BRIEF REPORT

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Turkish Hematologists' Preferences for Related Donor Selection: Results of a Multicenter Survey

Türk Hematologlarının Akraba Donör Seçimindeki Tercihleri: Çok Merkezli Anket Sonuçları

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a widely utilized treatment for various hematological diseases. While selection criteria for unrelated donors are well established, there is a lack of consistency and standardization in the selection of related donors. This study investigated the current approach of hematologists to the selection of related donors at Turkish HSCT centers. The study employed a cross-sectional survey design, distributing a self-administered questionnaire to 95 adult and pediatric transplantation centers in Türkiye to investigate their approaches to related donor selection for allo-HSCT. The questionnaire collected data on various topics including the center's experience in performing allo-HSCT, patient groups treated, number of allo-HSCT procedures conducted between 2015 and 2021, preferences for related donors, considerations in related donor selection (such as sex and past pregnancies), guidelines utilized for related donor selection, upper age limit for related donors, and the use of specialized advanced analyses for elderly donors. The response rate to the survey was 38.9%. Variability was observed across centers in terms of sex consideration and the impact of past pregnancies on related female donor rejection. Different guidelines were employed for related donor selection, with the European Bone Marrow Transplantation guidelines being the most commonly used. Regarding the upper age limit for related donors, 8.1% of centers accepted an upper age limit of 55 years, 48.7% preferred an upper age limit of 65 years, and 43.2% selected related donors aged 65 and above. The lack of standardized guidelines for related donor selection in HSCT centers leads to variability in criteria and potential risks. Collaboration among centers is essential to establish consensus and develop standardized protocols.

Keywords: Donor selection, Hematopoietic stem cell transplantation, HSCT, Standardized protocols, Survey

Öz

Allojenik hematopoietik kök hücre nakli (allo-HKHN), birçok hematolojik hastalığın tedavisinde yaygın olarak kullanılan bir yöntemdir. Akraba dışı kök hücre donörleri için seçim kriterleri iyi belirlenmiş olsa da, akraba kök hücre donörlerinin seçiminde tutarlılık ve standardizasyonda eksiklik bulunmaktadır. Bu çalışmada, Türkiye'de HKHN merkezlerindeki hematologların akraba donör seçimine yönelik yaklaşımları araştırıldı. Çalışmada kesitsel bir anket tasarımı kullanıldı ve Türkiye'deki 95 yetişkin ve pediatrik nakil merkezine allo-HKHN için akraba donör seçimi yaklaşımlarını araştırmak üzere kendilerinin yanıtlayacağı bir anket iletildi. Ankette, hematologlara merkezin allo-HKHN gerçekleştirme deneyimi, tedavi edilen hasta grupları, 2015-2021 yılları arasında gerçekleştirilen allo-HKHN sayısı, akraba donör tercihleri, akraba donör seçimindeki değerlendirmeler (cinsiyet ve geçmiş gebelikler gibi), akraba donör seçimi için kullanılan kılavuzlar, akraba donörler için üst yaş sınırı ve yaşlı donörler için özel ileri analizlerin kullanımı gibi çeşitli konularda sorular soruldu. Ankete yanıt oranı %38,9 idi. Merkezler arasında cinsiyet değerlendirmesi ve geçmiş gebeliklerin akraba kadın donör reddine etkisi açısından değişkenlik gözlendi. Akraba donör seçimi için farklı kılavuzların tercih edildiği görüldü ve Avrupa Kemik İliği Nakil Kılavuzu en yaygın kullanılan kılavuz idi. Akraba donörler için üst yaş sınırı konusunda, merkezlerin %8,1'i 55 yaşı, %48,7'si 65 yaşı üst sınır olarak tercih ederken, %43,2'si 65 yaş ve üzeri akraba donörleri tercih edebildiğini belirtti. Hematopoietik kök hücre nakil merkezlerinde akraba kök hücre donör seçimi için standartlaştırılmış kılavuzların olmaması, kriterlerde değişkenliğe ve potansiyel risklere yol açmaktadır. Konsensus oluşturmak ve standartlaştırılmış protokoller geliştirmek için merkezler arasında işbirliği gereklidir.

Anahtar Sözcükler: Donör seçimi, Hematopoietik kök hücre nakli, HKHN, Standartlaştırılmış protokoller, Anket

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a rising treatment option for hematological malignancies and non-cancerous blood disorders. Stem cell sources include bone marrow, peripheral blood, or cord blood from an identical twin, a sibling, or a related or unrelated donor, and these may be human leukocyte antigen (HLA)-matched, mismatched, or haploidentical. The outcomes of allo-HSCT depend on the underlying disease, the timing of the transplant, patient comorbidities, and the choice of donor. Donor-recipient histocompatibility is one of the key variables in allo-HSCT; nevertheless, non-HLA factors such as cytomegalovirus serostatus, sex, age, ABO compatibility, previous pregnancies, and greater body weight also affect transplant outcomes [1,2,3,4].

