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Donor Selection in Allogeneic Stem Cell Transplantation

Mehmet Ali ERKURT, Ilhami BERBER*, Irfan KUKU, Emin KAYA, Ilknur NIZAM

Department of Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
*Corresponding author: drilhamiberber@hotmail.com

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Abstract Allogeneic hematopoietic stem cell transplant is safe and curative treatment modality for many hematologic diseases. Expanding alternative donor options such as haploidentical hematopoietic stem cell transplantation and umbilical cord blood, taken together with enhanced outcomes of matched unrelated donors, has resulted in a advisable donor for most patients with an hematopoietic stem cell transplantation indication. This review article provides improved patient selection, offers hope for decreasing relapse and improving outcomes for in patients applied allogeneic hematopoietic stem cell transplant.

Keywords: *allogeneic, donor selection, stem cell transplantation*

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) includes transplanting hematopoietic stem cells from a Human Leucocyte antigen (HLA) matched, healthy donor to a recipient who is rendered myeloablative/tumor-ablative by a certain preparation regimen, which is followed by configuring the donor's hematoimmunopoetic system in the recipient's body [1]. Bone marrow transplantation, peripheral stem cell transplantation, and cord blood transplantation are collectively called hematopoietic stem cell transplantation (HSCT). Allogeneic donor selection is of critical importance for HSCT success. Appropriate donor selection is based on choosing the best hematopoietic stem cell source. This selection directly affects HSCT success and overall survival of the patient [2].

Age, gender, patient's diseases and comorbid diseases are important factors in patients applied allogeneic HSCT. The recommended age is under the age of 40 years. Female to male transplants, patients with acute myeloid leukemia than myelodysplastic syndrome and comorbid diseaese like active infection, coronary artery or cerebrovascular disease, inflammatory bowel disease, obesity, diabetes, and psychiatric history have worse prognosis [3].

2. Allogeneic Donor Selection

Hematopoietic stem cells can be obtained from a variety of sources. a) Monozygotic twins (syngeneic) b) Siblings or other relatives, c) Unrelated persons, and d) Cord blood.

a) Monozygotic twins (syngeneic): Graft Versus Host Disease (GVHD) does not develop in HSCT from monozygotic twins. There is also no need for post-transplantation immunosuppressive therapy. Graft-versus leukemia effect is not observed, either. Risk of relapse is higher compared with transplantations from HLA matched siblings. It has been reported to portend a transplantation-related mortality rate and relapse-related mortality rate similar to fully HLA matched sibling transplantation. The most appropriate donor is, if any, a monozygotic twin in allogeneic HSCT. However, it may not be appropriate in patients with a high relapse risk [1].

b) Siblings and other relatives: A fully matched sibling is the donor of first choice in allogeneic HSCT practice. The chance of a person to have a fully HLA-matched sibling is, on average, 25%. The chance of having a fully HLA-matched sibling increases when the number of siblings is higher. This probability is calculated with the following formula: $p= 1-(0.75)^n$, (n= potential sibling donor). For example, in case of 5 siblings, the chance to find a matched marrow is around 76% [2,4,5]. Patients not having a fully HLA-matched sibling may undergo HSCT even when a sibling had 1 mismatch. In case of multiple mismatches [8/10 to 5/10), a haploidentical transplantation can be carried out from a 1st degree relative. In this case, the haploidentical transplantation is indicated when no fully matched unrelated donor is present [6,7].

c) Unrelated transplantation: Compared to SCT from a HLA genotypically identical sibling donor, unrelated SCT is associated with a higher post-transplant complication risk. This condition is usually due to serologically undetectable HLA mismatch. GVHD, graft failure, and recurrence rates are increased compared to fully matched siblings [8].

d) The cord blood: The cord blood is quite rich in hematopoietic precursor cells, as is bone marrow. Cell counts are similar to those of adults but majority of cells are immature; cytokine production is low; and it is more favorable owing to being poor in alloreactive T cells [9].

Stem cells with high proliferation rate and low number can be tolerated. The engraftment is slower but the risk of GVHD and transplantation-related mortality are lower in SCT carried out with cord blood. Graft failure and increased risk of infections due to late engraftment may produce some problems. SCT with cord blood may be a good alternative to unrelated SCT especially in pediatric age group. The mismatch should not be more than 2 in number [10,11].

