Review Article

Transfusion Medicine and Hemotherapy

Transfus Med Hemother 2019;46:348–354
DOI: 10.1159/000502422

Received: May 20, 2019
Accepted: July 23, 2019
Published online: August 28, 2019

HLA Matching in Pediatric Stem Cell Transplantation

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Keywords
HLA matching · Stem cell transplantation · Donor selection

Abstract
For several malignant and nonmalignant disorders such as leukemias, lymphomas, or inborn errors of hematopoiesis, stem cell transplantation is the only curative option. Depending on the underlying cause of the disease, the conditioning regimens, source of the stem cells, and graft composition may vary. Possible stem cell donors are selected from databases considering existing major histocompatibility genes of the donor and the recipient. This is currently performed by matching human leukocyte antigen (HLA)-A, -B, and -C for class I, as well as HLA-DRB1 and -DQB1 for class II. Stem cell transplantation for nonmalignant disorders is a specialty of pediatrics. While algorithms for donor selection in these cases are generally similar, the objective of optimizing a possible graft-versus-leukemia effect is less important. In this article, we aim to provide an overview on the current methods for HLA typing and the algorithms for HLA matching. We also address ethical aspects regarding children and minors as stem cell donors. © 2019 S. Karger AG, Basel

Introduction

Finding a suitable donor for a patient in need of a stem cell transplantation based on HLA matching seems to be a straightforward procedure. However, advances in our knowledge about the HLA system and new technical achievements necessitate a constant adaption of the search algorithms. Furthermore, the patient's age and a distinct spectrum of diseases in children impact the criteria for selecting the best available donor. This review article aims to provide some insight into the general algorithms for HLA matching and stem cell donor selection and to emphasize some relevant considerations regarding donor selection in pediatrics.

General Guidelines for HLA Matching

The major histocompatibility complex (MHC) describes a fundamental mechanism for recognizing and segregating self from non-self structures. MHC proteins are heterodimeric proteins with an interaction surface for T cells. The human MHC is referred to as the human leukocyte antigen (HLA). The underlying gene loci are located in close genetic vicinity on the short arm of chromosome 6 (6p21.3). HLA molecules are both polygenic and polymorphic, with a high sequence homology overall. These features provide a certain challenge to accurate sequencing.

HLA typing has a long history and undergone continuous development of technical and computational improvements. Currently, serological typing results are still present in certain databases (at least for certain loci), but minimal sequencing standards have been implemented. In general, laboratories providing full HLA typing have to be accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), the European Federation for Immunogenetics (EFI; www.efiweb.eu),

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the United Kingdom Accreditation Service (UKAS) (www.ukas.com), or Clinical Pathology Accreditation (CPA). Typing definitions (i.e., low, intermediate, and high resolution) and result reporting should follow the official nomenclature [1]. General guidelines on HLA matching have recently been published in the guideline of the British Society for Histocompatibility and Immunogenetics (BHSI) [2].

Mismatches in HLA alleles can result in different immunological effects, depending on whether the mismatch is in the host-versus-graft or the graft-versus-host direction. Host-versus-graft reaction denotes the recognition of donor MHC molecules (or at least of unknown donor-specific peptide sequences presented by donor MHC) by recipient T cells. This reaction results in graft rejection and is of major importance in organ transplantation. In allogeneic stem cell transplantation, this reaction might be of relevance in the context of low-intensity conditioning; however, our knowledge about the antigens driving these reactions is very limited. In contrast, graft-versus-host reactions have been extensively investigated over the last decades. Mismatches of several HLA alleles between donor and host cause lethal graft-versus-host disease, necessitating profound T-cell depletion of the graft (see section Haploidentical Donor Selection below). Yet, graft-versus-host reactions also occur in transplantations without obvious HLA mismatches. These cases (making up the vast majority of all cases of graft-versus-host disease) are caused by differences in polymorphic peptides between donor and host. The list of well-characterized and -validated so-called minor histocompatibility antigens – which are generated by single nucleotide polymorphisms, indels, or gene deletions – is steadily growing and subject to ongoing research [3]. Unraveling the complexity of minor histocompatibility antigen differences between donor and host will be key to separate graft-versus-host disease from a positive graft-versus-leukemia effect.

