Donor Selection

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Abstract

Allogeneic haematopoietic stem cell transplant (HSCT) is the treatment of choice for a variety of malignant and non-malignant disorders. The aim of HSCT is to replace the patient's haematopoiesis with that taken from a donor, and a prerequisite is the identification of a suitable donor. It is an intense and demanding process and puts considerable strain on both recipients and donors. The choice of donor has an impact on the transplantation process from scheduling to outcome. There are several common donor issues whether the donor is related or unrelated including eligibility, confidentiality, informed consent and right to refuse consent.

Keywords

Eligibility • Confidentiality • Informed consent • Donation • HLA match • Donor selection

3.1 Introduction

Allogeneic haematopoietic stem cell transplant (HSCT) is the treatment of choice for a variety of malignant and non-malignant conditions. The aim of HSCT is to replace the patient's haematopoiesis with that taken from a donor, and a prerequisite is the identification of a suitable donor. There are three conditions which have to be met for a donor to be considered suitable – the donor needs to be suitably matched, healthy and willing to donate (Kisch 2015). Allogeneic HSCT is an intense and demanding process and puts considerable strain on both recipients and donors.

Donors can be related or unrelated (Fig. 3.1), and the primary consideration is the degree of HLA compatibility of the donor to the recipient and this is considered the most important factor to determining overall success and the transplant-related mortality (Kulkarm and Treleaven 2009).

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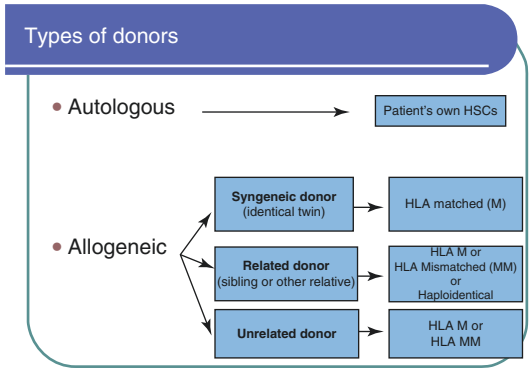

Fig. 3.1 Types of donors

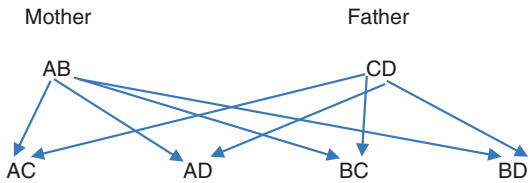

Fig. 3.2 HLA typing

3.2 Human Leukocyte Antigens

Human leukocyte antigens (HLA) are part of the major histocompatibility complex and is highly polymorphic, meaning that there are a lot of variations of the HLA type with humans, and they are found on the short arm of chromosome 6. The primary role of HLA molecules is to preserve peptide to T cells, enabling them to recognise and eliminate "foreign" particles present in an individual and also to prevent the recognition of self as foreign. Due to the Mendelian[1] inheritance of HLA types, the first place to look for a potential donor is within the immediate family (Fig. 3.2). Our HLA type is inherited from our parents – one haplotype from each parent giving rise to a one in four chance that sibling may match another.

Table 3.1 shows the wide variety and number of HLA alleles (the variant forms of the gene) that have been identified. HLA typing can be serological or DNA based though currently the majority of HLA typing is DNA based.

Table 3.2 shows an example of the nomenclature used for HLA typing. HLA typing looks at matching recipients and donors at HLAs A, B and C (class I typing) and HLAs DR, DQ and DP (class II typing). The nomenclature used is the gene name followed by an asterisk with a four-digit allele name; the first two digits indicated the serological groups and the last two digits the number of the allele within the group.

When we speak of matching, we describe the potential donors as being fully matched (6/6 within the related setting or 10/10 when referring to unrelated donor), a one- or two-antigen mismatch or a haplotype match (i.e. 3/6 or 5/10). The example below shows a patent and his potential sibling donors.

