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TRANSFUSION CLINIQUE ET BIOLOGIQUE

Transfusion Clinique et Biologique 24 (2017) 124–130

State of the art

What compatibility in 2017 for the haematopoietic stem cell transplantation?

Quelle compatibilité en 2017 pour la greffe de cellules souches hématopoïétiques ?

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Available online 11 July 2017

Abstract

The diversification of potential donors to perform stem cell allografts now enables to propose a compatible graft cell source adapted to the different clinical situations. Transplants with a geno-identical sibling donor, otherwise with the most HLA-compatible unrelated donor, remain the first-line solutions. Alternative transplants allow to graft patients having no donors in international registries, owing to the rarity of their HLA typing. They are carried out with fairly incompatible grafts and are therefore limited by the existence in the recipient of preformed anti-HLA antibodies which predispose to their rejection. The simple prevention of acute Graft-versus-host disease in haplo-identical transplants, as well as the availability of donors, explain why they have very often replaced placental stem cell transplants. These latter remain useful for pediatric patients or in the absence of family donors.

Keywords: Immunogenetics; Histocompatibility; HLA; Allograft; Stem cells; Placental blood; Anti-HLA Antibodies

Résumé

La diversification des donneurs potentiels pour la réalisation des allogreffes de cellules souches permet désormais de proposer une source cellulaire de greffon compatible adaptée aux différentes situations cliniques. Les greffes avec un donneur géno-identique issu de la fratrie ou à défaut avec un donneur non apparenté le plus HLA-compatible possible, demeurent les solutions de première intention. Les greffes alternatives à celles-ci permettent de greffer les patients n'ayant pas de donneurs sur les registres internationaux en raison de la rareté de leur typage HLA. Elles s'effectuent avec des greffons assez largement incompatibles et par conséquent sont limitées par l'existence chez le receveur d'anticorps anti-HLA préformés qui prédisposent à leur rejet. La prévention aisée post greffe de la réaction du greffon contre l'hôte dans les greffes haplo-identiques, ainsi que la disponibilité des donneurs, expliquent qu'elles aient remplacé très souvent les greffes de cellules souches placentaires. Ces dernières conservent une place pour les patients pédiatriques ou sans donneurs familiaux.

Mots clés : Immunogénétique ; Histocompatibilité ; HLA ; Allogreffe ; Cellules souches ; Sang placentaire ; Anticorps anti-HLA

1. Introduction

Allogeneic haematopoietic stem cells transplantation (HSCT) has become over the last 30 years a major therapeutical approach for numerous haematological diseases and immunodeficiencies, although impaired by numerous complications. Because of its important influence on post-graft clinical outcome, human leukocyte antigen (HLA) compatibility became the cornerstone of donor selection. Today, grafts with geno-identical or pheno-identical donors are still the first-line transplants for most clinical teams. If no sibling donors are available and if no acceptable unrelated donors can be found rapidly on registries, mismatched allo-HSCT with haplo-identical related donors or with umbilical cord blood (UCB) units constitute a strong alternative. The histocompatibility laboratories must find and propose potential donors the more appropriate to a given situation, in the context of constant

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http://dx.doi.org/10.1016/j.tracli.2017.06.006
1246-7820/

evolution of patient clinical management and technologies for HLA typing and antibodies determination, according to the accreditation standards edicted by the European Federation of Immunogenetics.

2. Geno-identical donors

For patients needing an allo-HSCT, the first step in finding a suitable donor is usually to search HLA geno-identical individuals within the relatives. There are only 4 possible combinations of parental chromosomes in the progeny. As a consequence, there is a theoretical probability of 25% for an individual to have a sibling identical for all HLA genes, including class I to III, and non-classical HLA genes.

Consanguinity between patient's parents, and/or sharing common haplotypes can sometimes lead to identity between the patient and one parent, at least for locis HLA-A, B, C DRB1 and DQB1. Moreover, crossing overs may occur during the gametogenesis in parents, creating a new haplotype in the progeny and decreasing the probability to find an HLA-identical sibling. Monozygotic twins as potential donors, are generally not recruited, because these transplantions have similar results to autologous grafts.