Describing distinct HLA gene loci provides the lowest level of information and reflects whether the expressed genes belong to class I or class II. All transplantation-relevant genes are expressed codominantly. Currently, 3 class I loci (HLA-A, -B, and -C) and 2 class II loci (HLA-DRB1 and -DQB1) need to be analyzed. These 5 genes on the diploid human genome add up to 10 loci and finally consider a fully matched donor-recipient set as 10/10. Of note, more class I loci exist, and their gene products fulfill essential functions during embryogenesis: HLA-G and HLA-E (which are clustered as class Ib genes) are expressed on fetal tissue and trophoblasts, and their interaction with maternal CD94/NKG2 receptors allows that the non-self fetal tissue is not recognized by the mother's immune system, thereby maintaining immune tolerance during pregnancy.

The chromosomal organization of the HLA gene cluster at one single locus and our limited knowledge of additional gene functions or regulation within this gene cluster emphasize that the mere selection of "fitting" alleles between donor and recipient (which finally translates into a 10/10 score) does not reflect the biological significance as found in identical siblings. To address this issue, algorithms and programs are in place not only to identify donors with identical single HLA alleles but also to ensure that these alleles are best selected as complete haplotypes [4]. This becomes even more relevant to recipients with poor coverage in stem cell donor databases, i.e., those with a rare or mixed ethnicity [5].

The HLA nomenclature has been repeatedly revised and constitutes a system of four fields, each separated by a colon. The first field often reflects the "classic" serological or "allelic" number, whereas the second field reflects the specific allelic variation that results in a defined amino acid sequence. The third field reports synonymous variants that will encode for the same protein, whereas the fourth field reflects alterations in noncoding regions [6]. One attempt to facilitate readability was to include immunologically equivalent groups (A*02:01:01G) that comprise several distinct genes or to state that the resulting protein (for the parts of the protein encoded by exons 2 and 3) is identical (HLA-A*02:01P).

Typical molecular biological approaches to HLA genotyping include (a) sequence-specific primers, which allow low-to-high resolution (i.e., A*02); (b) sequence-specific oligonucleotides, which provide low-to-intermediate resolution (i.e., A*02 BNT); and (c) sequence-based typing, which will lead to high resolution (A*02:02 or A*02:02:01G).

When donor-derived material has arrived, confirmatory typing is usually performed by intermediate-resolution assays (sequence-specific oligonucleotides). Relevant to stem cell transplantation are the interaction domains of the MHC molecule with the T-cell receptor (TCR). An MHC class I molecule contains 8 exons and shares a stabilizing β_2-microglobulin light chain. The interaction domain to CD8-positive cytotoxic T cells is encoded by exons 2 and 3. In contrast, MHC class II molecules are heterodimers with a rather hypomorphic β-chain. The interaction domain is thus effectively only encoded by exon 2 of each gene. Identical in this context of stem cell transplantation is the translation into the same amino acids derived from these exons. This antigen recognition site match represents the lowest standard for identity.

Next-generation sequencing has been adopted for HLA typing. Its development has been hampered by the highly polymorphic features of the HLA loci, with the addition of several pseudogenes. Overall short read lengths in second-generation sequencing have led to sequence

ambiguities that did not allow defining whether two variants are in cis or in trans position, especially when a cosegregation analysis was impossible due to limited access to family members (parents and siblings). New approaches that are referred to as third-generation sequencing have bypassed and solved many of these problems [7]. Targeted sequencing allows inclusion of the complete gene sequence (including introns) rather than only the minimally required exons 2 and 3.

Null Alleles

The detection of null alleles poses an additional challenge. If a null allele is not recognized (i.e., due to a stop codon in exon 1 or a mutation in the promoter region), the regular sequence derived from exons 2 and 3 might suggest normal surface expression. Thus, the mismatch between donor and recipient could result in graft failure or in an increased graft-versus-host disease. German consensus guidelines [8] require an analysis of the three most common null alleles when certain additional loci are detected: A*24:09N when B*27 or B*40 is detected; B*51:11N when the haplotype A*02:01 & C*15:02/15:13 & DRB1*04:02 is present. C*04:09N represents the most common null allele and needs to be tested for when B*44:03 is present. However, additional null alleles might occur. As serotyping is hardly performed for stem cell transplantations, the presence of these HLA proteins on the cell surface is typically not tested. The new deep sequencing approaches might help to detect these null alleles.

