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LETTER

# Increased and persistent absolute CD4+ T cell count in an HIV-associated Burkitt lymphoma patient with central nervous system involvement after axicabtagene ciloleucel therapy

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Because human immunodeficiency virus (HIV)-associated Burkitt lymphoma (BL) has a poor prognosis new therapeutic approaches need to be developed[1]. Axicabtagene ciloleucel (axi-cel) is an anti-CD19 CAR-T cell commercially available FDA-approved product for patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL). However, axi-cel has not been approved by the FDA for use in patients with R/R BL. In addition, prospective clinical trials have mainly focused on patients with active disease. Several retrospective reports with small sample sizes have evaluated the outcomes of patients with a complete response (CR)[2,3].

Herein the outcomes and safety of axi-cel as consolidation therapy in an HIV-associated BL patient with central nervous system (CNS) involvement who had achieved a CR after first-line intensive chemotherapy are reported. Specifically, effective expansion of CAR-T cells without affecting HIV infection was demonstrated. The current study highlights the potential of axi-cel as consolidation therapy for HIV-associated BL with CNS involvement and a CR. Moreover, axi-cel was shown to have lower complications. Unexpectedly, the absolute count and proportion of CD4+ T cells gradually increased after axi-cel CAR-T cell infusion.

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An adult patient was admitted with abdominal distension lasting for 1 month. An abdominal enhanced CT scan revealed multiple nodular lesions in the liver that was suggestive of lymphoma. The liver biopsy was diagnosed as BL. The results of a PET/CT scan are shown in **Figure 1A**. The patient was confirmed to have Ann Arbor stage IVB BL and the international prognostic index (IPI) score was 3. Furthermore, the patient was diagnosed with HIV infection upon admission with an HIV viral load of $1.65 \times 10^4$ copies/mL and an absolute CD4+ T cell count of 98 cells/μL. He was started on combination antiretroviral therapy (cART). Specifically, the initial treatment included two cycles of first-line immunochemotherapy regimen for BL with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, and cytarabine (Hyper CVAD/MA) with rituximab. The patient had facial nerve paralysis after two cycles, but no abnormalities were detected on a head CT scan. Flow cytometry analysis revealed 26% abnormal monoclonal B lymphocytes in the cerebrospinal fluid (CSF) (**Figure 1D**). A diagnosis of HIV-associated BL with CNS involvement was made. Standard intrathecal methotrexate and cytarabine were subsequently administered until the symptoms resolved and abnormal monoclonal B lymphocytes in CSF were not detected by flow cytometry analysis (**Figure 1E**). The patient continued to receive two cycles of Hyper CVAD/MA. An interim PET-CT scan did not reveal typical malignant tumor-like hypermetabolic lesions after 4 cycles of Hyper CVAD/MA and the Deaville score was 2, which indicated a complete metabolic response (**Figure 1B**).

Anti-CD19 CAR-T cell therapy was selected as maintenance therapy due to failed hematopoietic stem cell collection.

