INTRODUCTION

In HIV-infected (HIV+) individuals with high-risk hematologic malignancies, allogeneic bone marrow transplantation (alloBMT) is a life-saving treatment. Components of alloBMT include cytotoxic therapy and alloengraftment with HLA-mismatched hematopoietic stem cells (HSCs), which may lead to a reduced HIV reservoir. The development of antiretroviral therapy (ART) during alloBMT is a challenge, often requiring an interruption of ART. This can be due to drug interactions between protease inhibitors and immunosuppressants, intermittent organ dysfunction, and chemotherapy-associated mucositis and vomiting, thereby compromising ART delivery.

METHODS

HIV+ adults with a clinical indication for alloBMT were eligible. Optimized ART was achieved to include the avoidance of protease inhibitors to minimize drug interactions, ART changes to avoid organ dysfunction, and subcutaneous injection of enfuvirtide (ENF) during post-transplant cyclophosphamide and if oral ART was not tolerated.

The HIV LR within resting memory CD4+ T cells (CD4+CD69-CD25-IL-2R-DC) was measured prior to transplant and then every 2 weeks post-transplant by the quantitative viral outgrowth assay (qVOA) using the MOLT-4/CORl cell line. Viral outgrowth was detected by a donor-specific linked immunosorbent assay for HIV p24 antigen in culture supernatant. Frequency of cells with infectious virus was determined by limiting-dilution maximum likelihood-based statistics and expressed as infectious units per million cells (IUPM).

HIV proviral DNA measurements were detected using droplet PCR. DNA was extracted from PBMCs and digested with BSAI-1. Primers and probes for HIV pol and RPP30 were used. The ddPCR HIV probe was a 3′ minor groove binder-non-fluorescent quencher with 6FAM 5′ dye and RPP30 had the same quencher but with a VIC 5′ dye.

For phylogenetic analysis, RNA from p24+ qVOA supernatants and DNA from PBMCs were sequenced using Sanger and Next-generation methods for the RT region of pol by Maximum likelihood analysis with bootstrapping was carried out.

RESULTS

Seven patients with HIV infection received alloBMT with optimized ART and remained suppressed (Table 1). There were no reported AE-related to ENF administration. All participants had successful engraftment (500 X10^6/mm³ neutrophil recovery) and 5/7 patients achieved complete donor chimera by week 24.

White ART was maintained through day 60, modification of ART was required in all patients (Table 2). Patient 3 self-interrupted ART post-transplant, and presented with acute rejection that required treatment with HIV viral rebound with a HIV RNA of 25,518 c/ml in plasma and 17,000 c/ml in cerebral spinal fluid. ENF was initiated where he recovered and was able to re-start oral ART upon discharge.

In the two patients who did not achieve complete donor chimera, the viral reservoir remained detectable without significant change in size by viral outgrowth assay post-transplant (Fig. 1A,B). In the four patients who achieved complete donor chimera, the latent reservoir decreased (Fig. 1C,D) with mean decrease of 2.71 log2.

All participants had detectable proviral DNA in PBMCs prior to transplant (Fig. 2). In patients who achieved complete donor chimera, HIV proviral DNA was undetectable at week 36 post transplant. However, at early timepoints, patients 1 and 6 had transient increases in proviral DNA measurements.

In participant 6, phylogenetic studies revealed that the proviral DNA virus from week 8 matched a pre-transplant outgrowth sequence (Fig. 3) and rare late post-transplant outgrowth sequence. In addition, at this week 8 timepoint the participant was clinically ill with CMV and possible histoplasmosis reactivation.

DISCUSSION

AlloBMT with optimized ART was safe and feasible in our cohort. In addition, ENF was well-tolerated with no adverse events. The importance of ART maintenance during alloBMT was highlighted by the participant 3, who experienced life-threatening HIV viral rebound upon self-interruption of ART.

The impact of alloBMT on the size of the latent reservoir depended on the extent of donor replacement of the recipient hematopoietic system. For those who achieved full donor chimera, there was significant log reduction in infectious virus by the outgrowth assay and disappearance of proviral DNA. However, in patient 6, despite full donor chimera, infectious virus was identified at one timepoint using the qVOA, indicating complete viral eradication was not achieved by this approach. In this case, detection of HIV post-transplant could represent de novo infection of donor cells or the persistence and/or clonal expansion of a rare residual host cell.

Future strategies for potential HIV cure in the context of alloBMT might include strategies to protect donor cells such as CCR5delta32 or enhancement of donor cell activity against HIV with generation of cytolytic donor T cells and adaptive transfer technologies.

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