HIV: Current Research

Extended Abstract

Progress toward curing HIV with cord blood transplantation

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Abstract

In 2007 a patient who was infected with HIV and who also had acute myelogenous leukemia received a hematopoietic cell transplant using stem cells from an adult donor who had a homozygous CCR5 mutation (CCR5-/-). Persons with this mutation are known to be resistant to infection by HIV and, indeed, the patient was cured of his HIV as well as leukemia. This patient remains the only person to have been cured of HIV. This cure has not been repeated because the CCR5-/- mutation is very unusual and transplants using stem cells from adults require a very close HLA match between donor and patient. Cord blood transplants require significantly less stringent HLA matching, and thus it is more feasible to transplant HIV-infected patients with CCR5-/- donor cells from cord blood. Combined haploidentical and cord blood (haplo/cord) transplantation eliminates two problems associated with cord blood transplants, i.e., prolonged time to engraftment and cell dose needs. Inventories of hundreds of cryopreserved CCR5-/- cord blood units have been developed and are now available for transplantation, and one such transplant was performed in 2017. Further, an estimated 800,000 cryopreserved cord blood units exist worldwide which indicates that transplantation with CCR5-/- cord blood units is feasible for large numbers of patients. Cure of HIV is very important because even patients who are adequately treated with antiretroviral drugs for HIV are not protected from serious adverse effects of long-standing HIV infection, including the life-long stigma associated with the infection. Cure by transplantation is also economically beneficial because the estimated lifetime cost for persons who become infected with HIV at age 35 is ~$326,500. A rigidly held opinion by many is that patients with HIV should not be transplanted with intent to cure the infection unless they also have an underlying indication for a transplant such as leukemia. However, even in this antiretroviral era, thousands of patients die of HIV annually, and it is our opinion that the serious adverse effects of long-standing HIV are greater than the adverse effects of haplo/cord transplants of young HIV-infected patients who have no co-morbidities. The time has come to accelerate research on this topic of tremendous public health potential including transplantation of CCR5-defective cells, especially those derived from cord blood.

Antiretroviral therapy (ART) inhibits various stages in the viral life cycle, reduces the rates of transmission, and improves life expectancy. Unfortunately, ART is non-curative, and nearly all HIV-infected individuals must adhere to daily drug regimens for the entirety of their lives. This requirement indefinitely prolongs issues such as drug resistance, adverse effects, and cost.1 While ART extends and improves the quality of life, it does not fully restore health. Individuals on ART can experience chronic inflammation, immunosenescence, bone density loss, premature aging, and increased non-AIDS morbidity and mortality.2 ART treatment interruptions in aviremic HIV-infected individuals lead to rapid viral recrudescence that reaches pretreatment levels.3 Thus, suppression of viral replication with ART does not eradicate the virus, as long-lived resting memory CD4+ T-cells can harbor latent virus, and while various reservoirs may produce low-levels of virus, such as microglia and astrocytes in the central nervous system, tissue-derived dendritic cells, macrophages, and natural killer cells.4 Further complicating matters, latently infected T-cells may undergo clonal expansion by homeostatic proliferation,5 while infected T-cells and macrophages can persist without undergoing apoptosis or cytotoxic T-lymphocytes (CTL)-induced killing.

Due to persistence of infection during ART, alternative therapeutic strategies are being explored to establish a cure for HIV-1. Current and emerging approaches to eradicate HIV include transplanting virus-resistant hematopoietic stem and progenitor cells (HSPCs) in an effort to generate an HIV-resistant immune system. To achieve HIV resistance, much focus has been placed on natural mutation of or engineered inhibition of the endogenous chemokine receptor CCR5.8 Owing to the role of CCR5 as a co-receptor for HIV entry in CCR5+ CD4+ T-cells, homozygous carriers of a 32-bp deletion in the CCR5 gene (CCR5-Δ32/Δ32) are naturally resistant to HIV.9,10 As an alternative to using allogeneic CCR5-Δ32/Δ32 HSPCs from human leukocyte antigen (HLA)-matched adult or cord blood donors who have this homozygous mutation, genome editing or gene therapy strategies aim to use therapeutic genes that disrupt CCR5 genetically or post-transcriptionally, respectively.

Hematopoietic cell transplantation (HCT) has produced the only known cure of HIV infection in a patient. The patient had AML and HIV infection and was transplanted in 2007 using peripheral blood stem cells from an adult CCR5-delta32/delta32 donor. The patient, now known as "The Berlin Patient", does not require antiretroviral drug therapy and, in the analysis of peripheral blood cells and numerous tissue samples, no proviral DNA can be detected. However, this successful HCT has not been repeated because the

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frequency of CCR5-delta32/delta32 is less than 1% in Caucasians and much less in other ethnic groups, and patients in need of an HCT generally have only a few potential donors. Moreover, a very close HLA match between donor and patient is required when an adult donor is used. In marked contrast, cord blood HCT requires a significantly less stringent HLA match between donor and patient making it much more feasible to find an appropriate unit for an HIV infected patient. We have tested more than 18,000 cord blood samples from our cord blood bank and collaborating cord blood banks, and have identified 121 cryopreserved CCR5-delta 32/delta32 units that are available for HCT. An adequate cord blood cell dose need be only 1 x 10(7) TNC/kg if a combined haploidentical/cord blood transplant is performed. Projections of HLA match rates for an inventory of 300 homozygous units indicates a probability of finding an adequately matched cord blood unit with an adequate cell dose 82.1% of the time for Caucasian adults and for 85.6% for Caucasian pediatric patients. For adult African-Americans, Mexican-Americans and Chinese-Americans the potential HLA match rates are 31.6%, 48.9% and 13.9%, respectively.