UNIKLINIK KÖLN

Institute of Virology
University Hospital of Cologne

UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Treatment of HIV and acute myeloid leukemia by allogeneic CCR5-d32 blood stem cell transplantation

Elena Knops[1], Guido Kobbe[2], Rolf Kaiser[1], Nadine Lübke[3], Gabor Dunay[4], Annemarie Wensing[5], Javier Martinez-Picado[6], Monique Nijhuis[5], Johannes Fischer[7], Falk Hüttig[8], Rainer Haas[2], Dieter Häussinger[8], Björn Jensen[8]

[1] Institute of Virology, University of Cologne, Germany; [2] Department of Hematology, Oncology and Clinical Immunology, University of Düsseldorf, Germany; [3] Institute for Virology, University of Düsseldorf, Germany; [4] Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany; [5] University of Utrecht University Medical Center Utrecht Netherlands; [6] Hospital Germans Trias i Pujol AIDS Research Institute irsiCaixa Barcelona Spain; [7] Institute of Transplantation Diagnostics and Cell Therapeutics, University of Düsseldorf, Germany; [8] Department of Gastroenterology, Hepatology and Infectious Deseases, University of Düsseldorf, Germany

BACKGROUND

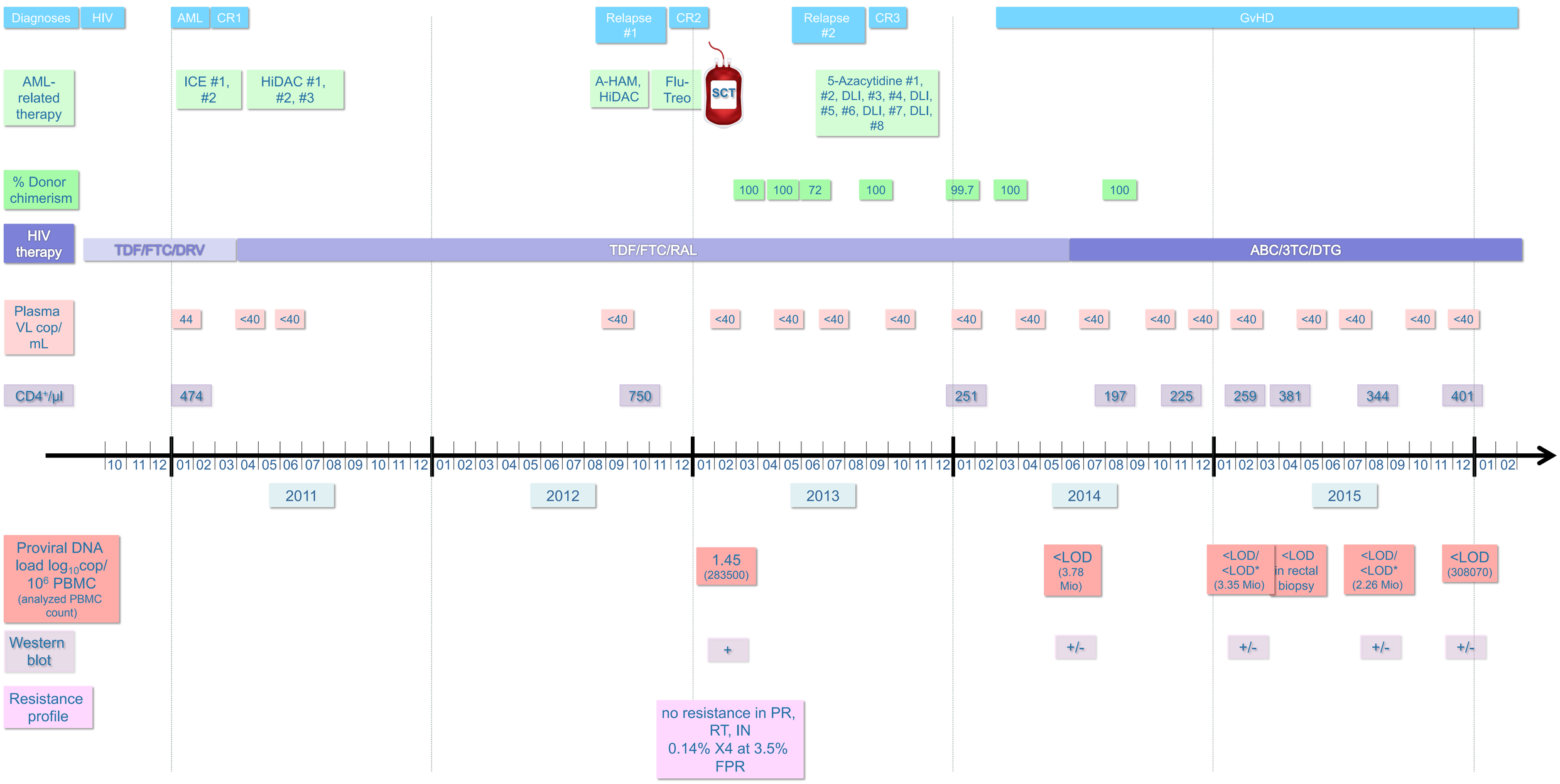
The Berlin patient is presumed to be the only person cured from HIV-infection by hemato-poietic stem cell transplantation (HSCT) from a homozygous CCR5-d32 unrelated donor. Attempts to reproduce cure by HSCT have failed because of either viral rebound or death due to the underlying malignancy. We here report a 46y old patient alive, well and undetectable for HIV (RNA/DNA) three years after allogeneic CCR5-d32 HSCT.