Below is a list of examples when describing degrees of HLA matching between recipient and potential donor.

Table 3.1 The number of HLA alleles currently named at each locus (April 2011)

HLA locus	Number of class I alleles	HLA locus	Number of class II alleles
HLA–A	1601	HLA–DRB	1027
HLA–B	2125	HLA–DQA1	44
HLA–C	1102	HLA–DQB1	153
		HLA–DPA1	32
		HLA–DPB1	149

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Table 3.2 An example of HLA nomenclature and its relation to HLA typing techniques

Typing method	Nomenclature
Serological	A1
DNA based: Low resolution	A*01
DNA based: Low resolution	A*01:01/01:4 N
DNA based: Low resolution	A*01:01

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[1]Mendelian inheritance is where a person inherits two alleles, one from each parent. These alleles may be the same or different.

	Patient	Donor
Full/Complete	A*1, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N	A*1, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N
HLA Mismatched	A*1, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N	A*3, B*7, DRB1*01 A*24, DRB1*15, DRB5*01/02/03N
Haplotype Match	A*1, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N	A*1, B*8, DRB1*03, DRB3*01 A*3, B*7, DRB1*01
Single Antigen Mismatch	A*01, B*8, DRB1*03, DRB3*01 A*31 , B*35, DRB*04, DRB4*01:02N	A*01, B*8, DRB1*03, DRB3*01 A*28, B*35, DRB*04, DRB4*01:02N
Single Allelic Mismatch	A*01:01, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N	A*01:0 2, B*8, DRB1*03, DRB3*01 A*31, B*35, DRB*04, DRB4*01:02N

The differences leading to the mismatch are highlighted in red

The possibility of having a suitably matched sibling donor varies depending on ethnicity as distinct HLA types that occur differ among ethnic groups and family size. If a suitable matched sibling donor is not available, a search can be undertaken of the volunteer unrelated donor panels that are part of BM Donors Worldwide. There are now in excess of 18 million volunteer unrelated donors registered on these panels.

Gragert et al. (2014) published the chances of identifying a suitable matched donor for a recipient requiring allogeneic HSCT. While a person of Caucasian background has a relatively good chance of identifying a potential donor, some ethnic groups have a much lower probability of finding a match through unrelated donor searching. This has led to an increase in the use of alternate donors, e.g. a haploidentical donors or alternative cell sources, e.g. cord blood stem cells. The use of haploidentical transplantation with improved conditioning and GVHD prophylaxis means that nearly all patients will gave the potential of a haploidentical donor (Table 3.3).

3.3 Eligibility for HLA Typing of Potential Related Donors

Every institution will have their own requirements regarding eligibility to be HLA typed, and there should be a policy available locally. The main eligibility criteria is willingness to be tested – this does not imply consent to donation – and that the potential donor is not suffering from any conditions that may be a threat or a risk to the recipient or that may be aggravated in themselves by the donation process. As a result potential donors who have had a malignancy previously or have an autoimmune condition should be excluded or given special consideration. Relevant guidance can be found at http://www.worldmarrow.org/donorsuitability/index.php/Main_Page#Related_donors

Sibling donors actively participate in the quest for a cure for their sibling, but this exposes them to an invasive medical procedure that can lead to stress and anxiety and places them in a complex situation. While it can have a beneficial effect for the donor and the family unit as a whole, donors often feel responsible for the recipient outcome.

