The Probability of Finding a Fully Matched Related Donor: Can it Be Helpful to Determine the Best Alternative Donor Source?

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Background: In Western society, only one-third of patients who need bone marrow transplantation (BMT) would have a fully matched sibling donor (MSD). In Arab countries, there is scarce information about the likelihood of finding a fully MSD, although higher chance might be expected due to large family size.

Objective: To report the probability of finding a fully matched sibling/related donor and probe the best strategy for alternative donor source.

Design: A Retrospective Study.

Setting: King Fahad Specialist Hospital-Dammam (KFSH-D), Saudi Arabia.

Method: HLA-typing of 1,252 samples from 240 consecutive patients and their corresponding potential donors referred for HSCT were reviewed. HLA-low to medium resolution molecular typing by PCR –SSO for A, B, C, DR and DQ loci were performed on Luminex platform. The probability of finding a matched donor was determined by calculating the percentage of patients who are 10 out of 10 matched with corresponding donors.

Result: The probability of finding MSD or relative in our populations was 59%. Ninety-five percent had fully matched siblings, 4% had fully matched parent/s, and 1% had fully matched relative. However, this rate was age dependent (28% in young children, 50% in older children and 70% in adults).

Conclusion: There is an overall high-rate of finding fully matched relative donors in Saudi compared to Western societies. Strategies to develop alternative donor sources should be prioritized taking into consideration this high rate, the current difficulty in establishing large registries and the promising outcome of haploidentical and cord blood transplantation.

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Transplantations from fully matched sibling donor (MSD) have the best outcome of all the potential sources of Hematopoietic Stem Cell (HSC)[1,2]. Because HLA-genes are highly polymorphic, the chance of finding a fully MSD is about 30% in Western society. The programs for alternative donor source have been essential to extend BMT to the majority of patients lacking MSD. Accordingly, unrelated marrow donor registries developed in several countries; the cost and efforts to develop such program are substantial[3-5]. Nevertheless, the search process among these registries for matched unrelated donor is often hindered by the amount of time it takes from search initiation to donor identification[6].

In the Arab countries, there is scarce information about the likelihood of finding a fully MSD or relative; although higher chance might be expected due to large family size and high rate of consanguineous marriage. Consequently, finding an alternative donor source for the minority who lack matched relative may need a different search strategy, particularly in view of the increasing number of alternative donor sources and their promising outcomes observed over the last decade[7,8,9].

The aim of this study is to report the probability of finding a fully matched sibling/related donor in a closed community with the highest prevalence of thalassemia gene worldwide.

METHOD

The HLA-typing results for 1,252 samples were analyzed. These samples were received from 240 consecutive patients and their corresponding potential donors for HSCT assessment from June 2012 to April 2014. Fifty-four (22.5%) adult patients who underwent autologous BMT were excluded as no donor screening was requested for them; therefore, only 186 families were included in the study.

Patients' ages ranged from 1 to 73 year. Based on their age, they were stratified into three groups: group 1 eighteen (9.7%) children (ages 1-5 years), group 2 sixty-eight (36.6%) children (ages 5-17 years) and group 3 one hundred (53.8%) adults (ages 17 and above).

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HLA- low to medium resolution molecular typing by PCR –SSO for A, B, C, DR and DQ loci were performed on Luminex platform for all patients. Sibling donors were typed initially for ABC and only compatible donors would proceed to DR and DQ typing. Parents typing or extended family search was performed in cases where no available siblings or the initial sibling screening did not reveal MSD. HLA-identity was ascertained mainly by descent and SBT typing for DQ and DR for matched siblings. For matched parents and non-sibling donors, SBT typing for A, B, C, DR, DQ and DP loci were performed to confirm identity. In 2014, we started to perform A, B and DR for initial donor screening.

All haplotypes were reviewed for patients with matched siblings, particularly for those with multiple MSD and those haplotypes associated with no available matched relative despite extensive family search to see if there is a relation between certain HLA-haplotypes/phenotypes and the probability of finding or not finding MSD.

All patient and donor data were entered into a Microsoft Excel spreadsheet. The probability of finding a matched donor was determined by calculating the percentage of patients who were 10 out of 10 matched with corresponding donors. Two-proportion z-test was used to find the statistical significances of different proportions of donors in the three age groups.

RESULTS

One hundred eighty-six families were studied. One hundred-nine (59%) patients were found to have fully matched siblings/relatives (95% had fully matched siblings, 4% had fully matched parents, and 1% had fully matched relatives with or without matched siblings).