METHODS

- Proviral DNA load: Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 v2.0 assay or the Roche cobas® 6800 system (Roche Diagnostics, Germany) and 1 mL of buffy coat.
- Total DNA extraction: Roche MagNA Pure System; PBMC count (PBMC/µL): content of β-globin (LightCycler® Control Kit DNA, Roche Diagnostics, Germany) in 1 µL of buffy coat eluate. The proviral DNA load was calculated to the final result of log_{10}cop/10^6 PBMCs.
- *ddPCR: in duplex mode using the QX200 platform (Bio-Rad) with primers and a probe binding a conserved region of the HIV-LTR ("Generic HIV DNA Cell", Biocentric, France) (single copy reference gene RPP30).
- Western blots (WB): New LAV Blot I (Bio-Rad).

PRE-TRANSPLANTATION

- AML diagnosis (acute myeloid leukaemia, inv16, CBF-MYH11) in 01/2011
- Diagnosis of HIV-infection in 10/2010; initial treatment TDF/FTC+DRV/r; switch DRV to RAL to avoid interactions with chemotherapy in 03/2011
- Complete remission (CR) of AML after 2 induction courses (ICE) + 3 consolidation courses (AML-SG07/04)
- AML relapse 09/2012, treatment: A-HAM + 2nd cycle high-dose cytarabine (HiDAC)
- 2nd CR: 8.74x10^6/kg unmodified peripheral blood stem cells from a female 10/10 CCR5-d32 donor after conditioning with fludarabine and treosulfan in 02/2013
- HIV resistance analysis: no significant resistance mutations and the coreceptor usage was predicted as R5-tropic (Sanger sequencing: FPR 44.5%; NGS: 0.14% X4 at 3.5% FPR; geno2pheno)
- Proviral DNA load: 1.45 log_{10}cop/10^6PBMC; WB: all anticipated bands could be detected



POST-TRANSPLANTATION

- Uninterrupted continuation of ART (since 06/2014: ABC/3TC/DTG)
- VL remained undetectable in plasma and liquor
- 2nd relapse of AML in 06/2013
- Molecular remission after 8 courses of 5-Azacytidine and 4 donor lymphocyte infusions
- Proviral HIV DNA: all samples negative (<LOD: limit of detection) by conventional and ddPCR* in two different labs, namely PBMCs, rectal biopsy and bone marrow*
- Western blots: incomplete patterns with fading bands

WESTERN BLOT

LATEST RESULTS

- Viral Outgrowth Assay (qVOA) from PBMCs: 23 Mio $CD4^+$T cells – negative (IUPM<0.031/106 CD4 T cells)
- Proviral DNA in ileum biopsy: 0.1 Mio cells – 1/4 replicates positive with LTR-, but negative with gag-primers
- HIV-LTR DNA not detected in >2 Mio PBMCs via ddPCR or qPCR, but weak positive signals in T-cell subsets (T_{CM} and T_{EM})

SUMMARY & CONCLUSION

Like in the Berlin patient, all tests from the Düsseldorf patient performed so far suggest that HIV may have been eradicated and that he may be the second individual cured from HIV by allogeneic CCR5-d32 HSCT. Further investigations, proviral DNA (ddPCR) and qVOA in lymph node, cellular immune response response assay and more, will be performed before considering the discontinuation of ART.

We are grateful to the patient for his participation.

ICISTEM

HPI Heinrich-Pette-Institut Leibniz-Institut für Experimentelle Virologie