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Cure of HIV-Infected Leukemia Patients with Cord Blood Transplantation

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Introduction

More than forty years after the onset of the HIV pandemic the disease has not been cured using Highly Active Antiretroviral Treatment (HAART), by gene therapy, or by Hematopoietic Cell Transplantation (HCT) using cells from the general pool of stem cell donors. The most important reason for natural protection against HIV transmission is a mutation in the CCR5 gene leading to a 32-base-pair deletion (CCR5-Δ32/Δ32) [1,2]. Carriers of this mutation are resistant to HIV-1 infection.

A commonly used treatment for selected patients with leukemia is hematopoietic cell transplantation. For those patients who have an indication for a HCT and also have an infection with HIV, a therapy that has been shown to cure both disorders is HCT with CCR5-Δ32/Δ32 stem cells.

In February, [3] performed a HCT in Berlin, Germany on a patient with acute myelogenous leukemia who was infected with HIV. The stem cells used for this transplant were obtained from the peripheral blood of a CCR5-Δ32/Δ32 adult donor. More than 7 years after the transplant the patient, now known as the "Berlin Patient", does not require antiretrovial therapy and there has been no detectable HIV in the blood stream as determined by analysis of viral RNA and cellular proviral DNA. In addition, the $CD4^+$ T-cells have returned to a normal range. Therefore, the investigators have concluded that transplantation of CCR5-Δ32/Δ32 stem cells has led to a functional cure or a "sterilizing cure" of HIV infection [4].

Cure of HIV with Hematopoietic Cell Transplantation

One would expect that the procedure that led to a cure of HIV in the "Berlin Patient" would be performed repeatedly in other HIV-infected patients. Obstacles to frequent use of HCT for cure of HIV are that persons who are homozygous for the CCR5-Δ32 allele are quite unusual (<1% of Caucasians, and much lower in other ethnic groups), and most patients in need of an HCT have only a small number of potential donors from among registries of adult volunteer donors. Moreover, when the donor stem cells are obtained from adults, as in bone marrow or peripheral blood stem cell transplants, a very close HLA match is required between donors and recipients for 8 of 8 or 7 of 8 high-resolution alleles at 4 loci (A, B, C, DRB1)[5]. Thus, finding a donor who has a very close HLA match to a patient in need of a transplant and who is also homozygous for the CCR5-Δ32 allele is extremely difficult and will only rarely be possible. Indeed, no further HCTs of patients with HIV infection using CCR5-Δ32/Δ32 stem cells from adult donors have been performed.

Development of an Inventory of Ccr5-Δ32/Δ32 Cord Blood Units

In marked contrast is the fact that using stem cells from umbilical cord blood for HCT provides a major advantage in that much less stringent HLA matching between donor and recipient are required. Indeed, acceptable HLA-matched units include those that are matched at 4 of 6, 5 of 6, or 6 of 6 alleles at 3 loci using low resolution testing at the A and B loci and high resolution testing at the DRB1 locus, disallowing 2 mismatches at the same locus for 4 of 6 matching. Therefore, our hypothesis is that an inventory of cryopreserved umbilical cord blood units that are CCR5-Δ32/Δ32 will provide a significantly improved probability of finding an appropriately HLA-matched CCR5-Δ32/Δ32 donor for HCT of a patient with HIV infection.

Accordingly, we have developed an inventory of cryopreserved CCR5-Δ32/Δ32 cord blood units to be used for HCT of appropriate patients. We have tested samples from approximately 25,000 cryopreserved cord blood units obtained primarily from Caucasians and have identified 190 CCR5-Δ32/Δ32 units for an incidence of approximately 0.8%. Testing an additional 15,000 samples from Caucasians is expected to increase the special inventory to about 300 units.

Testing of large numbers of samples requires the collaboration of multiple cord blood banks since no single bank has enough units. Collaborating cord blood banks are St. Louis; Duke University; University of Colorado; MD Anderson Cancer Center; Sydney, Australia; and Barcelona, Spain. CCR5 genotype analysis is performed on DNA extracted from cord blood using a PCR based assay for homozygosity of the CCR5-Δ32 bp deletion.

