Haploidentical Hematopoietic Stem Cell Transplantation: Rationale, Development, and Jefferson's Method

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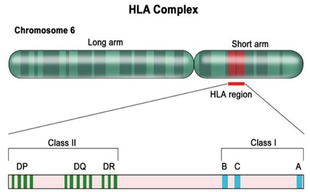
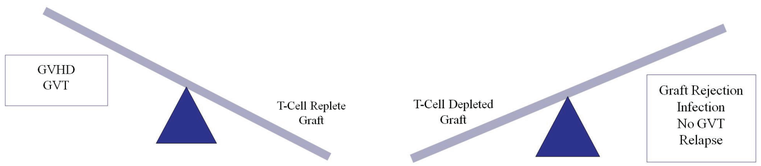
INTRODUCTION

There are many indications for hematopoietic stem cell transplantation. In addition to hematologic malignancies, transplants are performed in certain non-hematologic malignancies, for marrow disorders such as Sickle Cell Anemia, and for various inherited disorders such as SCID. Traditionally, transplants have been performed between donors and recipients that are a complete HLA match (typically matched siblings). That is, patients have identical HLA alleles on both copies of chromosome 6. HLA alleles code for major histocompatibility complex molecules, which are the proteins that cause transplant rejection when a mismatch between donor and recipient is present. Thus, matched transplants have been historically favored in order to avoid both rejection of the graft by the recipient, as well as disease in the recipient due to graft vs. host disease (GVHD) in which the donor immune cells attack the host's tissues.



However, matched transplants have several disadvantages. First, only about 30% of patients requiring a transplant have a matched sibling available as a donor. For the remaining 70%, the search for an unrelated matched donor can be time consuming, expensive, and especially difficult for patients of minority racial and ethnic groups. Many conditions requiring transplant are so acute that patients often die during the search for a donor. Accordingly, several institutions pioneered the research and implementation of haploidentical transplants as a viable option.

A haploidentical transplant refers to the situation when the recipient and donor have identical alleles on one copy of chromosome 6, but not on the other. In terms of advantages, haploidentical transplants greatly increase the pool of available donors since biological parents are by definition haploidentical to all of their children, and there is a much greater chance that a sibling will be a half match than a full match. Additionally, haploidentical transplants allow for a critical Graft vs. Tumor effect (GVT), whereby the donor's immune cells attack the recipient's cancer cells because of the HLA mismatch present. The caveat, however, is that this mismatch also promotes GVHD that can be lethal. Accordingly, different institutions have attempted various methods of manipulating the donor graft to try and maximize the GVT effect while minimizing GVHD. Jefferson's regimen is one such method that has had success thus far.

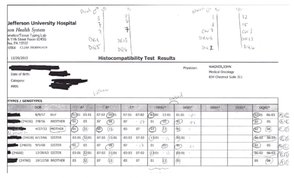


CHOOSING A DONOR

Jefferson takes many factors into account when choosing a suitable haploidentical donor. Three particularly important criteria are (1) the donor's HLA profile, (2) the presence of KIR ligand mismatch between donor and recipient, and (3) the implications of pregnancy-induced immunologic effects.

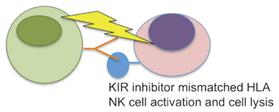
HLA Typing

HLA typing is the most important component of picking a donor. It is done via a blood test, and the results look like the example on the right. By looking at the pattern of inheritance of HLA alleles, one can deduce the chromosomal makeup of the patient's parents and siblings. In this example, all but one of the patient's tested family members is at least a half match, thus allowing selection of a donor based on even more specific criteria. This is illustrative of one of the main advantages of haploidentical transplant.



KIR Ligand Mismatch

KIR receptors are present on Natural Killer (NK) Cells, and their ligands are MHC-I proteins. When an NK cell encounters a self MHC-I molecule, it's killing function is inhibited. Conversely, when it encounters non-self MHC-I, it causes cell lysis. Thus, a mismatch between donor and recipient results in lysis of recipient cells by donor NK cells. Interestingly, donor NK cells preferentially kill blood cells but not tissue cells. Thus, KIR mismatch between donor and recipient causes a GVT effect, but no GVHD. This effect is especially robust in AML patients.



Pregnancy-Induced Immunologic Effects

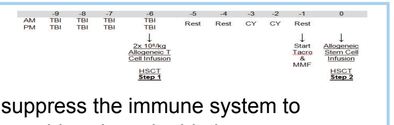
As a result of exposure to each others' antigens in utero, the immune systems of mother and child react to each other in unique ways. Furthermore, women who have carried a male child have antibodies to Y-chromosome antigens. Donors are thus picked to maximize the potential GVT effect based on these variables.

Recipient	Preferred Donor	Rationale
Child	Mother	↑ GVT
Mother	NOT Offspring	↓ GVT
Male	Parous Female	↑ GVT

PERFORMING THE TRANSPLANT

Jefferson's method is myeloablative with respect to the donor's bone marrow and T-cell replete with respect to the donor graft. It is a two-step process, meaning that the myeloid and lymphoid lineages are infused separately. The goals of this method are as follows:

1. Provide optimal T-cell dose (maximize GVT, minimize GVHD, avoid graft failure)
2. Avoid exposure of HSCs to Cyclophosphamide to prevent potential cell damage
3. Avoid polarization of T cells to TH2 phenotype



Days -9 to -7: Patient is subjected to total body irradiation (TBI; 12 Gy) to reduce the amount of cancer cells and suppress the immune system to prevent graft rejection. This regimen is considered myeloablative.

Day -6: Patient receives $2x10^8$ T-cells/kg (Step 1). The protocol was designed so that this dose could be adjusted as necessary, but the dose was not changed due to high rates of engraftment, good immune reconstitution, and low rates of GVHD.

Days -5 and -4: Rest. Patients develop high fevers, diarrhea, and rash as a result of the T-cell infusion.

Days -3 and -2: Cyclophosphamide (Cy) administration. Cy targets rapidly dividing cells, and thus selectively kills the infused alloreactive T-cells while sparing non-alloreactive T-cells. Fevers disappear after the second dose of Cy.

Day -1: Rest. Patient is given additional GVHD prophylaxis.

Day 0: Infusion of hematopoietic stem cells (Step 2)

RESULTS AND FUTURE IMPLICATIONS

To date, over 180 patients have received this type of transplant at Jefferson. Patients have experienced low incidences of severe GVHD, relapse, and infection, and in general results have been comparable to those received with fully matched transplants. This will potentially allow virtually every patient in need of a transplant to receive one, and will widen the spectrum of diseases that can be treated with such methods.

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