The percentage of finding matched siblings/relative according to age categories were as follows:

Group 1 with an average number of screened donor of 4.7; five (28%) had fully matched donor. Group 2, with an average number of screened donor of 5.8; thirty-four (50%) had fully matched donor. Group 3 with an average number of screened donor of 5.3; seventy (70%) had fully matched donor. The percentage of patients having fully matched donors in each age category is shown in figure 1.

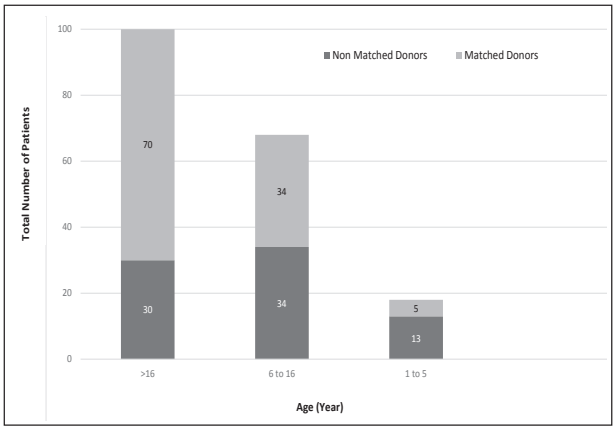

Figure 1: Percentage of Patients with Matched Donor According to Patient Age

Patients found to have compatible donors were either having one, two, three or multiple (4 and above) fully matched donors. The percentage of patients with compatible donors according to the number of donors is shown in figure 2. Ninety-one (49%) patients had, at least, two compatible donors.

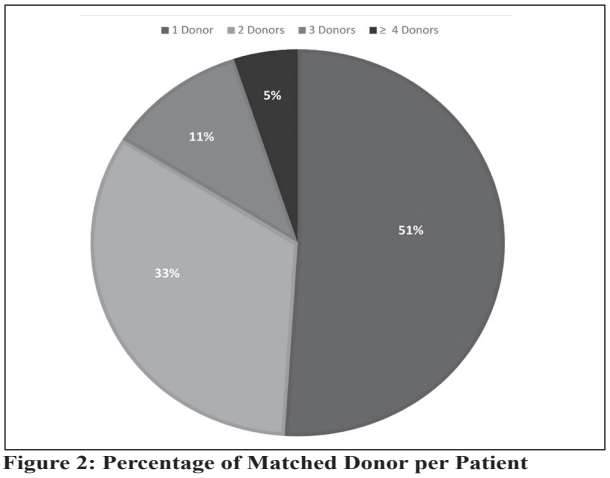

Figure 2: Percentage of Matched Donor per Patient

The HLA- phenotypes for five different families in whom multiple (≥4) matched relatives were identified are illustrated in table 1.

Table 1: HLA- Phenotypes for Patients with Multiple (≥4) Matched Donors

Number of Matched Donors per Number of Screened Donors	A	B	C	DRB1	DQB1
5/12	24/29	35/55	01/04	13/16	05/06
5/10	11/29	35	04	11/16	03/05
4/6	26/68	08/38	07/12	16	05
4/7	30/31	42/51	17/15	03	02/04
4/9	02/03	15/35	04/12	03/16	02/05

Apart from the 3 (1.6%) patients demonstrated HLA-gene recombination (crossover), no unusual haplotypes and/or linkage disequilibrium in patient's HLA-typing to explain the failure to find matched sibling in large families who have ten or more screened siblings or underwent an extended family search. The HLA-phenotypes for families in whom more than ten siblings and relatives that were screened failed to find a match revealed three patients inherited haplotypes having gene crossovers, see tables 2 and 3. The haplotypes of the corresponding siblings were omitted from the table for the sake of simplicity.

