Histocompatibility testing for allogeneic hematopoietic stem cell transplantation in Albania: Evidence for the need of an unrelated donor stem cell national registry

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Abstract

Aim: The purpose of this study was to determine the actions that should be taken to improve the situation of Hematopoietic Stem Cell (HSC) donation in Albania.
Methods: In this study there were included 813 individuals (patients and donors), that have been examined at our laboratory for allogeneic stem cell transplantation purposes and for the definition of normal Human Leukocyte Antigens (HLA) allele frequency distribution in the Albanian population. HLA-A, -B, -DRB1 genotyping was performed by polymerase chain reaction sequence specific methods. The statistical analysis was conducted using Fisher's (two-tailed) exact test.
Results: Overall, there were included 70 patients and 233 related donors. The age of the patients ranged from 1 year to 62 years (mean: 23 years). Of these, 44 (62.9%) were males and 26 (37.1%) were females. The age of the donors ranged up to 78 years (mean: 33.8 years). In the donor group, 108 (46.4%) were males and 125 (53.6%) were females. An HLA identical sibling donor has been found in 27 (38.6%) of our patients. HLA-A, -B and DRB1 profile of 43 (61.4%) patients that lacked a full HLA matched sibling was compared with HLA genotyping data of 510 normal Albanian unrelated individuals. Fifteen unrelated potential donors were HLA compatible with 10 out of the 43 patients.
Conclusions: The data reported in this preliminary study underline the actual necessity of organizing an Albanian national unrelated donor registry which can withstand the needs of Albanian patients for allogeneic HSCT.

Keywords: Albania, hematopoietic stem cell transplantation, histocompatibility testing, HLA Antigens.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently a well-established curative therapy for an increasing number of hematologic and genetic diseases (1-3). Successful HSCT depends on many non-genetic factors (disease, disease stage, age, sex, or treatment regimen), but the role of the Human Leukocyte Antigen (HLA) system remains a key issue for the outcome of HSCT (4-6).

The development of molecular typing techniques has allowed a refined HLA matching, thus contributing to the reduction of the immunologic conflict risk due to the host-versus-graft or graft-versus-host allorecognition. Full HLA matching between the donor and the recipient has demonstrated a significant positive effect on allogeneic HSCT outcome (7). Related family members are primarily considered as candidates for the hematopoietic stem cell (HSC) donation and siblings are most often selected since they have the greatest chance of being full HLA-matched with the recipient (8-10). Due to the fact that about 70% of patients needing a HSCT lack a suitable sibling donor, the availability of HLA matched unrelated donors (UD) is the only alternative for increasing the number of patients who might benefit from allogeneic HSCT (11). The advances in the field of immunogenetics, together with the growth of donor registries and umbilical cord blood banks worldwide have increased the possibility of life-saving HSCT from UD (12,13). Several studies have reported that the best fitted HSC-UD are those found within the same population as the patient, since they have the best chances to offer not only full allele but also full HLA haplotype matching (14). In this context, the availability of an UD-HSC registry in a defined population is extremely useful in order to provide all the available donor options for the patients from this population needing a HSCT.

The purpose of this study was to analyze the data collected in our center, in order to point out the actions that should be taken for the improvement of the situation of HSC donation in Albania and particularly for highlighting the current need for an Albanian donor stem cell registry.

Methods

Patients

In this study there were included a total of 813 individuals (patients and donors), that have been examined at our laboratory during the time interval January 2008 to December 2013 for allogeneic HSCT purposes and for the definition of normal HLA allele frequency distribution in the Albanian population.

Collection and analysis of DNA samples

The tested individuals were studied using their period in order to find a HLA compatible related donor for HSCT purposes. Thirty seven (52.9%) of the patients have been referred from the Department of Hematology and 33 (47.1%) from the Department of Pediatric Oncohematology, both from the University Hospital Center "Mother Teresa" in Tirana, Albania.

Fifteen (21.4%) of the patients have been referred from hospital centers abroad, such as Italy, Greece or Turkey where Albanian patients needing HSCT were hospitalized and these centers have sent a request for finding a HLA compatible donor among the family members living in Albania.

The age of patients ranged from 1 year to 62 years (mean: 23 years, median 18.5 years, 95%CI=18.4-27. 6 years). Of these, 44 (62.9%) were males and 26 (37.1%) were females.

The main etiologic diagnoses with the corresponding number of patients in a decreasing order are presented in Table 1.

