiologist (including an echocardiography), and a pediatric neurologist evaluated all children with X-ALD and MLD. Skeletal manifestations were assessed with radiology images including *X*-rays. Visual evoked potential and brainstem auditory evoked potential tests were performed in all children. Neuroradiologic assessment included MRI brain in children with conditions including *X*-linked adrenoleukodystrophy. Neuropsychologic assessment was performed in the neurodevelopment clinic with a trained pediatric psychologist. In those with X-ALD, HSCT was offered only if the Loes score in their MRI brain was less than 8 [5]. All family members, particularly the siblings, were screened for the underlying condition at the time of the diagnostic evaluation.

High resolution HLA typing was performed for the child, siblings (if any), and both parents. In case of no compatible match within the family, search was performed

for unrelated donors in registries worldwide. The decision to proceed with an available matched unrelated donor or a haploidentical family donor was based upon the underlying condition, the urgency for transplant, and the family's decision. The study was approved by the Institutional Review Board, and written informed consent was obtained from parents/guardians of all children at the time of the conduct of the study.

RESULTS

Twenty-four children (18 boys) (mucopolysaccharidosis – 13 (MPS I –10, MPS II–1, MPS VI-2), Gaucher disease –4, X-ALD – 4, MLD – 2, Krabbe disease –1) underwent 26 HSCTs at our center for IEM.

Among the children with Hurler syndrome, eight were 2 years of age or younger at the time of HSCT, and one child each was aged 3 year and 5 year, respectively, with normal develop-mental milestones. The five-year-old boy with MPS I was diagnosed to have Hurler-Scheie syndrome, with pre-dominantly skeletal involvement and mild developmental delay. The child with MPS II was three-year-old, and among the two children with MPS VI, one each was younger and older than two year. Among the children with X-ALD, Loes score was 2 in three children and 8 in one child. Among the four children with Gaucher disease, two had undergone splenectomy before HSCT. We docu-mented mild peripheral neuropathy in the children with MLD, and right-sided foot drop in the child with Krabbe disease.

Of the 26 transplants, six children (24%) had fully matched family donors (MFD), nine (34%) had matched unrelated donors (MUD), and eleven children (42%) had a haploidentical father as the stem cell donor. Twenty one children (84%) received myeloablative conditioning. The conditioning regimen included treosulfan/fludarabine/thiotepa in 14 children, busulfan/cyclophosphamide in three children, and fludarabine/busulfan in four children. Reduced-toxicity conditioning was used in five children (16%), of whom three children received fludarabine/treosulfan, one child received fludarabine/melphalan, and one immediate second transplant received TBI 4 gray. Twenty children (76%) had received peripheral blood stem cells as their stem cell source, and we used bone marrow and umbilical cord blood unit in three children (11.5%) each.

One child died before engraftment due to diffuse alveolar hemorrhage. Of the remaining 23 children, 21 (91%) engrafted with complete chimerism. Two children had primary graft failure, and two children had secondary graft failure within 90 days. The engraftment rate and overall graft failure in this cohort were 91% and 17%, respectively.

Acute GVHD was documented in 14 children (56%) with grade I/II skin GVHD in 4 (17%), grade III/ IV skin in four children (17%), grade I/II gut GVHD in four children (17%), grade III/IV gut GVHD in one child (5%) and grade II acute liver GVHD in one child (5%). One child had limited chronic GVHD involving the skin (5%), and one had musculoskeletal GVHD (5%). Treatment included steroids and second line agents, including etanercept and ruxolitinib. Grade IV gut GVHD was the cause of death in one child who underwent MFD HSCT for Hurler's syndrome.

The median (IQR) overall survival was 72% (55-100%) with a median follow up of 76.5 (10-120) months and progression-free survival of 68%, with a median follow up of 68.5 months (**Fig. 1**). Disease-specific survival in our cohort was 76% in MPS, 60% in X-ALD, 50% in Gaucher disease, and 100% in MLD and Krabbe disease. Survival based upon donor source in our cohort was 83% in MFD, 75% in the MUD, and 70% in the haploidentical HSCT group (**Fig. 2**).