HLA-DP and HLA-DRB3/4/5

Expression levels differ between certain HLA molecules: HLA-A, -B, -C, and -DR are usually expressed at a higher level than HLA-DQ or HLA-DP. The latter ones are also less polymorphic, so that the necessity of a match for these loci is less clear. Over the last decade, the association of HLA-DP matching with clinical outcome has been investigated extensively. Several reports have described that certain allele constellations are associated with increased T-cell cytotoxicity. Besides classic matching for HLA-DPB1, the group of Fleischhauer have developed the T-cell epitope (TCE) algorithm, which categorizes DP alleles into three (or four) groups of antigens that elicit similar T-cell reactivity [9, 10]. The TCE model has been implemented in several search algorithms and is also included in the OptiMatch platform [11]. HLA-DRB3, -DRB4, and -DRB5 are genes that are only present in certain haplotypes and behave like alleles of a single locus. Their overall expression level is low [12]. Nevertheless, programs used in search units might provide sequencing results for these alleles too, and matching should be considered when appropriate, i.e., when a match or mismatch is obvious from the matching data.

Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE)

The TCE algorithm was developed based on elegant experiments which directly addressed the recognition of HLA epitopes by cytotoxic T cells. In contrast, the presentation of foreign, non-self antigens by MHC molecules formed the basis for a model called Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE). In this model, relevant mismatches are considered for presentation, and scores for MHC class I and class II can be calculated. Studies have been made that clearly emphasize that the algorithms allow a functional correlation with the outcome [13, 14]. The underlying algorithms are continuously improved [15]. These models might be of value to those patients for whom no fully matched donor is available in the databases.

For solid organ transplantation, the recipient immune system will detect and recognize histocompatibility complexes of the transplanted organ (host-versus-graft direction). A homozygous locus (A*02:01/A*02:01) will thus be perceived as identical even if the recipient has two different alleles (A*02:01/A*03:01) for this locus. For stem cell transplantation, the point of view is more complex, with a focus on the graft-versus-host direction. Discrepancies regarding homozygosity have to be considered for the graft-versus-host direction as well as for the host-versus-graft direction, especially when planning the intensity of the preparative regimen.

The Search for a Suitable Donor

Currently, three sources of donors may be considered: (1) related donors, (2) unrelated donors, and (3) cord blood units. An evolving body of evidence suggests that matching for HLA alleles is more important than the degree of relationship. At least in the pediatric field, results after allogeneic transplantation for hematologic malignancies with either matched related or unrelated donors are considered equivalent. Although for historical reasons there still is a preference for matched sibling donors (MSD), in case of an available matched unrelated donor (MURD) such donations should be limited to siblings with the ability to reason, i.e., those above the age of 14 years. With regard to nonmalignant disorders such as sickle cell disease, the outcome data still are more beneficial with matched related donors, even if data with alternative donors are evolving. In case no matched donor is available, mismatched related donors or cord blood units represent feasible options, with a worldwide trend towards haploidentical transplantations. In Germany, cord blood transplantations essentially are not performed anymore, but they are still more common in other countries, such as the USA and France, with larger cord blood banks.

Thus, due to donor availability in daily clinical routine in developed countries, the transplant physician usually decides between a matched unrelated and a mismatched related donor, with a preference for the former.

Related Donors

Among related donors, the best choice is a full MSD. Such a donor matched for HLA class I and class II will typically also bring identity for class III genes that are situated between class I and class II genes. Identity for HLA-A, -B, and -C as well as for HLA-DRB1 and -DQB1 does not guarantee that all MHC are identical, as some crossing over might occur for those loci without a linkage disequilibrium, like HLA-DPB1.

A special situation arises with monozygotic twins. Here, not only are the donor and the recipient fully identical for all major and minor histocompatibility genes, but there is also an overall genetic identity. In this case, we expect no graft rejection or graft-versus-host disease; also, there will be no graft-versus-leukemia effect. Depending on the underlying medical indication for the hematopoietic stem cell transplantation, the monozygotic twin might be well suited or not. Of note, with increasing knowledge about epigenetic features, we know that relevant differences in protein expression might evolve, even between these otherwise identical siblings; however, our currently applied molecular sequencing approaches are blind in detecting these differences.

