HIV rebound and meningeophenilosis following ART interruption after allogeneic hematopoietic stem cell transplant: an investigation of HIV rebound


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INTRODUCTION

Antiretroviral therapy (ART) can control HIV-1 viremia, reducing its impact on immune cells and leading to immune recovery. Despite virologic control, ART is interrupted, HIV-1 viremia universally regresses within a few weeks. 

The only case of HIV cure was reported in the Berlin Patient who received an allogeneic hematopoietic stem cell transplant (alloHSCT) for treatment of acute myelogenous leukemia (AML). In this unique case, his donor cells were genetically modified and rendered resistant to HIV-1 infection by the specific genetic polymorphism CCR5Δ32, resulting in lack of CCR5 expression, one of the most common HIV-1 co-receptors.

There is interest in the alloHSCT with CCR5Δ32 donor as an alternative which may lead to reduction or eradication of HIV-1 reservoirs. Components of alloHSCT that may reduce reservoirs include cytokine therapy and allogeneic or graft versus host (GVH) effects, the process where targeted hematopoietic donor cells are recognized as foreign, leading to immune cell-mediated cytotoxicity and protection from HIV-1 replication.

We present the case of an HIV-1 infected patient enrolled in a study who received alloHSCT for AML, and experienced acute rebounds of viremia and meningophenilosis after self-deciding ART post-alloHSCT.

CLINICAL HISTORY

This is a 39-year-old African American male with HIV infection and multiple-released AML.

He was diagnosed with AML in 2004, and was initially treated with daunorubicin and high-dose cytarabine. He had a complicated oncologic history, including multiple preceding courses of chemotherapy. The patient had residual leukemias and remission was achieved with a chemotherapy regimen of cytarabine, etoposide, and cytarabine and he was referred for alloHSCT.

II- HIV-1 infection

The patient was first diagnosed with HIV-1 infection concurrently with AML, in 2004, asymptomatic during his role of AML. The patient's HIV-1 infection history has been complicated due to his multiple AML relapses, resulting in a long-term follow-up. During the period of alloHSCT, HIV-1 viremia was measured and nosocomial assays revealed the patient had developed the K100 and M184V drug resistance mutations (Dehner et al., 2006b; Dehner and Dehner, 2009). A Monogram Trolle demonstrated R5 virus prior to alloHSCT.

The patient’s ART regimen prior to alloHSCT was abacavir/lamivudine, ritonavir, and darunavir-based treatment. For his post-alloHSCT regimen, tenofovir-disoproxil fumarate was replaced with the CCR5 antagonist, maraviroc.

III- alloHSCT Course

On December 27, 2010, the patient received a reduced-intensity conditioning alloHSCT from an HLA-identical donor without complications. Per protocol, he received successive injections of immunosuppression on day 3 post-alloHSCT with the following events: ENgraftment (ANC > 500 cells/μL) on day 35. The patient underwent iatrogenic CSF depletions and was on ART stopped on day 100.

RESULTS

Reading memory CD4+ T cells obtained 100 and 245 days prior to alloHSCT were used in a limiting-dilution viral outgrowth assay (VOA) in which each well that demonstrates viral growth contains a single replication-competent virus-like particle. Peripheral blood mononuclear cells (PBMCs) were isolated using density centrifugation from whole blood. Repeating memory CD4+ T cells (CD4+CD25-CD127hiHLA DR-) were enriched using magnetic microparticles through negative depletion (Miltenyi Biotec). Purity of repeating CD4+ T cells was verified by flow cytometry (purity >89%). The repeating CD4+ T cells plated in limited dilution with healthy donor-irradiated PBMCs. The cells were subjected to maximum in vitro activation by the potent mitogen phytohemagglutinin (PHA). Replication of viruses released in the supernatants are amplified by the addition of MOLT-4/CCR5 cell line for targets. Viral outgrowth was measured by detection of p24 by ELISA in supernatant at day 14-21.

RNA was extracted from VOA p24 positive supernatants, and collected cDNA and cDNA and CSF and plasma at viral rebound. The RT-PCR region of the gag gene was amplified using Multiple Alignment Using Fast Fourier Transform (MAMFT) with minimal manual adjustments with high copy per cell. Best model of evolution for maximum likelihood (Ml) analysis was determined in ModelTest using the Akaike Information Criterion (AIC). Ml analysis was carried out mainly in PAUP*-v8.40b with the model parameter generated in jModelTest with bootstrapping of 100 pseudospecies.

METHODS

Before alloHSCT, 31 sequences were isolated from the VOA. At rebound, 14,449 and 5,033 sequence reads were obtained from CSF and blood, respectively, and were combined into consensus sequences using a cut-off of ≥20% of total sequence read. This generated 50 sequences from CSF, 49 from blood, 47 each from lymphocytes, and 41 from plasma.

A distinct sub-group branch of sequences (G31) isolated from the VOA with homologous drug resistance mutations (M184V and K100) did not group within the rebound virus clade (Fig. 2). The rebound virus was mainly comprised of wild-type sequences and only derived 9/134 (6.7%) from sequences with high sequence similarity between CSF and CSF plasma (Fig. 2). A small portion of rebound virus in the CSF (10/135 sequences) and peripheral blood plasma (5/52 sequences) had the M184V mutation (Fig. 2). A total of 83 (25%) of independent VOA sequences from both pre-alloHSCT time-points intersected with the peripheral blood and the meningeal rebound sequences had 2 star symbols, or identical with the other two viral clones having 1 nucleotide difference (Fig. 2).

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REFERENCES...

DISCUSSION

We present the case of an HIV-1 infected individual with acute myelogenous leukemias who underwent alloHSCT. After self-interrupting ART post-alloHSCT the patient experienced a severe acute rebound syndrome with meningophenilosis concurrent with HIV-1 viremia rebound in peripheral blood and CSF. Donor chimerism was greater than 95% measured in both the peripheral blood and bone marrow priming ART was restarted 150 days after alloHSCT. HIV rebound in peripheral blood CD4+ T cells. This virus was present at multiple time-points pre-alloHSCT and comprised nearly 10% of the replication competent HIV-1 genome. The virus was also present in the CSF at the time of rebound. It can be inferred from the phylogenetic analysis that the source of rebound virus is consistent from resting memory CD4+ T cells.

Potential explanations for viral rebound with ART interruption in this case may be a result of persistent recipient cells due to an incomplete donor chimerism at a relatively early point post-alloHSCT. Alternatively, the allogeneic effect/OX40 effect may not completely replace the host hematopoietic-derived cells regardless of time post-alloHSCT. In addition, incomplete adherence to ART may have allowed for infection of donor cells.

Further studies on the degree and time course of recipient cell replacement by donor cells necessitates additional, in particular, strategies to prevent acute rebound syndrome after alloHSCT are warranted.