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

A. Cash[1], A. Capoferri[1,2], D. Xu[1], H. Mchugh[1], O. Laeyendecker[1,3], S. Sakoian[4], L. Tony[3], C. Bullen[1], C. Pohlmeyer[1], P. Pham[1,5], J. Lai[1], J. Gallant[6], R.F. Siliciano[1,2], C. Flexner[4], K. Pratz[4], M. Levis[4], R. Jones[4], Y. Kasamon[4], R. Ambinder[4], C.M. Durand[1,4]

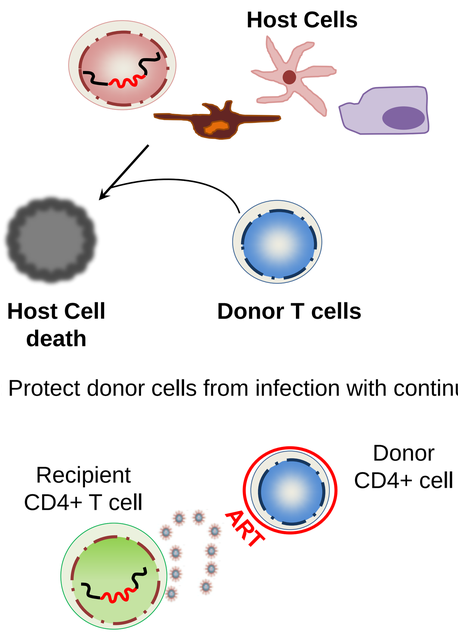
[1]Johns Hopkins University, Department of Medicine, Baltimore, United States, [2]Howard Hughes Medical Institute, Baltimore, United States, [3]National Institute of Allergy and Infectious Disease, National Institutes of Health, Division of Intramural Research, Bethesda, United States, [4]Sidney Kimmel Cancer Center, Baltimore, United States, [5]Johns Hopkins University, Department of Pharmacy, Baltimore, United States, [6]Southwest CARE Center, Santa Fe, United States

INTRODUCTION

Due to improvements afforded by ART, HIV+ patients receive standard of care treatment for hematologic malignancies, and this includes allogeneic hematopoietic stem cell transplantation (alloHSCT). Components of alloHSCT include cytotoxic therapy and allogeneic or graft versus host/tumor (GVH) effects. The GVH effect refers to the process where donor immune cells recognize recipient hematopoietic-derived cells as other and kill and replace them.

Fig. 1 The allogeneic effect refers to the process by which recipient cells are recognized and killed by donor CD8+ T cells.

Step 1: Eradicate or reduce HIV reservoirs as recipient (host) cells are replaced by donor cells (graft)



Step 2: Protect donor cells from infection with continued ART

There is interest in alloHSCT as a potential HIV cure. The major barrier to HIV cure is persistence of latent HIV in hematopoietic-derived cells, namely resting CD4+ T cells. The only case of HIV cure was observed in 'The Berlin Patient', who received alloHSCT for treatment of acute myeloid leukemia (AML) from a unique donor. This donor was homozygous for the CCR5Δ32 mutation, which results in lack of CCR5 expression on lymphocytes and resistance to HIV infection[3]. There is also interest in the possibility of cure using CCR5 wild-type donors. The proposed mechanism is shown in Figure 1, with reduction or elimination of HIV reservoirs by GVH effects and protection of donor cells by continuous ART (Figure 1). A proof of concept for this mechanisms came with initial reports of the two 'Boston Patients' who received alloHSCT from wild-type CCR5 donors for treatment of lymphoma[4]. Five and three years respectively after alloHSCT, no HIV was detected in peripheral blood. However, after analytical ART interruption, viral rebound occurred in both patients[5]. Because the 'Boston Patients' report was retrospective, the explanation for relapse (including other potential reservoirs or incomplete adherence to ART) is speculative.

It is difficult to maintain ART during alloHSCT. ART interruptions are frequent due to drug interactions between protease inhibitors (PIs) and immunosuppressants, intermittent organ dysfunction, and chemotherapy associated mucositis and vomiting compromising oral ART deliver. Here we report results from a clinical trial investigating the feasibility of continuing ART without interruption to protect CCR5 wild-type donor cells during alloHSCT for hematologic malignancy. We also report the impact of alloHSCT on the size of the latent reservoir and the potential impact on HIV cure.

HYPOTHESIS

Optimized ART can be well tolerated by HIV+ adult patients receiving chemotherapy and alloHSCT for hematologic malignancies. Furthermore, the combination of the allogeneic effect and continuous ART can reduce or complete eradicate HIV reservoirs.

METHODS

We evaluated the safety and feasibility of continuing ART during alloHSCT in HIV+ individuals with hematologic malignancy.

Optimized ART included:

1) Avoidance of PIs to minimize drug interactions
2) ART changes for organ dysfunction
3) Subcutaneous enfurvirtide (ENF) during posttransplant cyclophosphamide and if oral ART was not tolerated.

