BCMA CAR-T induces complete and durable remission in refractory plasmablastic lymphoma


ABSTRACT
Plasmablastic lymphoma (PBL) is a rare subtype of aggressive large B-cell lymphoma, with a dismal prognosis despite aggressive therapies. New approaches are needed for those with refractory disease. PBL expresses antigens similar to multiple myeloma (MM), including B-cell maturation antigen (BCMA). Chimeric antigen receptor T-cell (CAR-T) therapy directed against BCMA has shown efficacy for the treatment of heavily pretreated MM with low rates of grades 3 and 4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in a phase Ib/II trial (A Study of BCMA CAR-T for treatment of pretreated MM with low rates of grades 3 and 4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in a phase Ib/II trial (NCT03548207). However, data for the use of BCMA CAR-T for treating PBL are lacking.

We report a challenging case of multiple refractory PBL that emerged from B-cell acute lymphoblastic leukemia in an adolescent who failed to respond to an allogeneic hematopoietic cell transplant. The patient developed rapidly advancing disease despite withdrawal of immunosuppression, treatment with etoposide, ibritinib, and daratumumab, prompting consideration of BCMA CAR-T (under emergency investigational new drug (eIND)). The patient achieved a complete remission (CR), without recurrent acute graft versus host disease (GVHD), CRS or ICANS after BCMA CAR-T therapy. BCMA CAR-T expansion was detected in vivo, peaking on day 15. The patient remains in CR for more than a year post-CAR-T therapy, supporting consideration of immunotherapy for future patients with refractory PBL, a disease with few treatment options.

Plasmablastic lymphoma (PBL) is a rare subtype of aggressive large B-cell lymphoma associated with immunodeficiency and confers a dismal prognosis despite aggressive therapies. Thus, new approaches are needed for those with refractory disease. PBL expresses similar antigens as multiple myeloma (MM), including B-cell maturation antigen (BCMA). While there are limited data in the literature, the one study showed that seven of seven PBLs demonstrated strong and diffuse BCMA expression. Cilta-cabtagene autoleucel (cilta-cel) is a second-generation chimeric antigen receptor T-cell (CAR-T) with two BCMA-binding single domains, the CD3ξ T-cell activation domain and a 4-1BB costimulatory domain. Cilta-cel has shown efficacy for the treatment of heavily pretreated MM with low rates of grades 3 and 4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in a phase Ib/II trial (NCT03548207). Cilta-cel has shown an excellent overall response rate of 98% at 28 months with 83% of patients achieving a complete remission (CR). Given the aggressiveness of PBL and limited treatment options, we hypothesized that cilta-cel would have efficacy against BCMA+ refractory PBL that arose from B-cell acute lymphoblastic leukemia (B-ALL) with manageable toxicity.

An adolescent patient was diagnosed with B-ALL (National Cancer Institute (NCI) high-risk by age), expressing CD10+, CD19+, partial CD20, partial CD22, partial CD34, CD38, partial CD200 (dim), HLA-DR, and partial CD45 (dim) by flow cytometry. The patient’s disease was refractory to high-risk ALL induction therapy but achieved CR following CD22 antibody–drug conjugate treatment (inotuzumab ozogamicin) combined with chemotherapy. Without evidence of marrow or central nervous system disease, but with a lung lesion of uncertain etiology identified.
on MRI for back pain, the patient subsequently received investigational humanized CD19 CAR-T therapy with 41BB costimulatory domain 5 months after diagnosis (NCT03792633). The patient relapsed 60 days later. Flow cytometry at the time of relapse was similar to that at diagnosis with addition of CD9+, partial CD58, partial CD123, and dimerterminal deoxynucleotidyl transferase (TdT), retaining CD19 expression. Cytogenetics revealed t(14;18), der(4)t(1;4), and focal loss of IKZF1 and PAX5 on microarray. Reinduction with idarubicin–fludara-bine, cytarabine, and venetoclax achieved CR of B-ALL. However, a chest mass, first identified directly prior to CD19 CAR-T infusion, worsened, accompanied by a new tibial lesion. Biopsies of each lesion revealed PBL with a t(14;18) translocation. Immunohistochemistry (IHC) showed CD138+, MUM1+, CD43 majorly, CD56 majorly, vimentin majorly, INI1 retained, negative for CD19, CD20, HHV8, and EBV-EBER, confirming the diagnosis of PBL. Extensive testing for underlying immunodeficiency was negative. PBL-directed therapy with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and bortezomib achieved resolution of the chest mass and reduced but persistent tibial uptake on imaging (figure 1Aa,b). With PBL in partial remission and B-ALL in CR3, the patient underwent myeloablative total body irradiation-based matched sibling peripheral blood stem cell transplant (PBSCT) with boosts to the tibia (20 Gy), lungs (200 cGy), and brain (600 cGy). Full donor chimerism was achieved, but unfortunately, the patient relapsed with PBL 60 days after PBSCT with progression at the prior tibial disease site and abundant liver and bone lesions (figure 1Ba,b). Tibial and liver IHC showed CD138+ and MUM1+, variable CD45, focal positivity for lambda light chain with Ki-67 of >70%, t(8;14) fusion, and gain of Myc. Targeted testing showed CD38+ and BCMA variably posi- tive. Despite acute calcineurin inhibitor withdrawal and treatment with etoposide, ibrutinib, and daratumumab, the disease progressed (figure 1Ca,b).