With respect to unrelated donors, each registry will have their own inclusion/exclusion criteria, but they usually follow the advice of the WMDA (World Marrow Donor Association) on whose website there is comprehensive guidance with respect to donor eligibility. To be listed as a volunteer donor on a blood stem cell registry, you must be:

- Between 18 and 60 years old (age limits may vary per country)
- In good health
- Ready to donate stem cells to *any* patient in need

Table 3.3 Likelihood of identifying HLA-matched adult donors and cord blood units

U.S. Racial and Ethnic Group	Likelihood of identifying an adult donor[a]		Likelihood of identifying a cord-blood unit for patients ≥20 Yr of age[b]			Likelihood of identifying a cord-blood unit for patients <20 Yr of age?		
	8/8 HLA match	≥7.8 HLA match	6/6 HLA match	≥5/6 HLA match	≥4/6 HLA match	6/6 HLA match	≥5/6 HLA match	≥4/6 HLA match
				Percent				
White European	75	97	17	66	96	38	87	99
Middle Eastern or North African	46	90	6	46	91	18	75	98
African American	19	76	2	24	81	6	58	95
African	18	71	1	23	81	5	56	95
Black South or Central American	16	66	2	27	82	7	58	96
Black Caribbean	19	74	1	24	81	6	58	95
Chinese	41	88	6	44	91	19	77	98
Korean	40	87	5	39	89	17	73	98
South Asian	33	84	4	41	90	14	73	98
Japanese	37	87	4	37	88	16	72	97
Filipino	40	83	5	42	89	19	76	98
Southeast Asian	27	76	3	37	89	12	70	98
Vietnarnese	42	84	6	44	89	20	76	98
Hawaiian or Pacific Islander	27	72	3	32	84	10	64	96
Mexican	37	87	6	45	91	19	75	98
Hispanic South or Central American	34	80	5	43	90	17	73	98
Hispanic Caribbean	40	83	5	40	89	17	71	98
Native North American	52	91	10	54	93	25	80	99
Native South or Central American	49	87	11	53	93	26	79	98
Native Caribbean	32	77	4	35	86	14	66	97
Native Alaskan	36	83	7	47	91	18	75	98

Gragert et al. 2014

[a]Data are the probabilities of identifying an adult donor who is available

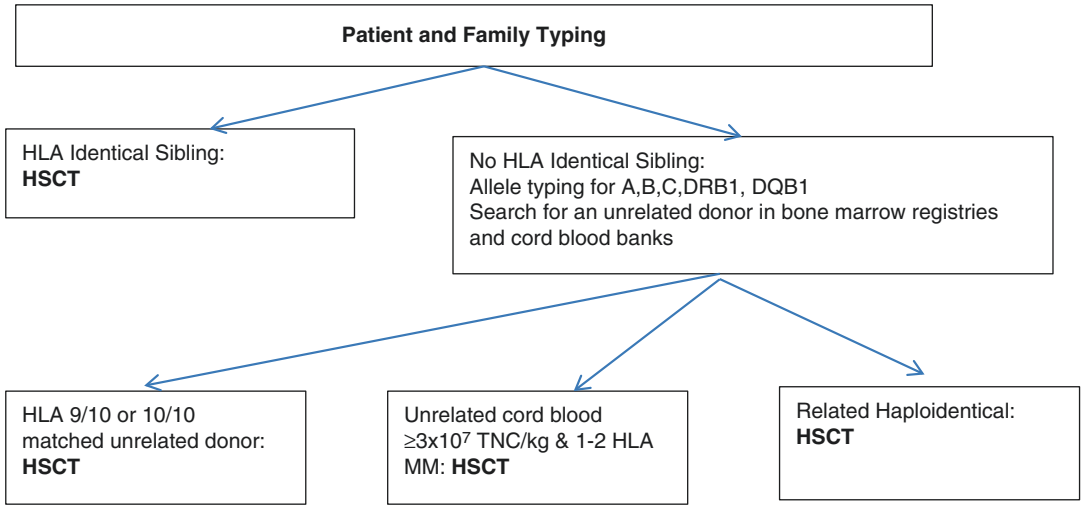
[b]Data are the probabilities of identifying a unit with an adequate cell dose

To donate umbilical cord blood, a future mother must generally be:

- Over 18 years of age
- In good health
- Pregnant without complications
- Registered well before the onset of labour

3.4 Algorithm of Donor Choice and Selection

Many factors affect the choice of donor, and with the selection of donor sources now available, the possibility of offering HSCT has extended to almost all patients who require it (Apperley et al. 2012).



