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Optimized antiretroviral therapy during allogeneic hematopoietic stem cell transplantation in HIV-infected individuals

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Background: A reservoir of latently infected memory CD4+ T cells is a major barrier to HIV cure. With allogeneic hematopoietic stem cell transplantation (alloHSCT), host hematopoietic cells are replaced with donor hematopoietic cells after cytotoxic therapy and graft versus host (GVH) effects. If antiretroviral therapy (ART) is continued during alloHSCT, it should protect donor hematopoietic cells from infection and result in a reduction or elimination of HIV. However, ART is often interrupted during alloHSCT due to drug interactions, mucositis and vomiting, or organ dysfunction.

Methods: We performed a pilot study on the safety and feasibility of continuing optimized ART during alloHSCT in HIV-infected individuals being treated for hematologic malignancy. Optimized ART included:

1) avoidance of ritonavir-based ART to minimize drug interactions,

2) ART changes for organ dysfunction and

3) subcutaneous enfurvirtide (ENF) during post-transplant cyclophosphamide and if oral ART was not tolerated.

Primary endpoints were incidence of adverse events (AE) from ENF and maintenance of ART through day 60. Secondary outcomes included HIV persistence measures.

Results: Six HIV+ individuals enrolled; five received alloHSCT and one died from malignancy prior to alloHSCT. The remaining 5 patients tolerated ENF without AEs. Patients 1-4 reached day 60 without interruption of ART but required ART changes. Patient 1 achieved 100% donor chimerism by week 8, with undetectable plasma HIV and negative viral outgrowth assay (VOA). The patient died at week 49 with liver failure. Patient 2 has mixed chimerism (87% donor) at week 52 with undetectable plasma HIV, but positive VOA. Patient 3 achieved 100% donor chimerism by week 4 with undetectable plasma HIV but became non-adherent with ART, and at month 5 had viral rebound and meningoencephalitis. Patient 4 has mixed chimerism at week 24 (73% donor) with undetectable plasma HIV but positive VOA.

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Cancer	Hodgkins	Non-Hodgkins	AML	AML	Burkitt lymphoma	Non-Hodgkins
Phase of Treatment	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Pre alloHSCT CD4 Count	85 cells/ul	231 cells/ul	274 cells/ul	57 cells/ul	260 cells/ul	227 cells/ul
Pre alloHSCT Viral Load	79 c/ml	<20 c/ml	<20 c/ml	<20 c/ml	<20 c/ml	<20 c/ml
PBMC Donor Chimerism	100%	87%	100%	73%	N/A	TBD
CD3+ Donor Chimerism	100%	74%	100%	95%	N/A	TBD
Number of ART Changes	6	2	2	2	N/A	TBD
ART Maintenance	73%	95-100%	Poor	95-100%	N/A	TBD
Oncology outcomes, survival	Died at week 49, liver failure	Alive, cancer free at week 76	Alive, cancer free at week 45	Alive, cancer free at week 31	Died, prior to BMT	Received BMT on Jan 2nd 2015
[Patient Summary]						

Conclusions: During alloHSCT, with optimized ART, it is feasible to maintain ART but regimen changes are common due to drug interactions and organ dysfunction. ENF is a well-tolerated alternative to oral ART. Interruption of ART during alloHSCT can cause a severe acute retroviral syndrome. At early time-points, with mixed chimerism, HIV persists but further studies are needed over time.