Experiences Using Cord Blood Ccr5-Δ32/Δ32 Cord Blood Units for Transplantation

Some transplant physicians are aware of our inventory of CCR5-Δ32Δ32 units and as a result have referred patients to us for units to be used for transplantation. One concern is that the stem cell dose in an umbilical cord blood unit will be inadequate for transplantation of an adult patient. This issue has been resolved by [6] who demonstrated that the cell dose of a cord blood unit need be only $1x10^7$ TNC/kg when used as part of a dual haploidentical/cord blood transplant. This cell dose is readily attainable with a large percentage of cord blood transplants in adults. Another option is to use a double cord blood transplant when two adequately HLA matched CCR5-Δ32/Δ32 units are available. Indeed, when HLA matching for Caucasian patients we have found as many as 6 adequately matched units in the special inventory.

A patient in Utrecht was transplanted with a dual haploidentical unit and a CCR5-Δ32/Δ32 cord blood unit. He engrafted well and the CCR5-Δ32/Δ32 unit was the "winning unit". However, after about 2 months his underlying hematological malignancy relapsed and he died as a result.

A patient in Barcelona was transplanted with a dual haploidentical unit and a CCR5-Δ32/Δ32 cord blood unit. The patient engrafted with the haploidentical unit first and ultimately a CCR5-Δ32Δ2 cord blood unit dominated, but later his underlying hematologic disease relapsed and he died as a result.

Providing a Cure of HIV Infection Now

Although extensive research has been conducted, HIV has not been cured using Highly Active Antiretroviral Treatment (HAART), by gene therapy, or by hematopoietic cell transplantation (HCT) using cells from the general pool of stem cell donors. Further, finding an adult donor who has a very close HLA match to a patient in need of a transplant and who is also CCR5-Δ32/Δ32 is only rarely possible and, indeed has not been accomplished since the transplant of the "Berlin Patient" in 2007. Therefore, the only readily available option for cure of HIV at the present time is cord blood transplantation.

Patients with leukemia or other hematologic malignancy who have an indication for a transplant and who are infected with HIV should be transplanted using CCR5-Δ32/Δ32 cord blood units in an effort to cure the HIV as well as the underlying disorder.

The major risks associated with this approach are those related to transplant related morbidity and mortality. Since HCT is indicated for the underlying disorder, the risks associated with HCT would need to be borne by the patient in any case.

Nevertheless, when selecting a CCR5-Δ32/Δ32 unit to be used for transplantation of an HIV-infected patient who also has an independent indication for HCT, there may well be alternative donor units available that are not CCR5-Δ32/Δ32 and that have a higher cell dose and/or better HLA match. In such cases the transplant physician needs to discuss with the patient the risks and benefits of using the cord blood unit that has the potential to cure the HIV infection as well as the underlying malignancy.

Obtaining CCR5-Δ32/Δ32 Cord Blood Units for Transplantation

The inventory of CCR5-Δ32/Δ32 cord blood units is maintained at StemCyte International Cord Blood Center in Covina, California, USA, and is available to all transplant physicians. All that is needed is to send the HLA type of an appropriate patient to lpetz@stemcyte.com and a search of the inventory will be performed promptly and without charge. If an adequately HLA-matched unit is found in the inventory, it will be released through the National Marrow Donor Program.

CONCLUSION

HCT using peripheral blood stem cells from an adult CCR5-Δ32/Δ32 donor has produced a cure of an HIV-infected person who also had acute leukemia. Other therapeutic approaches including the use of antiretroviral drugs or gene therapy have not been successful. However, CCR5-Δ32/Δ32 donors are quite unusual, and this coupled with the fact that the use of stem cells from peripheral blood and bone marrow requires a very close HLA match between the donor and recipient makes it impossible to frequently perform HCT using CCR5-Δ32/Δ32 stem cells from adult donors for patients in need of treatment for HIV.

Therefore, since HCT using cord blood does not require as stringent an HLA match, it must be recognized that HCT using cord bloods from CCR5-Δ32/Δ32 donors is, at the present time, the only feasible means of treatment of reasonably large numbers of HIV-infected patients [7].

No patient with an indication for a hematopoietic cell transplant and who is also infected with HIV should be denied the option of being transplanted with CCR5-Δ32/Δ32 cord blood cells in attempt to cure the HIV as well as the underlying disorder.

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