



Treatment of HIV-1 Infection by Allogeneic CCR5- Δ 32/ Δ 32 Stem Cell Transplantation: A Promising Approach.

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Introduction

The entry of human immunodeficiency virus type 1 (HIV-1) into target cells requires both CD4 and predominantly CCR5, a G-protein-coupled chemokine receptor. A 32-base pair deletion in the CCR5 allele leads to an inactive gene-product and homozygous individuals are largely resistant against HIV-1 transmission. Here we report the first allogeneic stem cell transplantation of a 40-year-old HIV+ patient with acute myeloid leukemia from an HLA-matched unrelated donor selected to be homozygous for CCR5- Δ 32.

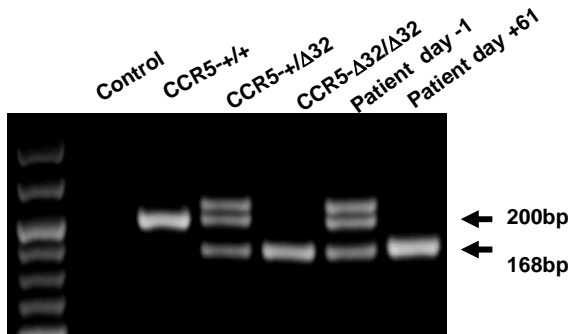


Figure 1
 PCR genotyping patterns of different CCR5-alleles. The patient displayed a heterozygous genotype before transplantation (day -1) and changed to CCR5- Δ 32/ Δ 32 ongoing engraftment after day +61.

Methods

The request at the German Central Bone Marrow Donor Registry revealed 232 appropriate HLA-identical donors. The frequency of CCR5- Δ 32 is about 1% in Central Europe. Donors were screened for the deletion using a genomic PCR assay. A pair of primers (5'-GACAAGTGTGATCACTTGGG-3'; 5'-

GTGCCTCTT-CTTCTCATTTCG-3') flanking the region of the deletion in the CCR5 gene was used to generate wild-type and deleted DNA fragments.

Results

The patient underwent allogeneic stem cell transplantation using CD34+ selected peripheral blood progenitor cells from donor 61, identified to be homozygous for CCR5- Δ 32, after conditioning with the FLAMSA regimen. With ongoing engraftment, CCR5-PCR patterns transformed into a homozygous Δ 32/ Δ 32 genotype (Figure 1).

High active antiretroviral therapy (HAART) was stopped from day of transplantation. GvHD prophylaxis followed standard regimens and engraftment was achieved on day +13. Complete chimerism as detected by competitive PCR was observed on day +60. The virus load was measured both by RNA-PCR and proviral DNA-PCR. DNA-PCR was negative from day +68 (Table 1).

Discussion

Homozygosity for CCR5- Δ 32 is associated with a high but not complete HIV-1 resistance. However, there is still possibility of infection by mutated strains (e.g. X4), but although exposure against X4 is frequent, the CCR5 tropic strain dominates during early infection irrespective of the route of transmission. In the past, the attempts to prolong survival during HIV-1 disease by stem cell transplantation failed. Here, we demonstrate the first successful allogeneic stem cell transplantation in an HIV+ patient with a donor selected to be homozygous for the CCR5- Δ 32-allele.

The patient managed transplantation and engraftment without any remarkable irregularities.

This switch of CCR5 genotype was not associated with an increased risk in terms of the transplant procedure. The patient developed a functional reconstitution of his T-cell immunity. Finally, although HAART was discontinued for over a period of 285 days, HIV-1-load could not be detected, as determined by RNA and proviral DNA PCR assays of peripheral blood, bone marrow, and rectal mucosa.

Our data are highly suggestive that the postulated "gatekeeper" mechanism for HIV-1 infection preferring the CCR5-tropic strain, has been re-initiated during engraftment leading to a disruption of virus replication. This finding provides the role of CCR5 during HIV-1 infection and disease progression and encourages further investigations of the development of CCR5 targeted treatment options.

Day	Source	cDNA env	cDNA LTR	Plasma viral load	Anti HIV-1/2 antibodies
-1	PB	>15	>15	<15	+
0		Allogeneic stem cell transplantation			
+20	PB	5-15	5-15		
+61	PB	5-15	<5	<15	
+68	PB	<5	<5	<15	
+97	PB/BM	<5	<5	<15	+
+145	RecB	<5	<5		
+187	PB	<5	<5	<15	
+285	PB	<5	<5	<15	+

Table 1

Measurement of HIV-1 viremia by RNA- and proviral DNA-PCR assays. HIV-1 RNA could not be detected in peripheral blood (PB) and bone marrow (BM) during the follow-up since HAART had been discontinued on day -1. Proviral DNA was not detectable from day +68 after allogeneic transplantation in PB, BM and rectal biopsy (RecB). HIV-1/2 antibodies were detectable permanently during the follow-up.