Unrelated Donors

Unrelated donors are now considered to be an excellent choice when they are fully matched (MURD). National and international databases have accumulated data on many potential donors, and for some patients, more than one fully matched donor is available. As the age of the donor has an important impact on the outcome, younger donors should be preferred over older donors, as well as over related donors. However, it is unclear whether this holds true for all donor-recipient constellations [16].

Besides HLA matching, additional criteria should be taken into consideration when selecting the best available donor. For instance, in haploidentical transplantations, using a female donor for a male recipient is associated with an increased risk of graft-versus-host disease [17], but this difference might also confer a better survival [18]; sensitization of a female donor with a history of multiple pregnancies to male minor histocompatibility antigens or HLA alleles is a potential mechanism for this phenomenon. In T-replete allotransplantation, the situation might be entirely different. Here, male donors have been shown to exhibit stronger T-cell reactivity against tumor-associated antigens than female donors [19], and female-to-male transplantations were associated with significantly reduced survival [20].

Virus reactivation poses a threat to immunocompromised patients; cytomegalovirus (CMV) and, to a lesser extent, adenoviruses and Epstein-Barr virus are the most relevant in this regard. Thus, CMV serostatus is a typical parameter; a CMV-negative recipient should receive stem cells from a negative donor, and a positive recipient from a seropositive donor [21].

Cord Blood Units

Cord blood units are a further stem cell source; however, clinical experience with and preference for this graft type vary widely between countries. Hematopoietic progenitor cells present in cord blood provide unique features, with a more fetal signature overall. Since the success of the first cord blood transplantation in 1988, it has been assumed that less active or hypoactive T cells in the unit might explain why there generally is less graft-versus-host disease after cord blood transplantation than after bone marrow or peripheral blood stem cell transplantation. Currently, HLA typing is often limited to HLA-A, -B, and -DR, partly assuming that, due to linkage disequilibrium, HLA-C and -DQ will match in the majority of cases. The mismatch in one or two HLA loci allows fostering a graft-versus-leukemia effect without the risk of excessive graft-versus-host disease. This aspect is especially relevant with malignant indications; however, cord blood transplantation has also been applied to nonmalignant indications including immune deficiencies or hemoglobinopathies [reviewed in 22 in references therein].

One major hurdle is the limited amount of available material [23]. A very recent study [24] has evaluated over 126,000 cord blood units in the USA and found that many units contain fewer cells than originally thought. As a matter of fact, cord blood units might be a feasible option for smaller children; however, the available numbers of cells in cord blood grafts are problematic for full-grown adults. The authors concluded that only about half of the units were acceptable for patients weighing 30 kg and 30% for patients weighing 40 kg; for adults weighing 80 kg, only 15% of the units were acceptable [24]. This problem was addressed by the concept of "double-unit cord blood transplantations," with considerable success although the transplantation immunology is only incompletely understood, due to the fact that there is a dominant unit that will finally take over hematopoiesis [25]. New technologies include ex vivo cord blood expansion, which might evade the issue of limited material [26, 27].

Haploidentical Donor Selection

In case there is no identical matched related donor and a patient cannot wait until a suitable MURD is found, a haploidentical donor should be considered, which typically is a parent or sibling. This approach using readily available donors dramatically expands the pool of possible

transplantation candidates and represents a good option for patients with high-risk diseases. Therefore, this transplant option has experienced steady growth rates, with impressive success over the last years, especially in East Asian countries with small unrelated donor registries [28].

Transplant regimens with a haploidentical donor require profound in vitro or in vivo T-cell depletion to counteract the increased risk of graft-versus-host disease due to HLA mismatching. In vitro T-cell depletion with the latest technologies, such as TCRab/CD19 depletion, is still a favorable option for graft manipulation in haploidentical transplantation, since patients need only minimal immunosuppression after transplantation and very promising outcomes have been reported with this technique [29]. In haploidentical transplants with ex vivo T-cell depletion, there are no reports that the type of HLA mismatch has any impact on the transplantation outcome. In these cases, donor selection criteria other than HLA matching might matter – e.g., KIR mismatching in myeloid malignancies [30], the general preference for male donors and donors of younger age [31], and matching for CMV IgG serostatus and the AB0 system. However, the algorithms rating these non-HLA-related selection criteria have not been validated in clinical trials so far.

