AVAILABILITY OF MATCHED DONOR FOR STEM CELL TRANSPLANTATION IN SEVERE APLASTIC ANAEMIA AT A TERTIARY CARE GOVERNMENT TEACHING HOSPITAL IN CHENNAI

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Abstract
Background: Hematopoietic stem cell transplant (HSCT) is curative of severe aplastic anaemia (SAA) but limited by donor availability. This study looks at the overall donor availability in severe aplastic anaemia (matched sibling and unrelated donors) in a tertiary care government teaching hospital in Chennai.

Materials and Methods: A retrospective observational study was conducted in the Department of Haematology at Rajiv Gandhi Government General Hospital and Institute of Child Health & Hospital for Children, Chennai, on 51 diagnosed cases of severe aplastic anaemia in two years. Objectives were to analyse the availability of 10/10 HLA-matched sibling or 10/10 HLA-matched unrelated donors in patients with severe aplastic anaemia. Result: A total of 51 cases were analysed. Males were 31, and females were 20, ranging from 1 year to 52 years. Siblings were available for 39 cases, in which 10/10 matches were seen only in 18 cases (35.3%). MUD donor search was conducted in 21 cases, and 10/10 matches were seen in 13 Cases (25.5%). Conclusion: In severe aplastic anaemia, inherited and idiopathic, matched sibling and unrelated transplants offer better disease-free survival and overall survival than immunosuppressive therapy. More studies are warranted to understand donor availability in genetically heterogeneous populations.

INTRODUCTION
Hematopoietic stem cell transplant (HSCT) is curative of severe aplastic anaemia (SAA) but limited by donor availability. SAA is usually a life-threatening condition with high mortality due to bleeding and infections. The preferred treatment for SAA in children and adult patients is upfront matched sibling donor (MSD) HSCT.¹² If an MSD is not available, horse anti-thymocyte globulin (ATG)-based Immunosuppressive therapy (IST) is indicated, and allogeneic-HSCT from an unrelated donor (URD) is considered the standard treatment after IST failure.³ However, IST has high failure rates, especially for long-term survivors.¹³ This study examines the overall donor availability (matched sibling and unrelated donors) in Chennai’s tertiary care Government Teaching Hospital.

AIM
The study aims to analyse the availability of 10/10 HLA-matched sibling stem cell donors for patients diagnosed with severe aplastic anaemia. Also, to analyse the availability of 10/10 HLA-matched unrelated donors in the Indian and International stem cell registry if no sibling donor is available.

MATERIALS AND METHODS
A retrospective observational study of 51 patients diagnosed with severe aplastic anaemia, both inherited and idiopathic, was considered from the Department of Haematology, Rajiv Gandhi Government General hospital, and Institute of Child Health & Hospital for Children, Chennai, from December 2020 to December 2022.
Inclusion Criteria
Patients between 1 and 60 years of age and diagnosed with idiopathic or inherited severe aplastic anaemia proven by bone marrow biopsy or genetic studies were included.

Exclusion Criteria
Transient aplastic crisis and other causes of pancytopenia were excluded.

High-resolution HLA (Human Leukocyte Antigen) typing was sent to NABL (National Accreditation Board for Testing and Calibration Laboratories) accredited laboratory for all the patients diagnosed with severe aplastic anaemia and for siblings if available. If a sibling donor is unavailable, a donor search was done in the Indian registry (DATRI) or the international registry (DKMS). All the reports were retrieved from the medical records. No additional tests were performed for the study, and the availability of donors was analyzed.

Data were entered into MS excel and calculated. All demographic data were presented as frequency and percentage.

RESULTS
During the study period, 51 cases were diagnosed as severe aplastic anaemia, including inherited and idiopathic. Out of 51 patients, 31 were males (60.8%), and 20 were females (39.2%), with male to female ratio of 1.5:1.

Age ranged from 1 year to 52 years, with a mean age of 19.62. Twenty-seven patients (52.9%) were aged less than 18 years, and 24 patients (47.1%) were aged more than 18 years [Table 1].

The predominant diagnosis was Idiopathic aplastic anaemia in 39 (76.5%) patients. 12 patients were diagnosed with inherited aplastic anaemia, which consisted of Fanconi anaemia in 10 patients (19.6%) and dyskeratosis congenita in two patients (3.9%).

Thirty-nine patients had siblings who underwent HLA typing, with the availability of one, two and three siblings in 26 (51%), 10 (19.6%) and three (5.8%) patients, respectively. In 26 patients with one sibling, 12 patients (46%) were found to have a 10/10 HLA match. In 10 patients with two siblings, four patients (40%) were found to have a 10/10 HLA match. Whereas in patients with three siblings, two out of three patients (66%) were found to have a 10/10 HLA match. Total patients with 10/10 MSD (Matched sibling donors) were 18 (35.3%). Matched unrelated donor (MUD) search results were available in 21 out of 33 eligible patients, out of which the Indian registry (DATRI) search was carried out in 19 cases, the International registry (DKMS) search was carried out in 12 cases, and both registries were searched in nine cases. 10 out of 19 patients had a 10/10 match in the Indian registry, and eight out of 12 had a 10/10 match in the international registry. MUD was available for 13 out of 21 patients, contributing to 25.5% of total cases (n=51) [Table 1].