3. Points to Consider in Allogeneic Donor Selection

Table 1. Conditions leading to temporary postponement

Condition	Duration of postponement
Endoscopic biopsy	12 months
Epilepsy	Three years after the last attack without therapy
Fever > 38 °C, flu-like infection	Two weeks later after resolution of symptoms
Renal Disease/Acute glomerulonephritis	Five years after recovery
Piercing (body, skin, ear etc.)	After 12 months
Pregnancy/Abortion	1 year after delivery
Rheumatic fever	In cases without ongoing cardiac disease two years after the last attack
Major surgery	6 months
Minor surgery	1 week (if there exists no complication)
Tattoo	12 months
Transfusion	Twelve months after blood or blood product transfusion
Drugs (Teratogenic and/or hematotoxic)	Depending on the pharmacokinetic properties of the drug
Hypertension	Three years after the last attack without therapy

Table 2. Conditions leading to permanent postponement

Condition	Comments
Asthma	If requiring therapy
Chronic inflammatory disorders	In case of cardiac, hematologic, thyroidal, renal, intestinal, vesical, pulmonary arterial and venous involvement
Coagulation disorders	von Willebrand disease, hemophilias, cerebrovascular diseases, recurrent venous thrombosis, arterial thrombosis
Diabetes mellitus	If requiring insulin or oral antidiabetic therapy
Transplantation	Solid organ or hematopoietic stem cell recipients
Hepatic disease	Hepatitis B and C, cirrhosis, Wilson disease
Trauma	Severe head or CNS trauma
Systemic autoimmune disorders	If more than 1 organ involved
Heart	Coronary artery disease, serious cardiac arrhythmias, angina pectoris
Latex allergy	Serious latex hypersensitivity
Drugs	Drug addicts

Allogeneic stem cell donor approval (voluntariness): Stem cell transplantation is not allowed from persons, whether a single candidate or one of multiple candidates, who do not give written informed consent. The general condition of the patient should be well and he/she should be healthy [12]. The patient's performance should be well enough to allow safe hematopoietic stem cell harvesting (Currently, peripheral stem cells are used as stem cell source except for special cases). The donor should have a satisfactory cardiac, pulmonary, hepatic, and renal function in order to be able to tolerate general or local anesthesia. Donors with active cancer or a history of cancer are generally excluded (conditions leading to temporary and permanent postponement are shown on Table 1 and Table 2, respectively) [12,13].

HLA match: Also called MHC system, HLA region on the short arm of 6th Chromosome is the gene region where Class I and II antigens as well as proteins providing immunologic recognition are synthesized. Class I antigens are: HLA A, B, and C; Class II antigens are: HLA DR, DQ, and DP. The best donor is HLA genotypically matched sibling. HLA-A, B, and DR low resolution typing (serology or 2-digit DNA typing) are sufficient to determine the paternal and maternal haplotype present in the patient and the possible sibling donor [12,13,14]. When a donor with only one HLA mismatch (5/6) is detected in an extended family search, HSCT can be performed with that donor even though GVHD risk may be increased. This case is a related antigen mismatch donor SCT. A high resolution class-I and class-II typing should be done to determine the precise extent of matching. The event of parents and some siblings having a common haplotype as the recipient is called a haploidentical related donor SCT and high-resolution HLA-A, B, C, DRB1, DQB1 should be studied in that case. DPB1 typing should be performed in the presence of multiple 10/10 match donors although the importance of HLA-DP has been shown. Post-transplantation survival has increased with class-I and class-II allele match. Multiple Class I mismatches in donor increase risk of graft failure while multiple Class II mismatches increase risk for GVHD. A single mismatch does not appear to affect survival rates. When several HLA identical donors are present, the donor who is male, ABO identical, and CMV negative should be selected [15,16,17]. Algorithm of HLA typing was shown on Figure 1.

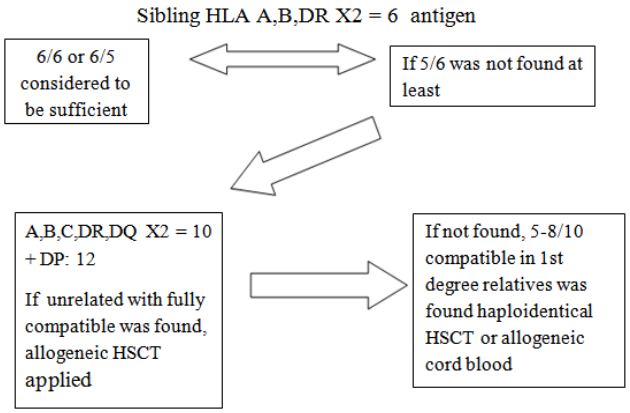

Figure 1. Algorithm of HLA typing

Hepatitis B infection: HBsAg-positive donors are usually excluded in allogeneic HSCT practice. However, a HBV-infected donor may be the only option due to a high intrafamilial prevalence of the disease. HBV-infected persons can be stem cell donors when there does not exist a more suitable candidate (especially when the recipient is also HBV-infected). The donor should be begun on anti-HBV therapy as soon as possible. The risk of disease transmission is minimized by reducing HBV DNA to trace levels in donor's serum [18].