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3.4.1 Donor Selection

The main determinants when selecting a donor whether related or unrelated are as follows:

The "perfect" donor does not exist – no current algorithm will guarantee a positive outcome will always occur.

3.4.2 HLA Match

The most significant factor in success and overall outcome is the degree of match between the donor and recipient.

1. Most data suggest a 10/10 match is the best choice.
2. In many circumstance a 9/10 match can be considered as good as a 10/10 but where the mismatch occurs is important. A mismatch at HLA DQB1 has been shown to have the least likely adverse outcome. Worse outcomes have been seen where the mismatch is at class I. Choosing a HLA A, B or C mismatch should be based on local studies and experience as it can be population or ethnically dependent.
3. Two or more mismatches are associated with a poorer outcome (Shaw 2009).

3.4.3 Cytomegalovirus (CMV) Status

Cytomegalovirus (CMV) is a common virus that can infect almost anyone. Most people don't know they have CMV because it rarely causes symptoms. However, if you're pregnant or have a weakened immune system, CMV is cause for concern. Once infected with CMV, your body retains the virus for life.

Where possible the donor-recipient pairing should be CMV matched with preference given to a CMV compatible donor, i.e. negative donor in a CMV-negative recipient. The CMV status of the donor is less important in a CMV-positive recipient, but there is some evidence that a CMV-positive donor is preferable in a CMV-positive recipient as it may protect the patient from CMV infection (Rovira et al. 2012). Analysis has shown that prior donor CMV exposure significantly reduces the risk of CMV reactivation in CMV-positive recipients as immunity against CMV seems to be transferred with the donor cells and protects CMV-positive recipients from reactivation.

3.4.4 Blood Group

Blood group mismatch is not a contraindication to HSCT, and there is conflicting data about the role of blood group mismatch in relation to post HSCT relapse, but the majority of research suggest that is does not influence HSCT outcome (Kulkarni and Treleaven 2009).

Matching donor and recipient blood group may benefit the recipient as it may reduce the number of transfusions and the period of transfusion dependency post HSCT. Blood group matching is an important consideration in transplants where BM stem cells are the product of choice as it removes the requirement for the product to be red cell depleted to reduce the risk of intravascular haemolysis in the recipient.

3.4.5 Sex Match

Donor-recipient sex match is an important predictor of transplant-related mortality (TRM) with the combination of a male recipient with a female donor known to have an increased risk of chronic GVHD and a higher TRM but not necessarily a reduced relapse risk in all diseases.

3.4.6 Parity

If only female donors are available, it is recommended where possible to use a nonparous female donor as -parous females have a higher chance of having HLA-specific antibodies due to exposure to foetal antigens in utero. It is accepted that recipients (either male or female) who have a HSCT from parous donors have a higher risk of chronic GVHD (Kollman et al. 2001).

3.4.7 Age

The younger the donor at the time of HSCT donation has a favourable outcome after HSCT. It appears that the risk of acute GVHD (Grade 3 or above) and chronic GVHD is higher, and overall survival can be lower with increased donor age (Kollman et al. 2001).

3.4.8 Donor Evaluation

All donors should be medically assessed and consented independently from the recipient medical team. The maxim of "Do No Harm" to the donor is paramount, and no donor should be selected where there is a risk of aggravating or exacerbating a potential medical issue in the donor.