An emergency use of investigation drug was obtained, and the patient was enrolled on a single patient protocol using cilta-cel. Following apheresis, rapid disease progression including multiple skin nodules and cachexia led to the addition of lenalidomide to daratumumab and ibruti-nib 150 days post PBSCT, resulting in a dramatic reduc- tion in disease burden (figure 1Da,b) but also grade III acute graft versus host disease (GVHD) of the liver (stage...
Figure 2  (A) Ferritin and ALC following BCMA CAR-T demonstrate a moderate elevation in ferritin following CAR-T and a robust response in ALC with a peak on day 12, demonstrating successful CAR-T expansion. (B) BCMA directed CAR-Ts expanded in vivo, peaking on day 15, and were detectable until day 29 by flow cytometry. At the time of peak expansion, the CD4:CD8 ratio was 1.2 and CD8 cells were effector memory phenotype. (C) Minimal residual disease by next-generation sequencing of B-cell receptor clones throughout his clinical course, showing no residual sequences detected since BCMA CAR-T. ALC, absolute leucocyte count; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell.

3), skin (stage 3), and lower gastrointestinal tract (stage 3). GVHD became quiescent with steroids and tacrolimus. Two weeks after cessation of steroids, the patient began fludarabine and cyclophosphamide lymphodepletion and 3 days later received 0.75×10^6 cilta-cell chimeric antigen receptor (CAR)+ T cells/kg, 217 days post PBSCT while on tacrolimus. CAR+ T cells expanded postinfusion peaking on day 15 and were detectable peripherally until day 29 (figure 2A,B). At the time of peak expansion CAR+ T-cell CD4:CD8 ratio was 1.2 with CAR+ CD8 T cells being mainly effector memory phenotype. The course was uncomplicated, without GVHD flare, CRS (figure 2B), nor ICANS, though with expected brief grade 2 neutropenia, grade 3 gamma-glutamyl transferase (GGT) increase and grade 1 alkaline phosphatase and aspartate aminotransferase increase, grade 2 lymphopenia, grade 1 thrombocytopenia, grade 1 adrenal insufficiency possibly attributed to CAR-T, all of which resolved. Positron emission tomography/CT demonstrated remission 28 days post CAR-T. At the time of this report, the patient remains in CR by imaging (figure 1Fa,b) 14 months following cilta-cell. The same B-cell receptor clone that identified B-ALL and PBL by next-generation sequencing was not detected after cilta-cell (figure 2C).

This case demonstrates response to cilta-cell in an adolescent with refractory PBL, an aggressive B-cell malignancy with an overall survival of 6–9 months.34 Our patient had already received the most effective first-line regimens including EPOCH, ALL regimens2 3 and second-line approaches, such as bortezomib and lenalidomide,2 9–13 as well as an intensive radiation-based allogeneic PBSCT with refractory PBL. Acute GVHD prior to relapse and severe acute GVHD after lenalidomide precluded the use of checkpoint inhibitors which have shown some benefit in PBL.14 While CD19 CAR-T has been used to treat PBL, lack of CD19 expression also excluded this therapy for our patient.15 Given the dearth of treatment options in our multiple refractory patient whose PBL expressed BCMA, we trialed cilta-cell based on the promising results in myeloma. While our patient experienced neutropenia, common in the patients who received cilta-cell for myeloma, our patient did not develop ICANS nor CRS. This is surprising, given the patient’s risk factors for these complications, residual disease burden and prior ICANS and CRS with a CD19 CAR-T. We hypothesize that the exposure to tacrolimus (target level 6–8 ng/mL) throughout the CAR-T infusion and expansion may have mitigated these inflammatory syndromes. The patient’s ferritin peaked at 6129 ng/mL (reference range 22–275 ng/mL), 11 days post CAR-T infusion, concurrent with peak CAR-T expansion (figure 2A,B). However, cilta-cell appears to have had anti-PBL activity despite the tacrolimus exposure, with remission recently documented 14 months post infusion on a tacrolimus wean.

In summary, we describe a challenging case of multiple refractory PBL in an adolescent who achieved CR after cilta-cell infusion. It was well tolerated despite acute GVHD that occurred prior to the cilta-cell infusion. This case shows PBL CR despite tacrolimus coadministration, with BCMA CAR-T expansion detected in vivo, peaking on day 15. Our data support the consideration of immunotherapy for refractory PBL, a disease with few treatment options.

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