Primary endpoints included adverse events (AE) from ENF and maintenance of ART through day 60. Donor chimerism and HIV infected cells per million (IUPM) by viral outgrowth assay were also measured.

RESULTS

PATIENT DEMOGRAPHICS

Patient ID	Pt. 1†	Pt. 2	Pt. 3*†	Pt. 4	Pt.6	Pt. 7
Cancer	Hodgkin	Non-Hodgkin	AML	AML	Non-Hodgkin	Hodgkin
Phase of Treatment	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Pre-alloHSCT CD4 (cell/ul)	85	231	274	57	227	N/A
Pre-alloHSCT VL (c/ml)	79	<20	<20	<20	<20	<20
Type of alloHSCT	MUD	MUD	MRD	MRD	Haplo	Haplo
PBMC Donor Chimerism	100%	87%	100%	73%	>95%	>95%
CD3+ Donor Chimerism	100%	73%	100%	<5%	>95%	>95%
Number of cART Changes	6	2	2	5	2	3
cART Maintenance	70%	95-100%	Poor	95-100%	90-100%	98-100%
Oncology Outcomes, survival	Died at week 49, liver failure	Alive, cancer free at week 104	Died at week 64, liver failure, possible GVHD	Alive, cancer free at week 48	Alive, cancer free at week 24	Alive, cancer free at week 14

Fig. 2 Six patients with chronic HIV infection and hematologic malignancy received alloHSCT and ART. There were no AEs, and five of the six patients tolerated and maintained an optimized ART regimen that included subcutaneous enfurvirtide (ENF).

Participants to date, n=6
*Has been taken off study due to lack of compliance
† Patient has died

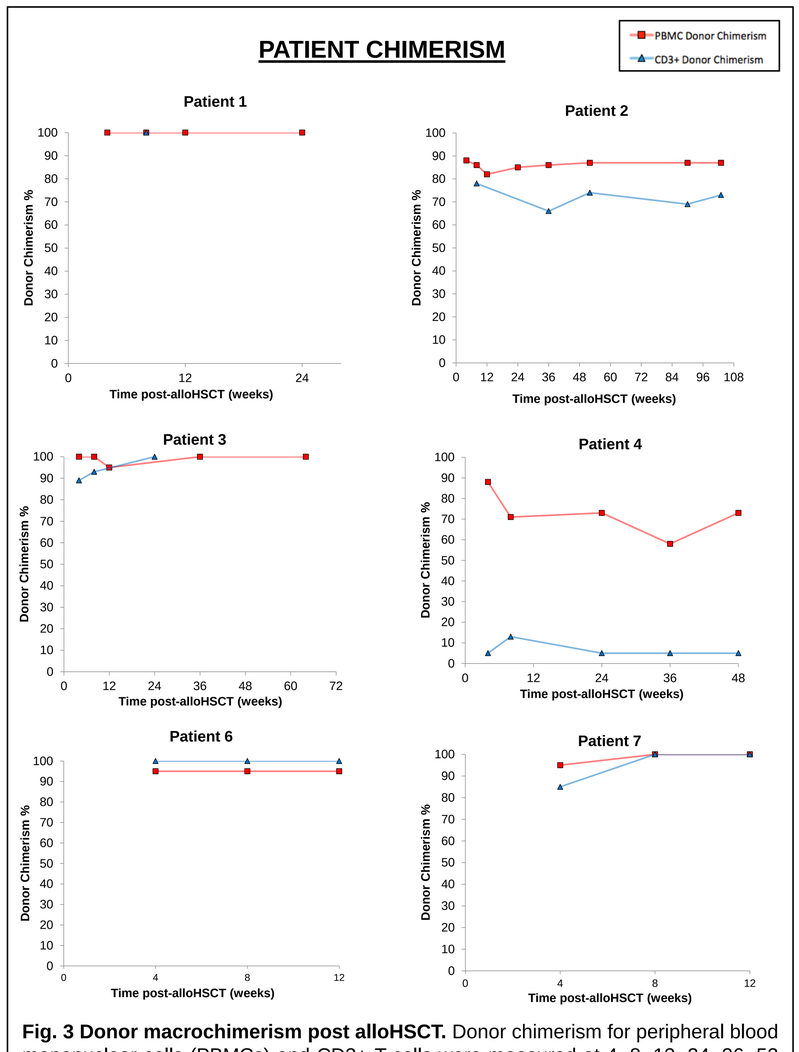


Fig. 3 Donor macrochimerism post alloHSCT. Donor chimerism for peripheral blood mononuclear cells (PBMCs) and CD3+ T-cells were measured at 4, 8, 12, 24, 36, 52 and 90 weeks post alloHSCT.