International regulatory bodies such as the European Directives for Donation of Tissues and Cellular Therapy Products and the US Food and Drug Administration have devised detailed donation processes to ensure the recipient's safety [5]. Criteria for the selection of unrelated donors have been determined within the scope of the guidelines created by national and international authorities, such as those supplied by the Worldwide Network for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, the Turkish Society of Hematology, and others, to ensure both the recipient's and the donor's safety and to obtain high-quality cellular products [2,5,6]. In many countries, lower and upper age limits have been set by local authorities for unrelated donors to be stem cell donors. The standards of the World Marrow Donor Association require donor registries to stipulate an upper age limit not exceeding 60 years. Many donor registries have set such upper age limits for unrelated donors, such as 55 years in Germany, 55 years in Türkiye, 50 years in Canada, 40 years in Australia and the United Kingdom, and 54 years in Japan [7]. However, the upper age limit for related donors is not always clear, and it is often left to the preference of transplant centers. The inadequate definition of exclusion criteria for elderly related donors puts these donors at risk in terms of possible adverse events [6]. The toxicity and long-term implications of using older related donors in these treatments are not fully known [8,9,10,11,12,13,14]. We present the results of a survey demonstrating the differences in related donor selection among Turkish hematologists in advance of our main study, which will be conducted within the framework of the Turkish Society of Hematology's Donor Research Team (DART) project to determine the upper age limit for related donors.

Materials and Methods

Study Design, Participants, and Survey Administration

This study was undertaken with a cross-sectional design to collect data on allo-HSCT practices and preferences among hematologists working at Turkish HSCT institutions. In February-May 2021, an electronic mail-based survey was distributed to hematologists working in HSCT centers in Türkiye. The survey was designed to acquire information about allo-HSCT practices and preferences. Participants were chosen based on their involvement in allo-HSCT procedures.

Survey Instrument

The survey included nine questions designed to collect relevant data. These questions addressed a variety of topics, such as the number of years of experience performing allo-HSCT, the patient groups for which allo-HSCT was performed, the number of patients who underwent allo-HSCT between 2015 and 2021, the preference for related donors, considerations of the sex of donors in related donor selection, the impact of the number of pregnancies on related female donor rejection, the guidelines used for related donor selection, the upper age limit for related donors, and whether specialized advanced analyses are conducted for elderly donors if selected.

Data Collection

The questionnaire was emailed to hematologists working in HSCT centers throughout Türkiye. We used SurveyMonkey, an online survey tool, to collect the data (http://tr.surveymonkey.com/r/63QNNPJ). The email briefly explained the study's goal and directions for completing the questionnaire. Participants were asked to submit their responses to the questions electronically.

Statistical Analysis

The survey results were evaluated by SurveyMonkey as percentiles.

Ethical Considerations

The protocols employed in this study conformed to the ethical guidelines outlined in the 1975 Declaration of Helsinki. Ethical approval was obtained from the Yeditepe University Non-Interventional Clinical Research Ethics Committee prior to conducting the survey (decision date: January 20, 2022; decision number: 202111110).

Results

Responses from 37 different centers were evaluated. Of those centers, 48.6% (n=18) had been performing allo-HSCT for more than 16 years. Adult bone marrow transplant units made up 83.8% of those that responded. When related donors are available, 86.5% of these centers said they consider the sex of the donor. Concerning the selection of related female donors, 67.5% of the centers stated that the number of pregnancies had no bearing on the decision to reject the donor, while 29.7% considered three or more pregnancies to be a reason for donor rejection and 2.8% considered five or more pregnancies to be a reason for donor rejection. The survey questions and answers are presented in Table 1.

Between 2015 and 2020, 40.5% of the facilities performed 201 or more allogeneic transplants, while 24.3% performed 101-200 transplants, 27% performed 51-100 transplants, and 8.1% performed 50 or fewer transplants. While 46% of these facilities performed 76 or more transplants from related donors, 2.7% performed 10-15 transplants from related donors. Regarding donor selection, the European Bone Marrow Transplantation (EBMT) guidelines were most commonly employed (48.6%), followed by the guidelines of the Turkish Society of Hematology (24.3%).

While 8.1% of the centers accepted an upper age limit of 55 years for related donors, 48.7% applied an upper age limit of 65 years and 43.2% selected related donors aged 65 and above. Among the centers that accepted elderly related donors, 7 centers did not perform additional advanced investigations, 26 centers performed advanced cardiac evaluations, 21 centers performed bone marrow evaluations, 20 centers performed advanced pulmonary evaluations, and 8 centers requested serum and urine immunofixation electrophoresis.

Discussion

We report the results of a survey distributed via email to adult and pediatric transplantation centers in Türkiye as part of the DART project of the Turkish Society of Hematology, designed to gather information on allo-HSCT practices and preferences, and particularly preferences for an upper age limit for related donors. Most of the participants stated that they preferred male related donors. If a female donor is to be selected, most participants stated that the donor's number of pregnancies does not affect donor selection. The upper age limit for donors applied by most participating hematologists is 56 years or above. Agreement with the EBMT guidelines was highest when choosing a related donor for transplantation. If an elderly donor is chosen, most participants agreed that the donor should undergo cardiac and pulmonary function evaluations.

The effects of donor sex, recipient sex, and donor-recipient sex matches have been extensively studied in risk-explained disease cohorts and were shown to affect transplantation outcomes. As such, the modified European Group for Blood and Marrow Transplantation risk score now includes female/male matching as a negative prognostic indicator [15]. Although our respondents had high agreement regarding male related donors, recent studies have shown that outcome disparities are driven solely by the sex of the recipient in the modern transplantation era, with less influence from donor sex [16,17].

Furthermore, in our survey, most respondents agreed that the number of pregnancies does not affect donor selection. In a National Marrow Donor Program analysis of unrelated donor data, parity was identified as an independent risk factor for chronic graft-versus-host disease (GVHD) [18]. Another study showed that the selection of parous female donors resulted in an increased risk of chronic GVHD in all recipients, that the magnitude of this increased risk was similar between male and female recipients, and that nulliparous female donors increased the risk of chronic GVHD in male recipients to a degree comparable to that from parous donors [19]. A decrease in the risk of relapse was not observed, and there was no effect on overall survival, acute GVHD, or transplant-related mortality [19]. Although some studies have shown that the sex of the donor and number of pregnancies adversely affect transplant outcomes, the urgency of the transplants and the availability of donors may be relevant factors for most participants of the present study stating that the number of pregnancies does not affect donor selection.

Due to advancements in allo-HSCT, more than 22% of allo-HSCT recipients for malignant diseases reported to the Center for International Blood and Marrow Transplant Research between 2007 and 2013 were over 60 years old [20]. Significant progress in allo-HSCT has extended its applicability to elderly patients thanks to innovations such as the implementation of reduced-intensity conditioning and non-myeloablative regimens [21], advances in supportive care approaches [22], and more accurate HLA typing methods [10]. The question of stem cell transplantation from older donors is currently under consideration for stem cell recipients. This has led to many studies examining how donor age affects allo-HSCT outcomes. Several studies have looked at the effect of donor age on allo-HSCT outcomes. In our survey, most participants agreed that the upper age limit for the selection of related donors was 56 or above. However, many studies demonstrated that increasing the donor age by a decade was associated with poorer overall survival [23,24].

There are a limited number of studies regarding the complications that may develop in the donor when an elderly donor is selected. Different age limits for related donors impact potential donor availability. If the age limits are set excessively low, otherwise healthy and qualified individuals may be excluded from consideration as donors, decreasing the pool of available donors. On the other hand, if the age limit is too high, it can include people at a higher risk of health problems or those who are less compatible as donors. Older donors may have a higher prevalence of age-related health disorders such as cardiovascular, cerebrovascular, peripheral vascular, or chronic respiratory diseases, as well as diabetes mellitus and malignancies, which could affect the transplantation's success [14,25]. Consequently, hematological malignancies, such as myelodysplastic syndrome and chronic myeloproliferative disorders, can also develop in the recipients [26]. Therefore, many of our survey participants plan to have cardiac and pulmonary evaluations in the event of the selection of an older donor.

Table 1. Survey questions and general responses.

Survey questions	Answers		
1. How many years has allo-HSCT been performed at your transplantation center?		**n**	**%**
	1-5 years	3	8.1
	6-10 years	8	21.6
	11-15 years	8	21.6
	>15 years	18	48.7
2. In your transplantation center, which patient group undergoes allo-HSCT?		**n**	**%**
	Pediatric patient	6	16.2
	Adult patient	31	83.8
3. Please specify the total number of allo-HSCT procedures performed at your transplantation center between 2015 and 2020.		**n**	**%**
	<50	3	8.1
	51-100	10	27
	101-200	9	24.3
	>200	15	40.6
4. Please specify the total number of allo-HSCT procedures involving related donors performed at your transplantation center between 2015 and 2020.		**n**	**%**
	10-25	1	2.7
	26-50	8	21.6
	51-75	11	29.7
	>75	17	46
5. Do you have a preference for donor sex when selecting a related donor for the transplantation?		**n**	**%**
	Yes	32	86.5
	No	5	13.5
6. If a related female donor candidate is available for a patient undergoing allo-HSCT, how many pregnancies would lead to the rejection of the donor?		**n**	**%**
	>3	11	29.7
	>4	0	0
	>5	1	2.7
	The number of pregnancies does not affect donor selection	25	67.6
7. Which donor selection guidelines do you apply when choosing a related donor for transplantation? (multiple selections can be made)		**n**	**%**
	CIBMTR	2	
	WBMT	5	
	EBMT	18	
	Chinese Society of Hematology consensus	1	
	NMDP	2	
	Turkish Society of Hematology Donor Guidelines	9	
8. What is the upper age limit for related donors at your transplantation center?		**n**	**%**
	55 years	3	8.1
	56-65 years	18	48.7
	>65 years	16	43.2
9. If you have chosen an older donor at your center, do you perform additional tests for the donor? (multiple selections can be made)		**n**	**%**
	No	7	
	Cardiac analysis	26	
	Bone marrow aspiration flow cytometry	8	
	Bone marrow biopsy	7	
	Bone marrow aspiration genetics	6	
	Pulmonary analysis	20	
	Immunofixation electrophoresis	8	
	Other	7	

Allo-HSCT: Allogeneic hematopoietic stem cell transplantation; CIBMTR: Center for International Blood and Marrow Transplant Research; EBMT: European Group for Blood and Marrow Transplantation; NMDP: National Marrow Donor Program; WBMT: Worldwide Network for Blood & Marrow Transplantation.

For the reasons outlined above, it is critical to thoroughly assess older donors' health status and eligibility individually, considering their overall health, comorbidities, and potential risks. It is also essential to remember that the success of transplantation procedures depends on several variables. In other words, age limits are not the only factor determining transplantation success. Standardized selection criteria in HSCT centers for related donors have many advantages. They ensure consistency in assessments, improve safety by reducing hazards, support quality assurance for high-quality stem cell products, simplify the selection process to increase efficacy, and ultimately optimize patient outcomes and donor safety [25].

Expertise is essential because skilled facilities may have developed their standards based on clinical expertise and data on outcomes. Practical considerations may force looser requirements due to limited resources, such as equipment or donor availability. Different institutes use different procedures because there are no established standards for related donor selection, and inconsistent criteria make assessing the suitability of potential donors difficult [25]. The application of inconsistent criteria can contribute to a lack of standardization in the evaluation process, making it difficult to compare and analyze donor data [12]. The results of our investigation and recommendations from other studies [14,15] show that additional research is needed to establish common standards for related donor selection.

Study Limitations

There are certain limitations to this study that should be considered. The cross-sectional design limited the identification of causal relationships and temporal changes. Relying on a self-report questionnaire may have led to biases and inaccuracies. The findings may not be applicable beyond Turkish bone marrow transplant centers. Due to the limited scope of the survey instrument, some relevant aspects may have been overlooked. Finally, the implementation of standardized guidelines should still be addressed.

Conclusion

Related donor selection guidelines in bone marrow transplant centers are inconsistent, leading to varying criteria and potential risks. Standardized criteria for donor selection would ensure consistency, increase safety, improve quality assurance, shorten the process, and optimize patient outcomes and donor safety. Collaboration among centers is critical for reaching consensus and developing standardized methods. More research is needed to define universal criteria and overcome implementation issues. In line with these goals, we will be conducting a research project within the framework of the Turkish Society of Hematology's DART project to determine the upper age limit for related donors.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Yeditepe University Non-Interventional Clinical Research Ethics Committee prior to conducting the survey (decision date: January 20, 2022; decision number: 202111110).

Informed Consent: Not necessary.

Authorship Contributions

Surgical and Medical Practices: S.G.Ö., M.S.P., H.A.Ö., M.A.; Concept: H.A.Ö., M.A.; Design: H.A.Ö., M.A.; Data Collection or Processing: S.G.Ö., A.K., A.H.K., M.S.P.; Analysis or Interpretation: S.G.Ö., A.K., A.H.K., M.S.P., H.A.Ö., M.A.; Literature Search: S.G.Ö., A.K., A.H.K., M.S.P., H.A.Ö., M.A.; Writing: S.G.Ö., A.K., A.H.K., M.S.P., H.A.Ö., M.A.

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