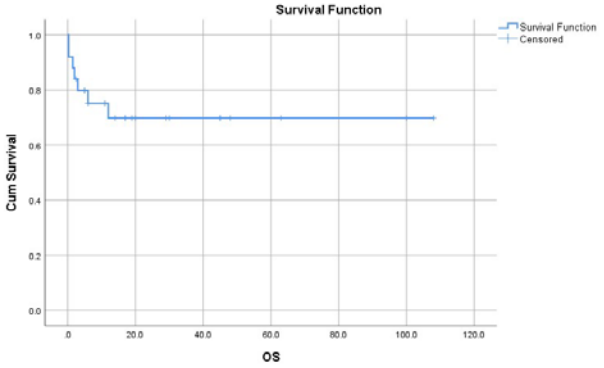

Fig. 1 Kaplan-Meier survival curve depicting overall survival of 72% with a median follow up of 76.5 (range 56.8-96.2) months.

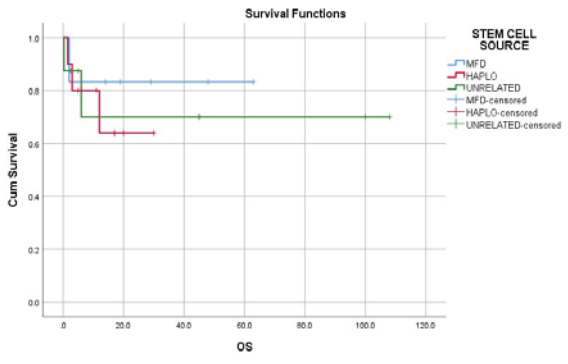

Fig. 2 Kaplan-Meier survival curve depicting overall survival based upon donor source - 83% in MFD, 75% in a MUD, and 70% in haploidentical HSCT.

WHAT THIS STUDY ADDS?

- Hematopoietic stem cells transplantation is an available curative option, and if offered early, may provide optimal outcome for these children.

Seven children died in our cohort. Among those who died, two children had Gaucher disease, two had X-ALD, and three children had Hurler syndrome. One child with X-ALD (Loes score 8) died of secondary graft failure and rapid disease progression.

Among those with MPS, the children who underwent matched unrelated HSCT had documented normal enzyme levels within one year post-HSCT (**Web Table I**). Children who received related and haploidentical HSCT had a low average enzyme level. Facial dysmorphism, corneal haziness, and organomegaly improved despite suboptimal enzyme levels. Bone disease with kyphoscoliosis required orthopedic correction. Children who underwent HSCT for Gaucher disease had resolution of organomegaly after six months. Children with X-ALD with a durable graft had stable MRI findings. Among children with MLD, we observed significant residual peripheral neuropathy requiring intensive physiotherapy and rehabilitation.

DISCUSSION

The present study reports outcome data on HSCT in children with inborn errors of metabolism in India, with overall survival of 72% and progression-free survival of 68%. Early referral for HSCT prior to onset of end organ damage resulted in better outcomes. The limitations of the study include the retrospective study design, the heterogeneous nature of underlying IEM disorders in the cohort, and the non-availability of enzyme levels for all children.

For HSCT in IEM, patient selection is the key to an optimal outcome. HSCT is better suited for MPS I, II, and VI and not suited for MPS type III and IV [6]. In X-ALD, the treatment options include observation for a score of zero to avoiding HSCT in a higher score (Loes score >9) as the HSCT accelerates the neurodegeneration in children with advanced disease [7].

The graft enzyme kinetics and the age at HSCT are the two main predictors of optimal outcome. HSCT performed early before the onset of organ damage results in a favorable outcome [8,9]. HSCT provides a constant source of enzyme production in vivo and helps in stabilizing the disease, particularly neuroregression, and corneal and cardiac-related issues [10]. The skeletal system is usually refractory to the HSCT and requires corrective surgery [6].