Table 3.4 lists the investigations that should be undertaken for all donors. There is a concern that related donors may not always be as forthcoming about their health as they do not wish to jeopardise their relative's transplant. The table lists the mandatory virology screening that is required on all donors – specific or additional testing may

Table 3.4 Pre-transplant investigations of the donor

Blood group and antibody screening
Coagulation studies
Complete blood count
Full/confirmatory HLA typing
Liver function tests
Urea and creatinine
Pregnancy test
Viral serology – Cytomegalovirus Epstein-Barr virus Hepatitis B surface antigen and core antibody Hepatitis C antigen HIV HTLV Treponemel screen Herpes simplex virus Varicella zoster virus Toxoplasma
Chest X-ray
Electrocardiogram
Under certain circumstances
Cytogenetic studies (chromosome fragility) if family history
Bone marrow examination
Echocardiogram or MUGA scan
Haemoglobin electrophoresis
Lung function tests
Haemoglobinopathy screen

be required in certain countries, e.g. screening for West Nile virus if donor resides in an at risk area, or if the countries' regulations require it, e.g. Tri-NAT assay.

3.5 Special Considerations

3.5.1 Screening of Elderly Donors

With more than 25% of HSCT now being performed in recipients >55 years of age, the chance of a higher age in matched sibling donors is also greater. This group of donors are more likely to have age-related medical conditions, and additional testing may be required to reduce the risk of donor-derived disease, e.g. transmission of an immune-mediated condition, e.g. asthma or psoriasis to the recipient, and reduce the risk to the donor. This includes PSA (prostate-specific antigen) in males, occult blood in stools, possible BM aspirate if results are abnormal, protein electrophoresis and CT chest if there is a history of smoking.

3.5.2 Screening of Paediatric Donors

Paediatric sibling donors are a unique underreported group with special challenges for the HSCT team and the family. Parents of the paediatric donor are in the difficult position of having to consent to both the donation and the transplant. JACIE and other professional bodies suggest the use of independent assessor and donor advocates in the case of paediatric donors to ensure the needs of the paediatric donors are met and that they are protected. Hutt et al. (2015) state that the intense experience of HSCT has a long-term impact on the whole family indicating the need for follow-up and psychological support. There can be a striking difference between the donors' and parents' view of the situation with the donor feeling a closer relationship with the recipient and also feeling responsible for them as well as the fact that the recipient owes them a debt of gratitude. Parents are concerned with two children and often feel that the donation process has a positive effect on family life not understanding any negative effect it may have on the donor feeling a pressure to donate or having that feeling of responsibility.

The needs of paediatric donor are sometimes left unmet since parents and healthcare professionals cannot always see the effect of the donation process on them. This can also be said to be the case in adult donors although they at least have life experience and knowledge which enables them to process and deal with their feelings in a way that a child often cannot.

3.5.3 Confidentiality

Information and care of the HSCT patients and their donor should be kept separate. Healthcare professionals must minimise their influence and that of the recipient and other family members which could complicate the potential donors' decision to donate or not. Families are complex entities, and potential donors and recipients can be estranged or influenced, and donors can feel pressured to donate. A model of care which is independent to the recipient (i.e. independent medical assessment and counselling of the potential donor) increases the potential donors' sense of security and allows for informed consent or refusal of donation. It is essential to separate the care of the donor from that of the recipient so that each individual can be focussed upon. The privacy of the donor must be respected and protected, and all potential donors should be given information at the time of the HLA typing about the potential process.

3.5.4 Donor Consent and Clearance

All donors should be reviewed and consented prior to the recipient commencing conditioning chemotherapy. They should be medically cleared and understand the implications if they withdraw their consent or participation once the recipient's conditioning has commenced.

3.5.5 Stem Cell Source

While this is primarily dictated by the transplant medical assessment and the type of HSCT that the recipient is undergoing, the donor will also influence that decision. The donor has a choice in which type of donation method that they prefer, and both should be discussed. The donor may also have medical issues which influence the cell source, e.g. donors with significant back injuries or issues may not be suitable for bone marrow harvest, and unrelated donors who do not have adequate peripheral venous access may not be considered for apheresis due to the reluctance to insert a central access device in an unrelated donor.

Conclusion

Allogenic HSCT is a standard therapy in a number of malignant and non-malignant conditions. The choice of donor is a complex issue with far-reaching consequences both for the recipient and the donor.

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