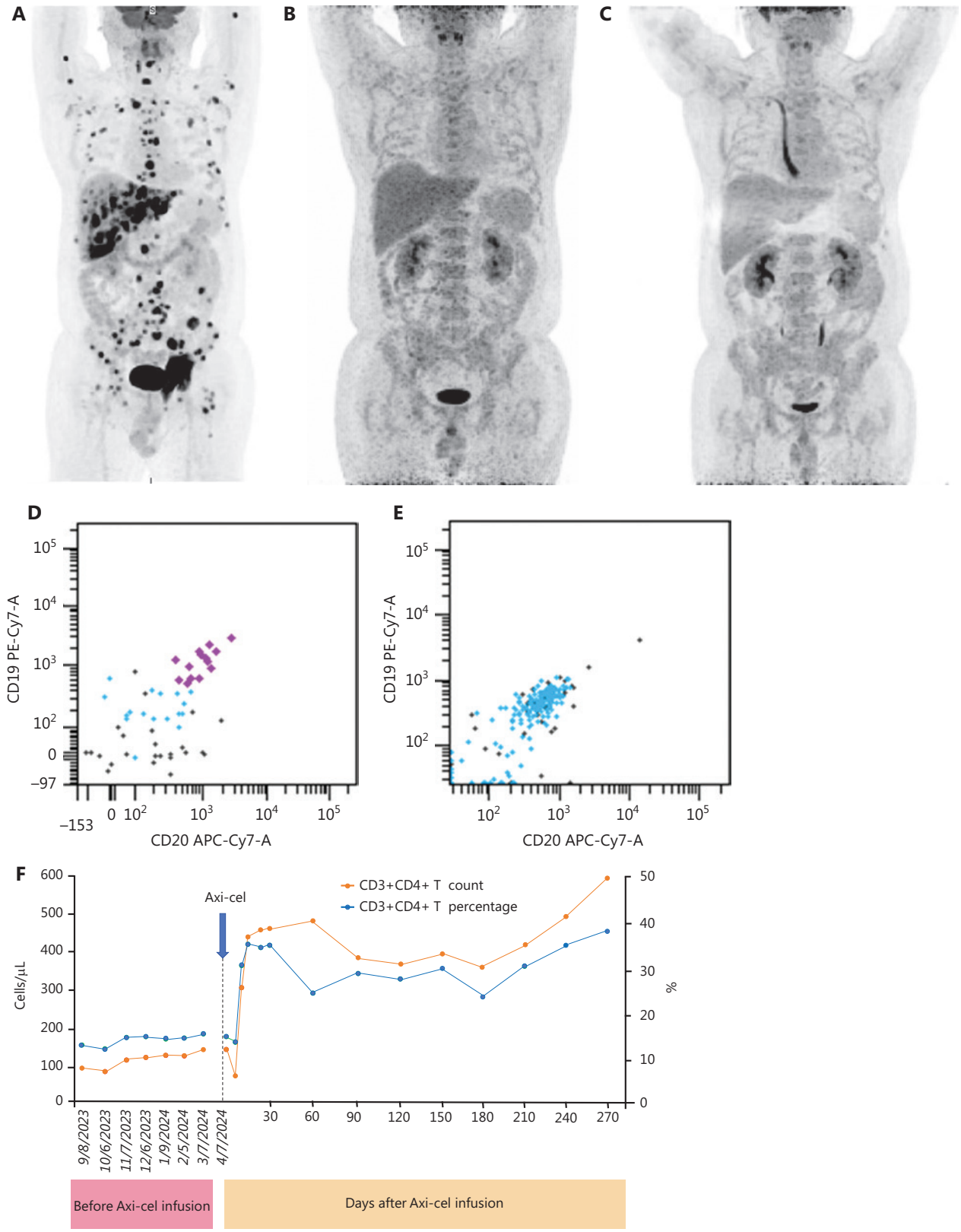



**Figure 1** (A) PET-CT images for the patient at the time of disease staging. Multiple nodules and masses were noted in the neck, axilla, abdomen, and iliac vascular region. Diffuse multiple low-density lesions are shown in the liver. The lesions exhibited hypermetabolism. (B) A PET-CT

scan demonstrated a complete metabolic response after 4 cycles of chemotherapy. (C) The patient remained in a CR status 6 months after axi-cel infusion. (D) Flow cytometry detected 26% abnormal monoclonal B lymphocytes in the CSF. (E) Abnormal monoclonal B lymphocytes were not detected in the CSF after standard intrathecal methotrexate and cytarabine were administered. (F) Dynamic change in the CD4+ T cell subset in the patient's peripheral blood, including the absolute CD4+ T cell count and percentage before and after axi-cel infusion. The absolute CD4+ T cell count fluctuated between 98 and 142 cells/μL before axi-cel infusion. The absolute CD4+ T cell count and proportion gradually increased after axi-cel infusion. The blue arrow denotes the axi-cel infusion.

Peripheral blood mononuclear cells were collected by leukapheresis to culture commercially available axi-cel after serum HIV was undetectable and the absolute CD4+ T cell count was 142 cells/μL. The patient received a standard lymphodepleting regimen based on fludarabine (25 mg/m$^2$ on days −5~ −3) and cyclophosphamide (250 mg/m$^2$ on day −5 ~ −3) 1 month after apheresis. Axi-cel was infused at a total dose of $1.8 \times 10^8$ on day 0. The patient developed grade 1 cytokine release syndrome (CRS) and received supportive treatment without steroids. No evidence of immune-effector cell-associated neurologic toxicity syndrome (ICANS) was observed. The levels of inflammatory factors (IL-6 and IL-8) were slightly increased on day 7 after the axi-cel infusion, which was consistent with the CRS grade (**Table 1**). The peak CAR-T cell count was reached 7 days after infusion with an absolute CD3+ T lymphocyte count of 158.12 cells/μL (19.49%). The absolute CD3+ T lymphocyte count decreased to 3.30 cells/μL (0.29%) on day 28 (**Table 1**). The patient was discharged to home without any clinical manifestations 1 month after axi-cel infusion. Zanubrutinib combined with continuous cART application was continued as maintenance therapy. The patient was still in CR status based on a PET-CT scan 6 months after axi-cel infusion (**Figure 1C**). The patient was still in CR status without long-term adverse effects after 9 months of follow-up evaluations. In addition, the HIV copies remain undetectable to date. Surprisingly, the absolute CD4+ T cell count and proportion gradually increased after the axi-cel infusion. The absolute CD4+ T cell count has remained > 600 cells/μL to date (**Figure 1F**).