Hepatitis C infection: There should be no antibodies against hepatitis C virus (anti-HCV) in the donor's serum. Anti-HCV positive donors are generally excluded in

allogeneic-HSCT practice. Alternative donors should be sought in that case. The donor should be treated for HCV infection and HCV RNA should be lowered to trace levels before harvesting stem cells [19].

HIV infection: Anti-HIV antibodies and/or HIV RNA must be negative in donor's serum [20].

Cytomegalovirus (CMV): Approximately 1/3 of allogeneic-HSCT patients have CMV infection. Half of these have lung disease. The remaining have retinitis, hepatitis, GI disease (esophagitis, gastritis, enterocolitis), polyradiculopathy, bone marrow suppression, graft rejection, encephalitis, sinusitis, and cystitis. Therefore, CMV positivity should be paid attention in allogeneic donors [21]. In case of multiple donors, CMV seronegative donors should be preferred in CMV seronegative recipients; the blood products should also be seronegative. Also, seronegative donors are preferred over seropositive donors in CMV seropositive recipients. An active CMV infection in the donor is a contraindication for allogeneic-HSCT [22,23]. Infections and duration of postponement in allogeneic donor selection are shown on Table 3.

Table 3. Infections and duration of postponement

Infection	Duration of postponement
Babesiosis	Permanent
Brucellosis	At least 2 years after full recovery
Chagas disease	Permanent rejection
Creutzfeldt–Jakob disease	Permanent rejection
Human T lymphotropic virus I/II	Permanent rejection
Leishmaniasis	Permanent rejection
Lepra	Permanent rejection
Lyme disease	Permanent rejection
Tuberculosis	After completion of therapy and at least 2 years after full recovery
Toxoplasmosis	Six years after clinical recovery
Typhus	Permanent rejection
Osteomyelitis	After completion of therapy and at least 2 years after full recovery
Meningitis	Permanent rejection
Syphilis	Five months after recovery
Q fever	Permanent rejection
Malaria	At least 6 months after completion of therapy

ABO Blood groups: Approximately 30-40% of HLA-matched allogeneic transplantations have ABO blood group mismatch. ABO mismatch does not interfere with a successful allo-HSCT [24]. Effect of ABO mismatch on GVHD and/or overall survival has not been entirely understood. ABO-matched donors may be preferable when other factors are comparable [25].

Rh Blood Group: A Rh mismatch between the donor and the recipient may lead to hemolytic anemia in allogeneic-HSCT. Anti-D alloimmunization is observed in 80% of D- healthy persons when they are administered D+ blood or blood products. Anti-D alloimmunization is observed at a lower rate in immunosuppressed patients. In D- patients anti-D alloimmunization has developed at a rate of 0.19% secondary to D+ thrombocyte transfusion. Compared to ABO mismatch, specific data regarding the effects of Rh mismatch on allogeneic-HSCT are scarce. Some studies have reported that Rh mismatch is independently associated with unfavorable prognosis [26].

Age: Age is the only donor-related factor that affects overall and disease-free survival. Mobilization failure may increase with aging. Increased donor age is associated with increased rates of acute and chronic GVHD and reduced overall survival [27,28]. Younger donors should be preferred first. However, being older does not preclude donorship. The age range is 18-79 years in healthy donors. In unrelated transplantations, on the other hand, any healthy person aged 18 to 55 years weighing at least 50 kg can donate stem cells [29].

Gender/parity: It is the state of having delivered a baby and is also called as parity. Female donors with previous deliveries increase risk of chronic GVHD in all recipients. Chronic GVHD risk has been found similar in all male or female recipients. No significant relationship has been found between gender/parity and overall survival, acute GVHD, and transplantation-related mortality rates. Allogeneic-HSCT from female donors to male recipients unfavorably affects the procedural results, especially in patients with standard risk. It is considered that the increased rate of GVHD in allogeneic-HSCT from female donors is a result of allo-reactive immunogenity in males created by minor histocompatibility antigens (DBY, SMYC, UTY, DFFRY) coded on Y chromosome [27,28]. In the event of multiple donors, male donors are preferable to female counterparts; in the event of multiple female donors, those without a history of delivery are preferable to those with previous deliveries; and in the event of multiple female donors with previous deliveries, those who delivered less are preferable to those with multiple deliveries [29].

4. Conclusions

A good improved patient selection in patients applied allogeneic hematopoietic stem cell transplant offers hope for decreasing relapse and improving outcomes.

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Competing Interests

The authors declare that they have no competing interests.

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