



## Matched unrelated donor hematopoietic progenitor cell transplantation: A report based on a single registry in India



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### ABSTRACT

**Introduction:** Currently, more than 10,000 matched unrelated donor transplants (MUDT) are performed annually worldwide. India has recorded a significant increase in the number of hematopoietic progenitor cell transplantation (HPCT) centers reporting transplants. The number of HPCTs increases by approximately 10% every year, with 1878 transplants reported by Indian stem cell transplant registries in 2016. However, published outcome data of MUDT in India are scant, with reports limited to autologous and allogenic matched unrelated transplants, which motivated us to present our MUDT data.

**Aims and objective:** To review the operations, and more importantly, the patient outcome data of a new registry in India.

**Materials and methods:** We accessed an Indian HLA donor database with high-resolution HLA typing results of 7682 (until 31st July 2018) volunteer HLA donors. The typing results were uploaded to proprietary software. The search result was considered a “match” when a 10/10 potential HLA match was found. Patients who were found to be alive through mail communication and did not exhibit signs and symptoms of disease were considered to have disease-free survival (DFS).

**Results:** During the six years of operations of the database, 1165 searches resulted in 68 10/10 matches from the registry. Of these, 11 were MUD HPCT records. At a minimum follow-up of almost 11 months, seven recipients continue to exhibit DFS.

**Conclusions:** The patient DFS data prove that even a small registry with slightly more than 7000 donors can yield reasonably good patient outcomes.

### 1. Introduction

Hematopoietic progenitor cell transplantation (HPCT) has been established as a curative management strategy for several hematologic malignancies, including congenital and acquired disorders of the hematopoietic system [1]. HPCT is feasible only if matched related donors (MRD) are found. Only 30% of the patients find suitable MRDs as a source for HPCT. However, for patients who do not find a suitable MRD, matched unrelated donors (MUDs) can be used as the potential source for HPCT treatment [2]. Globally, more than 32 million donors are registered as MUDs [3], out of which India has a low (though annually expanding) proportion of approximately 0.35 million. Because ethnicity plays a major role in identifying a suitable MUD for subsequent successful HPCT [4], finding an HLA-matched donor in India is difficult

due to its large patient population and vast ethnic diversity. A study published in 2014 revealed that the probability of finding an HLA match for an Indian patient from all the accessible global registry data was 16%; however the probability of finding a match from the Indian registries was a dismal 0.008% (donors in Indian registries were only 33,678 in 2014 compared with 22.5 million in a global HLA database called Bone Marrow Donor Worldwide) [5]. In 2008, a report revealed that 1540 Bone Marrow Transplants (BMTs) were performed at six BMT centers between 1986 and 2006 across India, but no record for MUD was available [6]. In another report, 52 HPCT centers across India reported 10,381 HPCTs between 1983 and 2015. Among these, 6240 were allogenic, whereas 4141 were autologous [7]. Even in this study [7], no data on matched unrelated donor transplants (MUDT) was available. We reviewed the operations and patient outcomes of a new

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HLA registry, Genebandhu [8], from its inception (May 2012) to demonstrate that suitable MUDs can be found by accessing an Indian HLA donor database.

## 2. Materials and methods

### 2.1. Donor (MUD) recruitment and registration

Genebandhu organized MUD recruitment drives at various institutions, predominantly in the north Indian states of Delhi-NCR, Haryana, Punjab, Rajasthan, and Uttarakhand. Drives were usually preceded by an awareness campaign comprising activities including one-to-many presentations, one-to-one interactions, banners, and posters. A total of 7682 (till July 31, 2018) donors were recruited and typed for HLA at high resolution (till July 31, 2018).