HSCT in IEM has an impact on the finances of the family as well. There has been a long-standing delay in diagnosis and treatment of children with IEM in India, with resultant late referral for HSCT [11]. The cost for a matched family donor HSCT in India would be approximately INR 15,00,000. For a 10 kg child with Gaucher disease, the cost for enzyme replacement would be approximately INR 7,20,000 per year, which needs to be continued throughout life.

The study highlights the curative potential of HSCT in inborn errors of metabolism and the impact of early HSCT on reversal of somatic features and halting further neuroregression. Long term follow-up with a multi-disciplinary team including cardiologists, neurologists, ophthalmologists, orthopedic surgeons and physiotherapists is essential to positively impact the quality of life. Shared care between pediatricians and specialists is paramount to early diagnosis and referral, particularly in developing countries where access to long-term ERT can be challenging.

Ethics clearance: IRB. Apollo Hospital, Chennai; No. ASH-C-S-004/03-22 dated March 23, 2022.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: VVS,RU,RR: conceptualized the study and wrote the manuscript; SKM,HV: data analysis; RC,MKM: data collection; IJ: proof reading; BR: statistical analysis. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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REFERENCES

1. Prasad VK, Kurtzberg J. Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status, and future directions. Br J Haematol. 2010;148:356-72.
2. Tan EY, Boelens JJ, Jones SA, Wynn RF. Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Front Pediatr. 2019;7:433.
3. Di Ferrante N, Nichols BL, Donnelly PV, et al. Induced degradation of glycosaminoglycans in Hurler's and Hunter's syndromes by plasma infusion. Proc Natl Acad Sci USA. 1971;68:303-7.
4. Muranjan M, Karande S. Enzyme replacement therapy in India: Lessons and insights. J Postgrad Med. 2018;64:195-99.
5. Loes DJ, Fatemi A, Melhem ER, et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology. 2003;61:369-74.
6. Wynn R. Stem cell transplantation in inherited metabolic disorders. Hematology Am Soc Hematol Educ Program. 2011;2011:285-91.

7. Raymond GV, Aubourg P, Paker A, et al. Survival and functional outcomes in boys with cerebral adreno-leukodystrophy with and without hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2019; 25:538-48.
8. Taylor M, Khan S, Stapleton M, et al. Hematopoietic stem cell transplantation for mucopolysaccharidoses: past, present, and future. Biol Blood Marrow Transplant. 2019; 25:e226-e46.
9. Chiesa R, Wynn RF, Veys P. Haematopoietic stem cell transplantation in inborn errors of metabolism. Curr Opin Hematol. 2016;23:530-35.
10. Boelens JJ, Orchard PJ, Wynn RF. Transplantation in inborn errors of metabolism: current considerations and future perspectives. Br J Haematol. 2014;167:293-303.
11. Kapoor S, Thelma BK. Status of newborn screening and inborn errors of metabolism in India. Indian J Pediatr. 2018;85:1110-1117.

Web Table I Pre- and Post-HSCT Enzyme Levels for Patients Who Underwent HSCT for Inborn Errors of Metabolism (*N*=10)

Type of donor	*Enzyme involved*	*Enzyme level at diagnosis*	*Post HSCT enzyme level*
Mucopolysaccharidosis I			
Matched unrelated donor	Alpha iduronidase	0.1	23(20-108)
Matched family donor	Alpha iduronidase	5.7	28 (20-108)
Haploidentical father donor	Alpha iduronidase	8.1	25 (20-108)
Haploidentical father donor	Alpha iduronidase	6.2	30(20-108)
Matched family donor	Alpha iduronidase	3.2	42 (20-108)
Matched unrelated donor	Alpha iduronidase	2.5	26 (20-108)
Mucopolysaccharidosis VI			
Matched sibling donor	Aryl sulfatase B	1.8	52 (84-452)
Haploidentidal father donor	Aryl sulfatase B	0.8	42 (84-452)
Gaucher disease			
Matched sibling donor	Beta glucosidase	0.1	6.2 (4-24)
Matched family donor	Beta glucosidase	0	4.7 (4-24)

HSCT – Hematopoietic Stem Cell Transplantation; [a]done 1 year post HSCT.