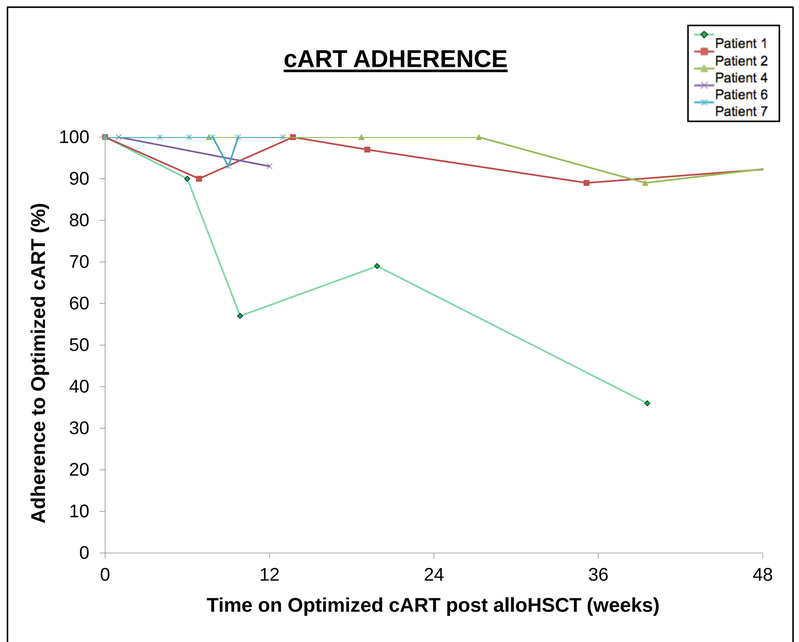
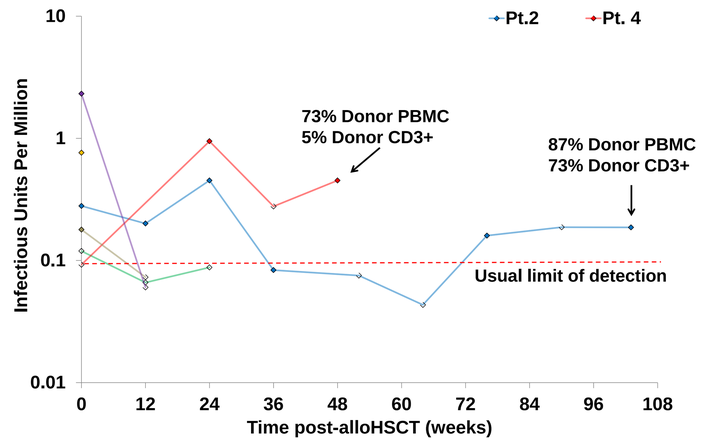


Fig. 4 cART adherence post alloHSCT. Adherence was measured using Medication Event Monitoring system (MEMS) electronic pill bottle caps that contain microprocessors to record every bottle opening as a presumptive dose.

PATIENT HIV LATENT RESERVOIR SIZE

PATIENTS WITH INCOMPLETE DONOR CHIMERISM



PATIENTS WITH COMPLETE DONOR CHIMERISM

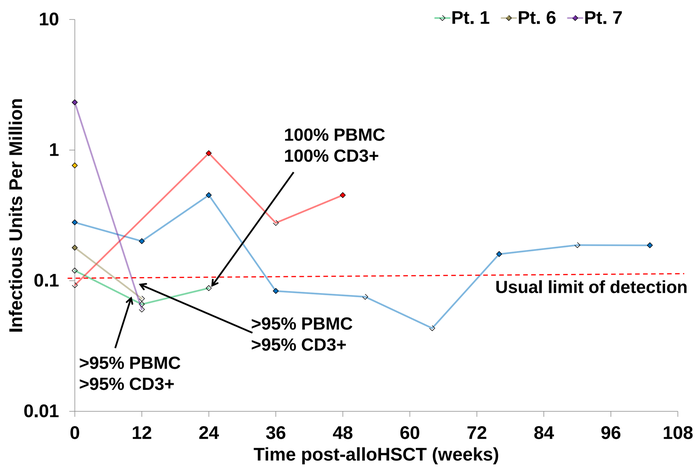


Fig. 5 Frequency of resting CD4⁺ T cells harbouring infectious HIV. Resting memory CD4+ T cells post alloHSCT were used in a limiting-dilution viral outgrowth assay (VOA). The frequency of cells harbouring infectious virus were determined by the maximum likelihood method and expressed as Infectious Units per Million cells (IUPM).

DISCUSSION

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. Newer, non oral and long acting antiretroviral agents may offer the same benefit. Notably, Patient 3 experienced viral rebound and meningoencephalitis after self-discontinuing ART despite 100% donor chimerism (see abstract #MOPDA0105 for a detailed case report). At early time points, in patients with mixed chimerism, HIV persists in the VOA, but further reports are needed over time to determine the size of the reduction of the HIV reservoir and the long term cure strategy implications.

CONCLUSIONS

There is a growing needed for alloHSCT in the HIV+ population. This strategy has cure implications for HIV+ individuals with hematologic malignancy. Further studies are needed over time to determine whether alloHSCT could be a successful cure strategy in combination with other potential strategies including latency reversing agents, or therapeutic vaccination.

Works Cited

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