### 2.2. HLA typing and database creation

Donors were typed using a high-resolution molecular method for HLA-A, B, and C; DRB1; and DQB1. HLA allele compatibility for the HLA-A, B, and C; DRB1; and DQB1 loci was defined as a 10/10 match. The HLA typing results were uploaded to proprietary software (Prometheus). Prometheus is a specialized information system for operational activities of stem cell donor registries specifically designed by Steiner Ltd. [9] for maintaining HLA databases and allowing patients to search for donors.

### 2.3. Preliminary MUD search and search strategy

On receipt of a pretransplant matching request from a transplant physician, the patient's HLA type was entered in Prometheus to initiate a “donor search.” The software can find matches and displays the best-matched entries at the top of the list, with other potential donors in a descending order. The search result was considered a “match” when a potential 10/10 HLA match was found.

### 2.4. Formal search request

Transplant physicians planning an MUDT generate a formal search request comprising several steps in succession, as illustrated in Table 1.

### 2.5. Collection center

Once the donor is found suitable for donation based on the physical examination, CT, and IDM test, a schedule of Granulocyte Colony Stimulating factor (GCSF) administration at 10 µg/kg body weight is planned, divided as two doses subcutaneously for four days and a single dose on the 5th day prior to harvest [10]. HPCs are collected either through apheresis (HPC-A) from the peripheral or central venous catheter or bone marrow (HPC-M). The collected HPC are transported from the collection center (CC) to transplant center (TC) through a human courier. All CC were accredited by national accreditation body (National Accreditation Board for Hospitals and Healthcare Institutions).

**Table 1**

Work flow of a formal search request.

S. No	Description
1.	The potential donor is contacted and asked to appear for a physical examination
2.	During the physical examination, fresh blood sample is obtained, and the HLA typing is verified through confirmatory typing (CT). Samples are also examined for infectious disease markers (IDMs) (anti-HIV 1 and 2, HBsAg, anti-HCV, anti-CMV [IgM and IgG]). Moreover, tests for malaria and syphilis and a nucleic-acid amplification test for HIV, HBV, and HCV are conducted.
3.	The transplant physician confirms the donor after examining CT, IDM, and physical examination records and proposes the desired type of donation (HPC-apheresis [HPC-A] or HPC-bone marrow[HPC-M])
4.	The donor is contacted again and counseled for HPC donation, and written consent for donation is obtained

### 2.6. Transplant center

The collected HPC were transfused in specialized patient rooms with high-efficiency particulate air filters under positive pressure. The filters, positive pressure, and barrier nursing reduce the risk of infections, particularly in the myeloablative postinfusion phase before actual white blood cell (WBC) engraftment. Post-transplant immunosuppression constituted Cyclosporine and Methotrexate. Cyclosporine (5 mg/kg/day) was administered by continuous intravenous infusion as a loading dose starting on day –2. The dose was reduced to 3 mg/kg/day on day 4, and increased to 3.75 mg/kg/day from day 15 to day 35. Thereafter, patients received 5 mg/kg/day of oral cyclosporine twice a day until day 83 followed by a tapering dose until day 180. Methotrexate was administered at a dose of 15 mg/m<sup>2</sup> on day1 and 10 mg/m<sup>2</sup> on day 3, 6 and 11, post-infusion).

### 2.7. Post-transplant follow-up

A calendar of posttransplant follow-up was prepared by the TC for the 1st and 3rd months and 1st, 2nd, and 3rd years. The patient was followed up and considered to have disease-free survival (DFS) if the patient was found to be alive through mail communication with no signs and symptoms of disease.

