Allogeneic Transplantation with CCR5 Δ32/Δ32 Cord Blood Hematopoietic Cells in a HIV-1-Infected Patient

Rafael Duarte1, Maria Salgado2, Isabel Sanchez-Ortega1, Sara Morón-López1, Mari Carmen Puertas1, Lawrenze Petz2, Sergi Quero2, Bonaventura Clotet1 and Javier Martinez-Picado1,4,6

1 Instituto Català d’Oncologia (ICO), L’Hospital del Llobregat, Spain; 2 AIDS Research Institute IrsiCaixa, Badalona, Spain; 3 StemCyte International Cord Blood Center, Covina, CA, USA; 4 Barcelona Cord Blood Bank, Barcelona, Spain; 5 Universitat de Vic – Universitat Central de Catalunya (Uvic-UCC), Vic, Spain; 6 Catalan Institute for Research and Advanced Studies (ICREA), Barcelona, Spain.

Background

The Berlin patient provides the only evidence to date of long-term control of HIV-1 infection after an allogeneic hematopoietic cell transplantation (HCT). Low prevalence of Δ32/Δ32 genotype (<1%) made the search for “patient number 2” unsuccessful for years. Since just a 4/6 match is necessary for cord blood transplantations (CBT), chances to find a CCR5 Δ32/Δ32 donor are higher.

Findings

Here, we describe a first reported case of allogeneic hematopoietic cell transplantation using CCR5 Δ32 homozygous cord blood cells in a patient with HIV-1 infection and a diffuse large B-cell lymphoma.

Methods

A myeloablative cord blood alloHCT was performed using CCR5Δ32/Δ32 CBU (from Stemcyte) plus CD34+ cells from a haploidentical brother. A second cord blood infusion (also CCR5Δ32/Δ32) was necessary because a poor engraftment of the first one. Characteristics of the recipient and donors are described in Table 1.

Table 1. Patient and Donor Characteristics, CCR5 genotypes, HLA compatibility and Cell Products Content

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>CCR5 genotype</th>
<th>HLA compatibility</th>
<th>Cell Products Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pa-HCT Center</td>
</tr>
<tr>
<td>Blood group</td>
<td></td>
<td></td>
<td></td>
<td>Total CFU (x10^4/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CD34 (x10^5/kg)</td>
</tr>
</tbody>
</table>

HIV-1 reservoir was measured before and post-transplantation. qVOA was performed in peripheral CD4+ T cells. Total cellular HIV-1 DNA and cell associated RNA was determined with ddPCR. Viral tropism was genotypic and phenotypically determined. Additionally, proliferation, activation and infectivity capacity of patient’s new CD4+ T cells were analyzed.

Case Report

A 36 year-old man with antiretroviral-treated HIV-1 infection from 2009 was diagnosed with DLBCL stage IIa in 2012. No HLA-matched sibling donors were available. A dual allogeneic HCT was performed following myeloablative conditioning combining CBU#1 and purified CD34+ cells from a haploidentical sibling. High-resolution chimerism analysis detected low level CB-derived hematopoiesis below 5% for up to 7 weeks after transplant (Figure 1). CBU#2 was subsequently infused on day +52. Within 3 weeks from CBU#2 infusion, CBU#1-chimerism increased very rapidly to 100% by day +73. In this process, the patient’s lymphocytes changed from homozygous wild-type CCR5 (recipient) to heterozygous wild-type/Δ32 (haploidentical sibling), and finally became homozygous for CCR5 Δ32 (Figure 1). Regrettably, our patient developed an aggressive progression of DLBCL, and following very rapid clinical deterioration, he passed away from disease progression three months after transplant.

HIV Reservoir Results

Previous to CB-HCT, plasma viral load was 2.5 log copies/mL (Figure 3), and the replication competent reservoir size was of 1.2 HIVcopies per 10^10 peripheral CD4+ T cells (Table 2). Indeed, viral reservoir was detected as HIV-1 DNA and cell-associated HIV-1 RNA in peripheral CD4+ T cells, as well as HIV-1 DNA in GALT and free HIV-1 RNA in cerebrospinal fluid. Ultrasensitive SCA viral load analysis decreased right after HCT, reaching minimal levels at the time of full CB-chimera. No HIV-DNA was detected using ddPCR quantification or semiquantitative tests of amplification after CB-HCT.

Patient’s CD4+ T cells (obtained at day +76 post-HCT) responded to stimuli of PHA and were able to express activation markers and proliferate (Figure 4). However, those cells were not able to generate a productive infection in vitro after spinoculation with laboratory viral strains, or the patient’s viral isolate or recombinant envelope virus (Figure 5).

Conclusion

This data suggest that CCR5 Δ32/Δ32 CB HCT is a good platform for a broader application to other HIV-1 infected individuals with severe hematological malignancies. Epistem is an European Project, funded by ARCHE, to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders. It also works to expand the availability of CCR5Δ32/Δ32 cord blood units in the study context.

Acknowledgements

We thanks all our collaborators and founders: