Impact of combination of chemotherapy and autologous hematopoietic stem cell transplantation for lymphoma on HIV-1 reservoir persistence

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Background

- HIV DNA integrates into long-lived infected cells : these long-lived reservoirs prevent cure
  - CD4+ T cells (blood, lymphoid tissue)
  - Tissue macrophages
- One patient was cured : the Berlin patient. 3 aspects of AML treatment can have participated in the functional cure :
  - Myeloablation : intensive chemotherapy + TBI
  - Graft Versus Host disease → Graft Versus Reservoir ?
  - Allogeneic hematopoietic tissue, resistant to infection (homozygous CCR5 Δ32 mutation)

High dose chemotherapy (HDC) / autologous stem cell transplantation (ASCT) treatment in HIV-infected patients allow us to study mainly the impact of intensive chemotherapy on blood HIV reservoir evolution

HDC/ASCT procedures lead to massive depletion of circulating CD4+ T cells. It has been suggested that the HIV reservoir in PBMCs does not grow with immune reconstitution and even decreases in the long term after HDC/ASCT

Objective of the study

To study the impact of HDC followed with ASCT for HIV-related lymphoma on blood HIV-1 DNA quantification

Patients and Methods

- Patients : with lymphoma (NHL and HL)
  treated with HDC/ASCT as a first-line or relapse treatment
  from a single center : Hôpital Saint Louis, Paris
  infected with HIV and on cART at the time of ASCT
- Methods :
  Samples : frozen (-80°C) blood samples collected during follow-up
  HIV DNA quantification : HIV DNA CELL qPCR, Biocentric (threshold 5cp/10^6 PBMC)
- Study design : longitudinal retrospective study
  HDC/ASCT from January 2012 to June 2014
  Endpoint date : January 15th, 2015
- Statistical methods : correlation was tested with Spearman test and Wilcoxon signed rank sum test, and overall survival was estimated with the Kaplan-Meier method

RESULTS

Outcome

- Follow-up : from lymphoma diagnosis (yr) : 3.4 [2.1-6.0]
  from ASCT (mo) : 19.3 [14.6-19.9]
- Death : n = 2
  Cause of death : Lymphoma progression : 1
  Unknown : 1
  Treatment adverse effect (HDC/ASCT) : 0
  AIDS : 0
- 1-year overall survival (95% CI): from lymphoma diagnosis 61.5% (7-91)
  from ASCT 92% (56.6-98.9)

Patient characteristics

n = 13 patients

Patient characteristics :	At lymphoma diagnosis n(%)	At ASCT n(%)
Demographic factors		
Male / Female	11 (84) / 2 (16)	
Age (yr) : median [IQR]	45 [40-49]	46 [43-51]
HIV infection		
Duration (yr) : median [IQR]	3,7 [0,2-14,1]	7,7 [2,2-16,9]
cART : n (%)	10 (77)	13 (100)
Duration (yr) : median [IQR]	1,0 [0-10,8]	7,6 [1,4-13,4]
Plasma HIV RNA < 50cp/ml	6 (46)	8 (62)
CD4+ cell count / mm^3 : median [IQR]	386 [230-590]	ND
Lymphoma		
Non-Hodgkin Lymphoma	8 (62)	
Hodgkin Lymphoma	5 (38)	
Duration from diagnosis to ASCT (mo) : median [IQR]		22,8 [7,6-43,9]
Disease status at ASCT :		
Relapse		10 (77)
First remission (CR or PR)		3 (23)
Conditioning regimen : BEAM/TBC		12 (92) / 1 (8)

CR : complete remission - PR : partial response

Virological results

HIV-1 RNA viral load at the time of ASCT
- n = 8 : RNA < 50 cp/ml
- n = 5 : RNA ≥ 50 cp/ml. Median (range) = 180 cp/ml (55-434)

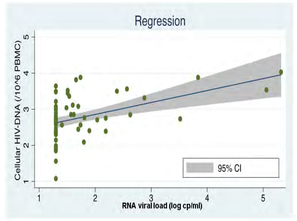
Total HIV-1 DNA (log copies / mL blood), n = 99

Pré-ASCT	]-18;-6 months]	2.97 [2.44 – 3.20]
	]-6;-0.5 months]	2.90 [2.40 – 3.32]
ASCT	]-0.5;+0.5 months]	1.68 [1.60 – 2.23]
Post-ASCT	]0.5;6 months]	2.80 [2.27 – 3.01]
	> 6 months	2.60 [2.48 – 2.81]

Cellular HIV-1 DNA (log copies / 10^6 PBMCs), n = 85

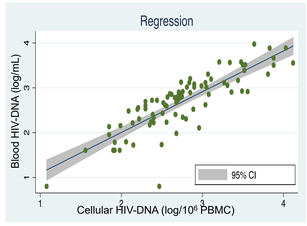
	nb samples	Median [IQR]	
Pre-ASCT	n = 34	2.87 [2.52-3.36]	NS
Post-ASCT	n = 51	2.62 [2.22-2.90]	

HIV DNA reservoir in PBMC was correlated with plasma HIV-1 RNA viral load and with blood total HIV DNA quantification :



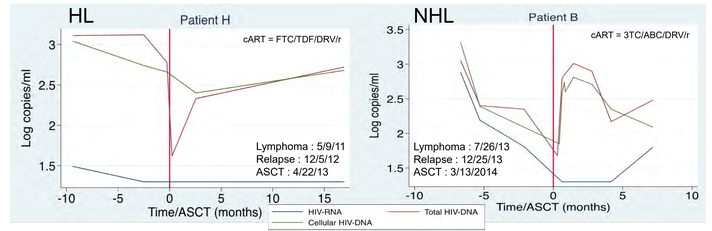
r = 0.45
P = 0.0001

r = 0.87
P < 10^{-4}



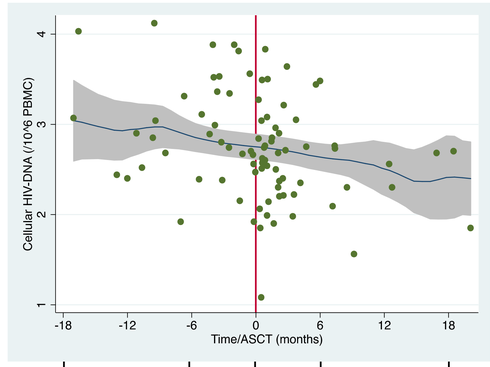
RESULTS

Follow-up through HDC/ASCT in 2 patients :



HIV-1 reservoir quantification in PBMCs (median +/- IQR)

- n = 85 samples
- Median HIV-DNA : **2.70 (2.38–3.07)** log cp/10^6PBMC



HIV-DNA (log/10^6 PBMC)	**2.88** (2.44-3.20)	**2.85** (2.56-3.52)	**2.65** (2.26-3.00)	**2.56** (2.09-2.73)

There is a slight decrease in mean HIV-1 DNA/10^e6 PBMC in blood after HDC/ASCT **but no significant difference compared to pre-graft numbers**

Conclusions

- HIV DNA levels in HDC/ASCT patients are similar to those previously described in treated patients (median HIV DNA = 2.3-2.7 log/10^6 PBMC)
- HIV DNA reservoir in PBMC correlates with plasma viral load (HIV RNA)
- Peripheral blood HIV reservoirs persist and **total HIV DNA levels in PBMC remain stable after HDC+ASCT**
- A slight decrease in the number of HIV-infected cells after 6 months post-ASCT is probably due to **long-term control of HIV viremia under cART, and not to HDC/ASCT**

Appendix :
BEAM : Carmustine, Etoposide, Cytarabine, Melphalan
TBC : Thiotepa, Busulfan, Cyclophosphamide