## 3. Results

During the six years (May 2012–June 2018) of operations at Genebandhu, 1165 preliminary MUD search requests were received. Among these, 68 10/10 potential matches (Table 2) were identified. Out of the 68 potential matches, 25 proceeded further to the CT and IDM stages (Fig. 1). Eventually, 11 HPCTs (Table 3) materialized from the MUD database. Out of these, nine were obtained for Indian patients and two for international patients (United States and Germany). The average age of the patients was 28 (4–72) years and male to female gender was in 6:5 ratio. The clinical diagnosis was AML ( $n = 5$ ), Thalassemia major ( $n = 2$ ), ALL ( $n = 1$ ), Aplastic anemia ( $n = 1$ ), MDS ( $n = 1$ ) and Myelofibrosis ( $n = 1$ ). The patients had a minimum follow-up of almost 11 months. Two patients (Case No. 4 and 9) expired before engraftment due to severe bacterial infection. Two patients (Case No. 6 and 10) underwent engraftment with 100% donor chimerism but died of graft-vs-host-disease within two months after HPCT. Seven patients with almost 100% chimerism (99.6%–100%) exhibited DFS. Both cases of Thalassemia major (P5 and P8) were transfusion independent at the time of follow-up.

## 4. Discussion

### 4.1. Autologous versus allogenic transplants

Classically, published reports have categorized transplants into autologous and allogenic. “Autologous transplants” are thought to be misnomers because they are not actually “transplants” but “bone-marrow rescue”, treatment, which usually follow high-dose chemotherapy for treatment. We also subscribe to this belief. Moreover,

**Table 2**  
Representation of Genebandhu donor and search data (May 2012–June 2018).

Year	Total number of searches	Yearly increase in the number of donors	Number of 10/10 matches found
2012	17	80	0
2013	109	143	3
2014	163	1477	7
2015	192	1039	9
2016	299	1081	12
2017	261	2809	26
2018(31st July)	124	1053	11
<b>Total</b>	<b>1165</b>	<b>7682</b>	<b>68</b>

registry data assist only allogenic transplants and therefore, in the present study, only allogenic transplants (MUDT) were investigated.

#### 4.2. Type of transplant and suggested algorithm

Currently, the prevalent types of transplant conducted in TCs are MRDT, MUDT, cord transplants, and haploidentical transplants, with each type having its benefits and limitations [11]. MRDT presents advantages of being relatively inexpensive and having relatively short turn-around-times (TATs). The donor is usually a sibling of the patient and is mostly willing to donate. The patient and graft outcome results have been proven favorable [12]. Therefore, MRDT is always the first choice of transplant.

MUDT is slightly more expensive and has longer TATs because of the several steps involved in the process such as preliminary search, formal search (Table 1), harvest, and infusion [13]. Various stakeholders (TC, registry, and CC) are involved in the process. Moreover, the volunteer donor may not be immediately available for harvest. Donor attrition is also a widely reported concern [14].

Cord transplants have the advantage of being immunologically naïve, and therefore, a 6/6 match (two alleles at HLA-A, and B as well as DR each) is as good as a 10/10 match in MRDT or MUDT. However, finding a matched cord is sometimes difficult, and the dose of a single cord may be insufficient for an older child or adult patient [15].

The haploidentical transplant is becoming increasingly common because of the accessibility of the donor (parent or child), low cost, and short TATs [16].

However, studies on patient and graft outcomes in haploidentical transplants are limited. Considering the benefits and limitations of the different types of transplants, the algorithm for selecting the type should possibly be in the order MRDT > MUDT > cord transplants > haploidentical transplants. This order may change over time when we

have more outcome data of haploidentical transplants, especially from our setting.

#### 4.3. Making a difference

The present study demonstrated how a small registry with a database of approximately 7000 donors can assist in managing transplants in 11 patients. Seven patients with DFS is a reasonably good outcome, and this finding is consistent with other published reports [17]. Five Indian HLA registries registered with the World Marrow Donor Association are currently operational [18]. Because outcome data from all five registries were unavailable, the number of patients who would have benefitted may be much higher than that reported on the basis of data from a single registry (Genebandhu).

#### 4.4. Coordination at national level

Although characteristics such as donor registration processes and search algorithms are similar among the Indian registries, organizing MUDT remains difficult for a patient (or a patient's family) because of the multiplicity of registries (five) and differences in the costs of tests and service standards among the registries. We suggest that all Indian registries be closely coordinated at the national level with uniformity at every level (such as service standards and costs). Thereafter, patient outcome data from all the five registries may be collated to obtain a nation-wide-data of the utility of HLA registries.