Related donors

There were typed 233 related donors in order to find a HLA full identical sibling. The age of the donors ranged up to 78 years (mean: 33.8 years, median 34.0 years, 95%CI=31.5- 36.1 years). Of these, 108 (46.4%) were males and 125 (53.6%) were females. The number of all family donors for each patient ranged from 1 to 9

Table 1. The diagnoses of 70 Albanian patients needing HSCT

Diagnoses	Number of patients (%)
Hereditary Hemoglobinopathy (Talassemia major/	21 (30.0%)
Drepanocitosis/Talaso-drepanocitosis)	
Acute Lymphoblastic Leukemia	15 (21.5%)
Myeloma	7 (10.0%)
Aplastic Anemia	6 (8.5%)
Chronic Lymphoid Leukemia	5 (7.1%)
Acute Myeloid Leukemia	5 (7.1%)
Chronic Myeloid Leukemia	3 (4.3%)
Non-Hodgkin Lymphoma	3 (4.3%)
Hodgkin Lymphoma	2 (2.9%)
Myelodisplasia	2 (2.9%)
Wiskott-Aldrich syndrome	1 (1.4%)

(mean: 3.4, median 3.0, 95%CI=2.9-3.8), whereas the number of sibling donors per patient ranged from 1 to 6 (mean: 2.1, median 2.0, 95%CI=1.8-2.4).

All the donors were family related volunteer donors, except three of them who were fetuses (of male sex) typed through DNA extracted from umbilical cord through amniocentesis.

Detailed data concerning the related donors are shown in Table 2.

Table 2. The data about the 233 HLA-typed related donors

Related donors	Number of donors (%)
Sisters	77 (33.1%)
Brothers	69 (29.6%)
Mothers	32 (13.7%)
Fathers	31 (13.3%)
Second degree relatives	24 (10.3%)

An HLA identical sibling donor (including the three fetus-donors) was found in 27 (38.6%) of our patients. An HLA haploidentical sibling was identified in 31 (44.3%) of the patients and in 12 (17.1%) of them only HLA full non-identical related donors were detected.

Unrelated donors

Among the 43 (61.4%) patients that lacked a full HLA matched sibling, we investigated for the eventual presence of a HLA-A, -B and -DRB1 allele-group full compatibility with 510 normal Albanian unrelated individuals that we considered as a pilot study group for an Albanian donor stem cell registry. This group consisted of healthy blood donors, students of the Faculty of Medicine or unrelated organ and HSCT donors that have been HLA-genotyped in order to study the normal HLA profile of the Albanian population or for living kidney or related HSCT donation.

We found among them 15 unrelated potential donors that resulted HLA-A, -B and -DRB1 full matched with ten out of the 43 Albanian patients, for whom a full HLA-identical related donor could not be found. A list of the HLA-A, -B and -DRB1 allele-groups shared between these ten patients and their 15 HLA full matched UD is presented in Table 3. In this table we have listed the allele-groups detected in the normal Albanian population in a decreasing frequency order (15). It is worth mentioning that almost all of these shared allele-groups have a high frequency (>5%) in the Albanian

population. Only HLA-A*68, HLA-B*41 and HLA-DRB1*01 allele groups that were shared only once had a frequency less than 5% (respectively: 4.68%, 0.31% and 3.64%). The shared allele-groups between the 15 potential donors and the ten patients represented the most frequent HLA-A, HLA-B and HLA-DRB1 allele-groups in the Albanian population (respectively: 90.6%, 53.1% and 68.4%).

Table 3. HLA-A, -B and -DRB1 shared alleles between ten of the patients lacking a HLA identical sibling and their HLA matched unrelated donors detected

*HLA-A Locus		*HLA-B Locus		*HLA-DRB1 Locus	
HLA-A allele groups (allele % in Albanian population)	**Number of copies of common allele groups found**	**HLA-B allele groups (allele % in Albanian population)**	**Number of copies of common allele groups found**	**HLA-DRB1 allele groups (allele % in Albanian population)**	**Number of copies of common allele groups found**
A*02 (30.62)	4	B*51 (17.25)	6	DRB1*11 (27.54)	8
A*24 (15.93)	3	B*35 (14.18)	6	DRB1*16 (12.41)	5
A*01 (10.00)	1	B*18 (11.64)	3	DRB1*13 (11.94)	1
A*03 (9.06)	4	B*44 (7.81)	-	DRB1*04 (7.84)	-
A*32 (7.81)	3	B*08 (5.62)	1	DRB1*15 (7.58)	-
A*11 (7.50)	2	B*07 (4.25)	-	DRB1*14 (7.49)	1
A*26 (5.00)	1	B*40 (4.13)	3	DRB1*07 (5.99)	-
A*68 (4.68)	1	B*37 (3.62)	-	DRB1*03 (5.40)	2
A*23 (2.18)	-	B*15 (3.30)	-	DRB1*01 (3.64)	1
A*33 (1.25)	-	B*48 (3.13)	-	DRB1*08 (3.29)	-
A*31 (1.25)	-	B*27 (2.50)	-	DRB1*12 (3.10)	-
A*29 (1.25)	-	B*38 (2.50)	-	DRB1*10 (2.06)	-
A*25 (0.93)	-	B*55 (2.50)	-		
A*43 (0.62)	-	B*58 (2.18)	-		
A*74 (0.62)	-	B*13 (1.87)	-		
A*30 (0.31)	-	B*39 (1.87)	-		
A*69 (0.31)	-	B*53 (1.56)	-		
		B*47 (1.25)	-		
		B*57 (1.25)	-		
		B*41 (0.31)	1		