Fully matched donor MSD 10/10 or MUD 10/10 match was available in 31 patients out of 51 (60.8%).

Table 1: Demographic data of the study.

<table>
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<tr>
<th>Gender</th>
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<tr>
<td>Male</td>
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<td>60.8</td>
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<td>Female</td>
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<tr>
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<td>11-20</td>
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<td>7.8</td>
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<tr>
<td>&gt;18</td>
<td>24</td>
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<table>
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<th>Percentage</th>
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<tbody>
<tr>
<td>&lt;18</td>
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<thead>
<tr>
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<tr>
<td>DC</td>
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<td>3.9</td>
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<td>FA</td>
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<tr>
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<td>58.9</td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>41.1</td>
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DISCUSSION
Aplastic anaemia (AA) is broadly classified into idiopathic AA and inherited AA. AA is usually a life-threatening condition with high mortality due to bleeding and infections. Severe AA (SAA) mortality approaches 70% without definitive treatment at two years. The two syndromes frequently associated with generalized bone marrow failure (BMF)/AA are Fanconi anaemia (FA) and Dyskeratosis congenita (DC), which can sometimes present with AA alone as their initial manifestation. The preferred treatment for severe AA in young and adult patients is upfront MSD HSCT. The availability of sibling donors is of limited availability. According to Center for International Blood and Marrow Transplant Research (CIBMTR), the two-year probability of overall survival after MUD HSCT was 76% in bone marrow transplant and 55% in peripheral blood stem cell transplantation.

HLA is known to be the most polymorphic genetic system in humans. Due to evolutionary history, kinship and endogamy, the Indian subcontinent has high genetic differentiation and substructuring. It is generally recommended to match for the HLA-A, HLA-B, HLA-C, HLA-DQA1 and HLA-DQB1.

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B, C, DRB1, and DQB1 alleles, also known as a "10/10 match", as this lowers the risk of acute graft-versus-host disease (aGVHD) and death following hematopoietic stem cell transplant.[10] The events such as graft versus host disease (GVHD), post-transplant viral infections, and relapse of the underlying disease mandate the success of allogeneic hematopoietic stem cell transplantation (HSCT). Selecting an immunogenetically optimal donor for each HSCT recipient who not only has a minimum allogeneic discrepancy with the recipient but also has an immunogenetic tendency for strong anti-leukemic and antiviral immune responses is the ideal strategy to reduce these unfavourable consequences.[11]

In Meta-analysis done by Peinemann F et al. in 2009 on unrelated donor stem cell transplantation in acquired severe aplastic anaemia found that potential prognostic factors for improved survival include recipient's age, interval time from diagnosis to transplant and degree of HLA match, topped the list.[12]

An unrelated donor search was done in the Indian registry (DATRI), India's largest Blood Stem Cell Donors Registry with more than 5,06,225 donors and an international registry (DKMS) with over 11 million blood stem cell donors till date. In the present study, donor availability was seen in 31 patients (60.8%), which includes both MSD and MUD.

According to EBMT 2018 data, out of 954 Allogeneic stem cell transplants done for aplastic anaemia, 450 (47.1%) were MSD and 363 (38%) were MUD transplants with bone marrow or peripheral blood stem cells as a source. Compared to our study, MSD was available in 35.3% of cases.[13] Mishra VC et al. analyzed the MUD search in 558 patients diagnosed with the haematological disorder in the Bone Marrow Donors Worldwide (BMDW) registry and found that MUD was located only in 135 (24.19%) patients. Of these 135 patients, 91 (63.0%) found a MUD in a global database and only 44 (7.88%) patients in India.[14] In a study done by Maiers M et al. on 18220 Indian patients seeking unrelated donor stem cell transplants found that 10/10 adult donor HLA match within India ranged from 14-4% with a registry size of 25 000 to 60-6% with a registry size of 1 000 000. They concluded that the proportion of matches increased logaritmically with increased registry size.[15]

**CONCLUSION**

In severe aplastic anaemia, inherited and idioopathic matched sibling and unrelated stem cell transplants offer better disease-free survival and overall survival than Immuno-Suppressive therapy. More studies are warranted to understand donor availability in genetically heterogeneous populations.

**Limitations of the Study**

1. Retrospective study
2. The study was done on a small population
3. An unrelated donor search was not done in all patients without MSD

**REFERENCES**

9. Majumdar PP. The ethnic population of India as seen from an evolutionary perspective. J Biosci 2001; 26:533–45.