Table 2: HLA- Phenotypes for Patients Who Underwent Extensive Search but No Match

	Patient	Number of Screened Siblings/ Relative	A	B	C	DRB1	DQB1
1	A S	23	01/02	18/73	12/15	03/15	02/06
2	F A	18	68	35	04	16	05
3	A S	16	11/31	35/51	04/16	03/13	02/06
4	S Q	16	03/24	18/35	12/15	10/14	05
5	*M K	12	26/30	18/39	02/07	11	03/05
6	A H	11	29/31	07/51	15	10/13	05/06
7	H G	11	01/32	37/73	06/15	10	05
8	A J	11	02/32	35/52	04/12	15/16	05/06
9	*M M	10	43/68	15/52	07/12	03/04	02/03
10	*M D	10	02/68	14/18	07/08	03/08	02/03

***patients with gene recombination**

Table 3: HLA-Haplotypes for Patients with Gene Recombination

		Haplotypes	A	B	C	DRB1	DQ
1.MK	Patient 1	ba	26	39	07	11	03
		d	30	18	02	11	05
	Father	a	02	39	07	11	03
		b	26	35	15	10	05
	Mother	c	30	18	02	11	05
		d	32	08	07	03	02
2.MM	Patient 2	a	68	15	7	04	N/A
		cd	43	52	12	03	N/A
	Father	a	68	15	N/A	04	N/A
		b	26	15	N/A	07	N/A
	Mother	c	43	15	N/A	07	N/A
		d	24	52	N/A	03	N/A
3.MD	Patient3	a	68	18	08	03	N/A
		cd	02	14	07	08	N/A
	Father	a	68	18	08	03	N/A
		b	01	18	07	16	N/A
	Mother	c	02	14	07	07	N/A
		d	02	58	07	08	N/A

DISCUSSION

HLA-genes are highly polymorphic with the frequency of alleles and haplotypes varying widely among different populations. In a setting with rarity and difficulty of establishing accredited HLA laboratories for volunteer HLA-typing, the implementation of other alternative donor sources may be a priority or at least of equal importance and should be assessed simultaneously with registries option.

The overall 59% probability of finding a fully matched sibling/ relative in our population is nearly twice of what was reported in western societies, and slightly lower than what was reported in Jordanian population[10]. Nearly half of the patients with matched donors had more than one matched relatives attributed to large families, leaving less than a third in need for alternative donor source.

The majority of patients with compatible donors were found in the adult group, while young children had the least chance of finding an MSD. These young children generally came from small sized families and usually were the only children in the family with no available siblings; therefore, parents or extended family are usually included in the initial donor search with less chance of having a full match. This low chance compared to older patients should influence alternative donor source strategies. We believe that variable options should be prioritized according to actual demand, availability of HLA laboratories and the ease of establishing high complexity testing for efficient volunteer registries.

Currently, only three laboratories are supporting HSCT program throughout the Kingdom of Saudi Arabia; they provide HLA typing mainly for their patients and corresponding donors. Establishing efficient HLA laboratories dedicated for large registries implicates huge cost and efforts not only for the establishment, but also public awareness is needed. Patients in the young children group (less than five) who really have the problem of lacking matched donor might benefit from registries. Establishing umbilical cord banks might be a better option and would be easier to establish.

In this study, older children and adults have a better chance of having matched donors. This was expected as the patients get older more siblings would be born and the chance of finding matched siblings would increase. The difference in the proportion of screened donors was statistically not significant in the three groups; P-Value=0.291 between group 1 and 3 and P-Value=0.911 between group 1 and 2. Non-sibling donors constitute the majority of screened donors in the younger groups compared to sibling donors in adults. In the latter group, haploidentical donor source should be thought of as the first option for patients lacking MSD. This option might be the fastest way to extend HSCT to high-risk adults. Furthermore, a haploidentical donor would be available for almost all patients and could be identified and mobilized immediately, particularly in our societies where families are closely bonded and remain linked throughout their lives. Obviously, one major advantage to this approach is saving the time needed for donor search in large registries that could be very critical for HSCT success.

Patients with multiple compatible donors might have favorable HLA-phenotypes, the haplotypes A29, B35, C4, DR16 and DQ5 were reported twice in all patients with compatible donors; in both of them, five fully matched donors were found. Whether carrying this haplotype increases the chance of finding MSD or this haplotype is more frequent in such group of diseases need further studies.

We found three HLA-gene recombination events had occurred in three patients making them difficult to match with their siblings. No other causes could explain the failure to have compatible donor even though up to 23 siblings were HLA- typed in some of these families. However, this number is too small to draw a solid conclusion, and further studies are needed to explore the relation between certain HLA- haplotypes and the chance of finding or limiting compatible donor.

CONCLUSION

There is an overall high-rate of finding fully matched relative donors in Saudi Arabia compared to Western societies. Strategies to develop alternative donor sources should be prioritized taking into consideration this high rate, the current difficulty in establishing large registries and the promising outcome of haploidenticlal and cord blood transplantation.

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