**Table 1** Changes in inflammatory factors and CAR-T cell during therapy

| | Day 0 | Day 4 | Day 7 | Day 14 | Day 28 |
|---|---|---|---|---|---|
| IL-2 (pg/mL) | 0.98 | 1.20 | 1.33 | 1.03 | 1.15 |
| IL-4 (pg/mL) | 0.72 | 0.54 | 0.11 | 0.61 | 1.65 |
| IL-6 (pg/mL) | 1.74 | 119.87 | 270.67 | 137.24 | 20.07 |
| IL-8 (pg/mL) | 2.51 | 76.28 | 347.96 | 138.22 | 21.40 |
| IL-10 (pg/mL) | 0.69 | 0.61 | 1.25 | 1.66 | 1.59 |
| IFN-γ (pg/mL) | 0.66 | 0.88 | 0.57 | 1.38 | 0.28 |
| TNF-α (pg/mL) | 0.68 | 1.15 | 1.66 | 1.80 | 1.31 |
| Ferritin (ng/mL) | 42.80 | 49.30 | 46.70 | 57.10 | 47.50 |
| CAR-T (%) | 0 | 0.13 | 19.49 | 9.75 | 0.29 |
| CAR-T (cells/μL) | 0 | 0.64 | 158.12 | 75.05 | 3.30 |

HIV-associated BL patients with CNS involvement carry an especially poor prognosis with a median overall survival (OS) < 6 months[4]. Patients with HIV-associated BL have been treated with axi-cel[5,6]. The OS at 6 months was 64%, which is comparable to the OS in patients without HIV. Of note, an HIV-associated BL patient with CNS involvement has not been reported.

A retrospective study reported the results of CAR-T cell therapy in 6 patients with HIV-positive R/R LBCL. The absolute CD4+ T cell count before treatment was 221 cells/μL[7]. Although the absolute CD4+ T cell count was only 142 cells/μL in the patient reported herein, CAR-T cells could be completed successfully during cell preparation and expanded rapidly in the process of therapy. Our patient has remained in CR status 9 months after infusion with absolute CD4+ T cell counts at approximately 600 cells/μL. The absolute CD4+ T cell count after axi-cel infusion was significantly higher than at the time of diagnosis and before axi-cel infusion. This result has not been reported previously in patients receiving CAR-T cell therapy for HIV-associated BL.

A low CD4+ T cell count is a significant predictor of an unfavorable progression-free survival and OS in patients with HIV-associated lymphoma[8]. We speculate that axi-cel may improve the immunosuppressive microenvironment by effectively clearing lymphoma cells, which possibly promote CD4+ T cell proliferation. Cytokines, such as IL-2 and IL-15, that are released after CAR-T infusion may stimulate CD4+ T cell proliferation. CAR-T may also indirectly inhibit immune suppressive cell function, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thus facilitating CD4+ T cell differentiation and proliferation. In addition,

cART treatment may lead to an increase in the CD4+ T cell count by reducing HIV viral replication damage to CD4+ T cells and immune function recovery. The characteristic changes in T cell subsets during treatment with axi-cel in HIV-associated lymphoma have important clinical implications. Nevertheless, elucidation of the specific mechanism is needed.

The patient described herein received axi-cel therapy while in a CR state, which might further affect CAR-T cell amplification. Some studies have reported the results of BL patients in CR receiving CD19 CAR-T cell therapy[2,9,10]. Specifically, CAR-T expansion was improved in the CR group compared to patients with active lymphoma might in part due to a decrease in immunosuppressive components within the tumor microenvironment. The CAR-T cell count achieved a peak of 158.12 cells/μL 7 days after axi-cel infusion in the patient described herein.

This is the first report to demonstrate the efficacy and safety of axi-cel in a patient with HIV-associated BL and CNS involvement who achieved a CR prior to infusion. Unexpectedly, the absolute CD4+ T cell count and proportion increased gradually after axi-cel CAR-T cell infusion and was a durable effect for > 9 months.

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## Conflict of interest statement

No potential conflicts of interest are disclosed.

## Author contributions

Conceived and designed the analysis: Qi Deng, Yao Qi.
Collected the data: Yao Qi, Jia Wang, Jingyi Li.
Wrote the paper: Yao Qi.

## Data availability statement

The data generated in this study are available upon reasonable request from the corresponding author.

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