Allogeneic stem cell transplant in HIV-1-infected individuals

Javier Martinez-Picado
Barriers to cure HIV infection

- Residual Replication
- Immune activation
- Inflammation
- Latent Infection

VIRAL PERSISTENCE
Strategies to cure HIV

- Sterilising cure or Lifelong remission
  - Treatment optimisation and intensification (eliminate all replication)
  - Reversal of HIV latency (increase viral production)
  - Therapeutic vaccination (enhance host control)
  - Immune-based therapies (reverse pro-latency signalling)
  - Cell/gene therapy (render host cells resistant to infection)
Long-term control of HIV by CCR5Δ32/Δ32 stem cell transplant

scBMT, allogenic transplant with peripheral blood stem cells
ARVs stopped, HIV rebounds

Adapted from Diana Finzi, U.S. National Institute of Allergy and Infectious Diseases
J Cohen, 2014 Science

Viral load (Log_{10} RNA copies/ml)

Time off ARVs (months)

- Timothy Ray Brown
- Boston bone marrow transplants
- Mississippi child
- Typical person suppressed 1 year

Undetectable
Why only one person has been “cured” of HIV
Stem cells sources for allogeneic transplant

- **HLA-matched Sibling Donor** (10/10)
- **≥9/10** HLA-matched Unrelated Donor
- **Cord Blood** (single/double) ≥4/6
  - *Potential problem: Limited CBU Cell Dose*
- **Haploidentical Family Donor** ≥5/10
Growth of Cord Blood Units on the BE THE MATCH registry
Allogeneic HCT using CB (CCR5Δ32/Δ32) in a patient with a HIV infection and a diffuse large B-cell lymphoma (DLBCL)
Allogeneic CBT in HIV-1+ patient with DLBCL

- ♂ 37 years-old
- HIV diagnosed in 09/2009
  - CD4+: 272/mm$^3$; pVL= 79,298 copies/ml
  - Initiates ART: Truvada (FTC+ TDF) + Viramune (NVP)
- Follow up shows good treatment adherence
  - CD4+ 300-500/mm$^3$; pVL <50 copies/ml
- Diffuse large B-cell Lymphoma (II-A) diagnosed in 11/2011
  - Great hemiabdomen tumour (23 cm, left kidney to lower inferior quadrant)
- Chemotherapy + Autologous SCT
  - No persistent response
  - Allogeneic SCT
Conditioning Regimen

-8    -7    -6    -5    -4    -3    -2    -1    0

- Flu 30 mg/m^2
- Bu 1mg/Kg/6h
- Cy 50 mg/Kg
- ATG 2 mg/Kg
- CsA 1.5 mg/Kg bd
- Methylprednisolone 1 mg/Kg
- Ig given weekly until D +60
- G-CSF from D+1 to engraftment

Infectious prophylaxis: Pentamidine/TMP-SMX, Posaconazole, Acyclovir, Ciprofloxacin
“Haplo-cord transplant”

Single CB transplantation with the co-infusion of a T-cell depleted CD34+ graft from a third party HLA-mismatched donor (TPD), to accelerate PMN recovery

Fernández et al. Experimental Hematol 2003;31:535-44
CB(CCR5Δ32/Δ32)+TPHD(CCR5Δ32/wt) microchimerism
CB(CCR5Δ32/Δ32) + TPHD(CCR5Δ32/wt)
Scientific Project to Investigate…

“Allogeneic stem cell transplant in HIV-1-infected individuals”
How viral persistence is measured?

Peripheral blood

- Free Virus

- Ultrasensitive Viral load
  (1 copy HIV-RNA per ml of plasma)

- CD4+ T cells

- Cell Integrated HIV (Proviral DNA)

- Replication competent virus
  (Quantitative viral outgrowth)

- HIV cell expression (Cell associated HIV-RNA)

- Abortive HIV integration (2LTR circles)

Tissues

- CD4+ T cells

- Cell Integrated HIV (Proviral DNA)

- HIV cell expression (Cell associated HIV-RNA)
Focusing on CCR5Δ32/Δ32

Impact of Chemotherapy for HIV-1 Related Lymphoma on Residual Viremia and Cellular HIV-1 DNA in Patients on Suppressive Antiretroviral Therapy

Persistence of Virus Reservoirs in ART-Treated SHIV-Infected Rhesus Macaques after Autologous Hematopoietic Stem Cell Transplant

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CCR5Δ32/Δ32 geographical distribution
Registry of CCR5Δ32/Δ32 donors

North Europe
London, Göteborg, Helsinki and Düsseldorf
10,000 cord blood units

Spain
Barcelona, Madrid and Málaga
22,000 cord blood units
Shift of HIV Tropism in Stem-Cell Transplantation with CCR5Δ32/Δ32

R5x4 → X4 → X4

Diagram showing the shift of HIV tropism from R5x4 to X4 with the use of antiretroviral therapy.
Open Considerations

- Haplo/cord vs. classical allo-Tx.?
- Which conditioning is best?
- Conditioning of patients without malignancies feasible?
- What is the best ART?
- How much immunosuppression is needed?
- How much GvH/GvD is necessary?
- What is the best ATI strategy?
- Ethical considerations
How to contact:
http://www.epistem-project.org

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