### 5. Conclusion

Collecting information on transplant activity and maintaining a database must be streamlined. To change the current scenario of HPCTs in India, stem cell registries should be actively involved in the streamlining of data, which will increase the probability of finding MUDs at lower costs and shorter TATs. This measure can make India self-reliant in finding and selecting donors for HSCTs and assist in extending the life span of hundreds of recipients. The challenges to this are the lack of awareness and government support in creating and maintaining a national stem-cell registry. Stem-cell donor registries such as Genebandhu have played an active role in improving MUD transplant rates over the past few years owing to factors such as efficient donor searches by acquiring competent technology, infrastructure, and personnel.

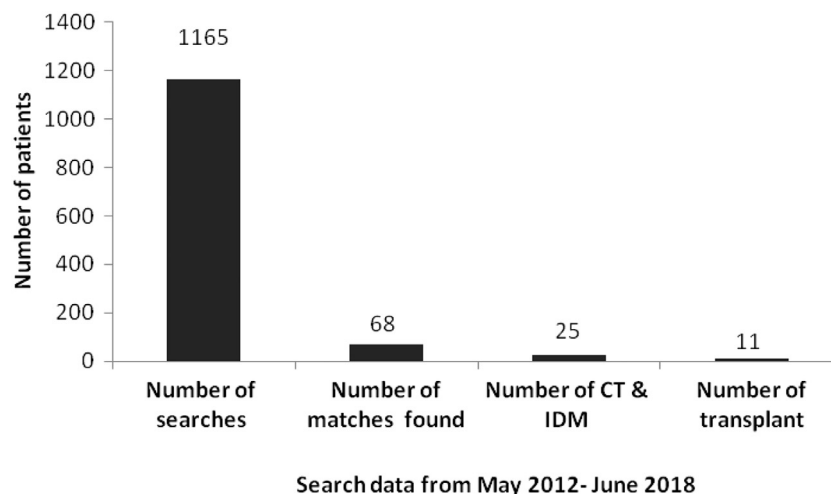


Fig. 1. Genebandhu search data (May 2012–June 2018).

**Table 3**  
Characteristics of all the 11 HPCtTs assisted by Genebandhu between May 2012 and June 2018.

Case	Age (years)	Sex	Disease	CD34 Counts (Million/Kg) recipient body weight	Infusion date	WBC Engraftment (days after infusion)	Chimerism (%)	Current status
P1	12	Male	AML (relapse)	4.51	03/03/2014	12	99.60	Disease free
P2	72	Female	AML	5.5	06/02/2015	14	100	Disease free
P3	20	Male	All	3.98	14/09/2015	15	100	Disease free
P4	9	Female	Aplastic anemia	49.7	31/08/2016	NA	NA	Expired; graft failure (day 13)
P5	4	Male	Thalassemia major	7.3	12/09/2016	18	100	Transfusion free
P6	59	Male	Myelofibrosis	5.3	13/03/2017	21	100	Expired; Acute GvHD (day 29)
P7	8	Male	AML	14.46	17/03/2017	33	100	Disease free
P8	4	Female	Thalassemia major	10.16	13/04/2017	15	100	Transfusion free
P9	35	Male	MDS	10.34	07/06/2017	NA	NA	Expired; graft failure (day 8)
P10	58	Female	AML	5.6	19/08/2017	15	NA	Expired; Acute GvHD (day 40)
P11	30	Female	AML	5.37	26/10/2017	13	100	Alive

Abbreviations: AML - Acute Myelogenous Leukemia; MDS - Myelodysplastic Syndrome; GvHD- Graft vs. Host disease.

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**Conflicts of interest**

The authors report that they have no conflict of interest.

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.03.003.

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