*HLA-A, -B and -DRB1 allele-groups are listed in a descending order according to the allele groups frequency rates found in the normal Albanian population

Discussion

Allogeneic HSCT is a last rescue, life-saving procedure for many fatal diseases, mainly of malignant or genetic nature. According to the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT rates differ substantially between European countries, ranging from zero reported rates in some Eastern European countries such as Albania, Armenia, Georgia and Moldova (referring to countries with a population more than one million inhabitants), to 198 per ten million inhabitants per year in Switzerland, and 311 per ten million population in Germany (16). The data reported from five developed European countries (Switzerland, France, Germany, Italy, and Netherlands) show that the related donor allogeneic HSCT rates vary little between these countries, ranging between 89 to 128 per ten million inhabitants per year. In contrast, the rate of unrelated donor allogeneic HSCT in these countries vary from 109 in Switzerland to a maximum of 218 per ten million population per year in Germany (17). Currently, no HSCT is carried out in Albania and, hence, the Albanian patients in need for this procedure must be sent abroad. At any case, these patients need a HLA matched donor as an obligatory precondition to undergo HSCT. Although

our laboratory is the only center for tissue typing in Albania, the average number of 11 patients tested annually for allogeneic HSCT purposes in this center does not reflect the real needs for this procedure in the Albanian population. If we refer to the data reported from other European countries (around 100 UD-HSCT per ten million inhabitants per year) (16), and taking into account the actual Albanian population size of about 3.3 million inhabitants, we can assume that the real needs for unrelated donor allogeneic HSCT in Albania must be about 30 procedures per year.

An HLA-matched related sibling has been found in 38% of our patients tested for allogeneic HSCT family donor. This is a higher rate than the maximum of 30% reported from other authors (8-10). This higher frequency can be explained by the relatively high rate of siblings tested per each patient and also by the relatively more restricted HLA heterogeneity in the Albanian population compared to other European populations (18). For example, we have observed in the Albanian population a lower estimated heterozygosity in the different HLA loci in comparison to the Swiss population (14,15). We have also shown that the HLA haplotype heterogeneity is more restricted in the Albanian population in comparison with the Croatian or German populations (15).

However, in 62% of the cases an HLA-matched related donor could be found in our patients. Finding an HLA matched unrelated donor for these patients becomes an emergency that can be resolved only through a good organized UD-HSC registry.

There are actually more than 20 million registered HSC unrelated donors worldwide, mainly in North America and the Western Europe (19,20). However, finding an available HLA matched unrelated donor within the same population as the patient is much easier, faster, and less expensive than trying to find it through searches in international registries (14,20). Moreover, the probability of finding an UD with not only matched HLA alleles, but also with identical HLA haplotypes is much higher within the same population of the patient than in other populations that are genetically (and geographically) more distantly located (14,20).

The size of different national UD-HSC registries varies greatly even between developed countries. The study referring to the data reported from Switzerland, France, Germany, Italy and Netherlands shows that the number of donors available in the respective national registries in these countries ranges from 23026 to a maximum of 456598 per ten million population (in Germany) (17). Considering that Germany has also the highest UD-HSCT rate, it is evident that the allogeneic HSCT rates are directly related with the UD-HSC registry size and also with macro-economic factors such as the gross national income per capita and the governmental health care expenditures (21,22).

Taking into account the considerable financial effort needed to build-up big sized UD-HSC registries, it is important to define the reasonable size for such a registry at the national level (23). In this preliminary pilot study, we tried to make such an estimation using a pool of 510 normal Albanian individuals that we considered as a start-up for an Albanian UD-HSC registry. We found among them 15 individuals HLA-A, -B and -DRB1 matched with 10 (23.3%) of our patients for whom an HLA matched related donor could not be found. From these results we can extrapolate that in order to find HLA compatible UD for 30 patients needing allogeneic HSCT per year, a preliminary start-up UD-HSCT register size of at least 1500 Albanian donors may be required. In our study, the HLA identical donors were found for those patients possessing the more frequent HLA alleles in the Albanian population. In order to find HLA matched donors also for those patients having HLA allotypes of lower frequency rates (20,24), the real size of an Albanian UD-HSCT registry must be at least two-fold higher than the above estimated number.

A search success rate of 75% for finding a matched unrelated donor has been reported in the USA population of European descent (25). The same

success rate has been found in a study conducted in Austria for individuals of South Eastern European descents (26). Taking into account the relatively restricted HLA heterogeneity of the Albanian population, a similar success rate for finding matched unrelated donors could be expected also in this population.

In conclusion, the data reported in this preliminary study clearly underline the actual necessity of organizing an Albanian national unrelated donor registry which can withstand the needs of Albanian patients for allogeneic HSCT.

Conflicts of interest: None declared.

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