Donor selection might differ in haploidentical transplantations with in vivo T-cell depletion, e.g., using post-transplant cyclophosphamide or anti-thymocyte globulin. In this transplantation mode, one study group has identified an HLA-B mismatch as an independent risk factor for acute graft-versus-host disease [32], whereas this could not be confirmed by others [31, 33]. Irrespective of the T-cell depletion method used, all recipients of a haploidentical stem cell transplant should be screened for donor-specific anti-HLA antibodies, as the presence of those is associated with primary graft failure and transplant-related mortality. Solid-phase approaches like the Luminex assays provide a reliable assay platform for detection of these relevant antibodies [34]. In case no donor-specific anti-HLA antibody-negative donor is available, inclusion of B-cell-depleting anti-CD20 antibodies (off label) and/or plasmapheresis in the preparative phase can help to minimize the risk of graft rejection or graft failure. Haploidentical stem cell transplantations open up new horizons in transplantation immunology, such as the discovery of the importance of noninherited maternal antigens [31] and HLA haplotype loss variants [35], giving the HLA system an entirely different significance.

Ethical Considerations

Over the last decades, HLA-matched children have been stem cell donors for their siblings in need of a stem cell transplantation. However, with more matched unrelated adult donors available in the national and international databases and the increasing equalization of MURD and MSD transplantations, it has become an ethical issue whether minors can or should be donating stem cells. The American Academy of Pediatrics provided a Policy Statement in 2010 with a series of 5 points that need to be fulfilled before a minor may be considered as a stem cell donor [36]. These discussions have been taken up in the UK [37]. The need of longitudinal observation and psychosocial assessment and management has now come into focus [38, 39]. German policies have been set this year in *Deutsches Ärzteblatt* (DOI: 10.3238/arztebl.2019.rl_haematop_sz02).

One further step, if no HLA-matched donors are available, is certainly the creation of "savior children" who are designed (or selected) by preimplantation HLA matching. There is a growing literature with comments and ethical considerations regarding this topic [40–45], as to whether children should be considered as stem cell donors at all when suitable MURD are available. Studies demonstrating comparable outcomes after MURD and MSD allotransplantations have prompted these reflections.

Finally, ethical recommendations need to be provided for guidance on the handling of accidental findings as a result of targeted sequencing, e.g., explanations of the HLA-associated disease prevalence with respect to autoimmune diseases [46].

Special Issues in Pediatrics

In general, the algorithms for HLA matching and stem cell donor selection are the same for pediatric and adult recipients. However, in adults, the vast majority of indications are malignant disorders with the need to eradicate the malignant cells and therefore to maximally exploit a possible graft-versus-leukemia effect. In children, malignant disorders like leukemias and lymphomas are also a typical indication for transplantation, but there are also nonmalignant indications (inborn defects of red blood cells [i.e., hemoglobinopathies], inherited thrombocytopenia [i.e., congenital amegakaryocytic thrombocytopenia], general immune defects [i.e., Wiskott-Aldrich syndrome], or metabolic disorders [adrenoleukodystrophy]). In these cases, a graft-versus-leukemia effect is not necessary, a reduced-intensity conditioning regimen can be applied and a stable mixed donor-recipient chimerism might be enough to cure the disease.

There is evidence that donors best suited for recipients with nonmalignant diseases might differ from donors for patients with a malignant disease. For example, among thalassemia patients, allogeneic transplantations from a matched sibling and from a MURD have resulted in similarly good results [47]. In contrast, among sickle cell disease patients, the good clinical results obtained with MSD trans-

plants [48] could not be reproduced with transplants from unrelated donors [49]; thus, MURD transplants are not recommended to patients with this disorder. Current clinical trials are investigating whether haploidentical transplantation with TCRαβ/CD19-depleted grafts represents a valuable option for these patients. Generally, the number of clinical studies with pediatric patients and nonmalignant disorders is rather low, and further multicenter trials are warranted to obtain more reliable data on this issue.

Acknowledgements

The authors would like to thank Dr. Kremena Todorova for critical comments on the manuscript.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors had no relevant funding that affected this review article.

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