Globally, geno-identical sibling donors (SD) represent the source of cells for about one third of all the HSCT performed in France.

3. Marrow unrelated donors

Nowadays, unavailability of SD can often be overcome by finding a compatible marrow unrelated donor (MUD) among the international registries.

Specifically for patients with high risk of acute myeloid leukemias in primary relapse, HSCT with 10/10 MUD can be even associated to better outcome than with matched SD [1]. Globally, MUD represent the source of HSC for about half of all the graft performed in France.

It is generally considered that the average probability for two unrelated individuals to be HLA-matched is about 1/1,000,000. By the end of 2016, more than 29 millions volunteer donors were available worldwide. The probability to find a compatible donor for a given patient exhibits considerable variations, between several hundreds of donors to. . . zero, depending on the frequency of patient's HLA typing.

The next generation of sequencing (NGS) recently introduced in several registries, allows to obtain for new donors a HLA typing at high or 4-digits resolution. This constitutes a great improvement since compatible donors can be identified immediately, whereas for previously registered donors, complementary typing are still required.

Before the formal request of HSC collection, a verification of the compatibility must be performed by the laboratory affiliated with the transplant centre [2] on a new blood sample. This requirement is an opportunity to check the donor availability, but explains why finding a MUD is a challenge, in so far as the time between the diagnosis and the transplantation influences the risk of relapse.

3.1. Molecular basis of HLA mismatches

A mismatch (MM) could be defined as an incompatibility between two individuals due to differences in allelic polymorphisms.

HLA compatibility can be determined at different levels of resolution [2]:

- at 2 digits, the typing roughly corresponds to the antigenic level, i.e. determined by specific antibodies;
- high resolution distinguishes alleles differing in the amino acid sequences of the peptide-binding domains (encoded by exons 2 and 3 for class I, by exon 2 for class II). High resolution, as defined by the EFI, requires also to identify/exclude non-expressed alleles, whatever the mechanism of this lack of expression;
- 4-digit resolution concerns the whole amino acid sequence of HLA molecule, whatever the polymorphic positions.

MM can be permissive (no impact in term of clinical outcome) or not, depending on their nature: MM can be at antigenic level, high or 4-digits resolution.

First, MM can be linked to non-expressed (« null ») alleles. These null alleles can be due to polymorphisms situated in exons encoding premature stop codons, or situated in introns and perturbing the excision/splicing mechanisms. Owing to the absence of expression, these individuals must be considered as homozygous for the expressed allele for determining the compatibility.

Secondly, MM can lead to different proteins with different functional properties in antigen presentation/protein–protein interactions, depending on the different polymorphisms positions (i.e. which exon).

Thirdly, impacts of MM depend on the level of protein expression of each allele.

The Next generation Sequencing is now the more informative method concerning the two first points (including in describing new alleles), but protein expression is not routinely evaluated.

Endly, if the recipient is homozygous, the heterozygosity in the donor constitutes an acceptable MM in the host versus graft direction, without any real impact on clinical outcome.

The exon 1 for *HLA* genes encodes for the leader peptide resulting from a cleavage after protein biosynthesis. HLA class I leader peptide has the particularity to be loaded by HLA-E molecules [3]. This non-classical HLA molecule is known to inhibit natural killer (NK) cells reactivity via CD94-NKG2A lectin-type NK cells inhibitory receptors. This system constitutes a global surveillance of HLA class I expression. It is not known if amino acid disparities for the peptide leader sequences influence the NK cells inhibition and consequently can generate a cellular response and have an impact on clinical outcome.

However, some alleles can display stop codons in exon 1, leading to null alleles (for instance A*68:11N, B*18:17N, B*44:19N, C*03:20N [4]). These alleles are rare: on 13000 typings performed by NGS with OMIXON° kits, 2 such new null