blood advances

TO THE EDITOR:

CAR T-cell therapy for mantle cell lymphoma with central nervous system relapse

Khoan Vu[1] and Matthew J. Frank[2]

[1]Department of Oncology/Hematology, Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA; and [2]Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University, Palo Alto, CA

Chimeric antigen receptor (CAR) T-cell therapy has been approved for the treatment of relapsed/refractory hematologic malignancies.[1-5] For relapsed/refractory mantle cell lymphoma (MCL), a single infusion of brexucabtagene autoleucel (brex-cel, KTE-X19), an anti-CD19 CAR T-cell therapy, was associated with an overall response rate of 93% and complete response (CR) rate of 67%. Importantly, remissions were durable with 57% of patients remaining in remission after 12 months.[1,6] Brex-cel-related toxicities were manageable; cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) occurred at grade $\geq$ 3 in 15% and 31% of patients, respectively. Notably, this study excluded patients with active or history of central nervous system (CNS) lymphoma. There is an unmet need for patients with CNS MCL. They have poor outcomes, and there are no consensus treatment guidelines for these patients.[7,8] Studies show CAR T-cell therapy is safe and effective in primary and secondary CNS diffuse large B-cell lymphoma (DLBCL).[9-12] Here, we report a case of relapsed MCL with active secondary CNS involvement successfully treated with brex-cel.

A 74-year-old woman with hyperlipidemia and hypothyroidism presented with fatigue and 20-pound weight loss over 2 months. Laboratory results showed a white blood cell count (WBC) 17.9 × 10^3/μL, hemoglobin level 9.9 g/d, and platelet count 146 × 10^3/μL. Flow cytometry (FC) on peripheral blood demonstrated a CD5-positive, κ-restricted B-cell population comprising 30% of nucleated white blood cells. Fluorescence in situ hybridization tests detected a t(11;14)(q13;q32) translocation consistent with MCL. Deletion of 11q22.3 (Ataxia-Telangiesctasia Mutated) and trisomy 12 were found and a 17p deletion was not. A staging positron emission tomography (PET)/computed tomography (CT) scan revealed diffuse lymphadenopathy and splenomegaly (Figure 1A). Bone marrow biopsy confirmed 70% cellular involvement by classical MCL with Ki-67 of ~30%. There was no evidence of blastoid or pleomorphic morphology. The modified MCL International Prognostic Index score was high-risk. The correlative sciences reported in this manuscript are approved by an institutional review board. It was conducted according to the Declaration of Helsinki.

She achieved a CR after 6 cycles of rituximab–bendamustine. Six months later, lower extremity weakness and pain occurred. Cerebrospinal fluid (CSF) analysis showed WBC 91/μL, protein 259 mg/dL, and glucose < 10 mg/dL. FC of the CSF demonstrated a CD5-positive, κ-restricted B-cell population comprising 33% of all cells, consistent with CNS relapse. Magnetic resonance imaging (MRI) of the brain and spine demonstrated enhancement of the lower lumbar nerve roots within the neural foramen and along the nerve roots of the cauda equina in addition to enhancing soft tissue posterior to the sacral spinal nerves at levels 2 and 3 (Figure 1B). A contemporaneous CT scan did not show systemic disease. The patient, now with an Eastern Cooperative Oncology Group performance status 2, underwent palliative radiation (4 Gy) to the sacral region and started ibrutinib 560 mg daily since more aggressive chemotherapy. Six weeks later, repeat CSF analysis showed persistent disease with 96 WBC/μL and FC showed a malignant B-cell population comprising 60% of all cells. Ibrutinib was stopped; high-dose methotrexate (MTX) 3 g/m^2 plus rituximab 375 mg/m^2 given every 2 weeks was initiated. After 2 cycles, repeat CSF analysis demonstrated 135 WBC/μL with FC showing persistent malignant cells

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Data sharing requests should be sent to the corresponding author, Matthew J. Frank (franklymatt@gmail.com).

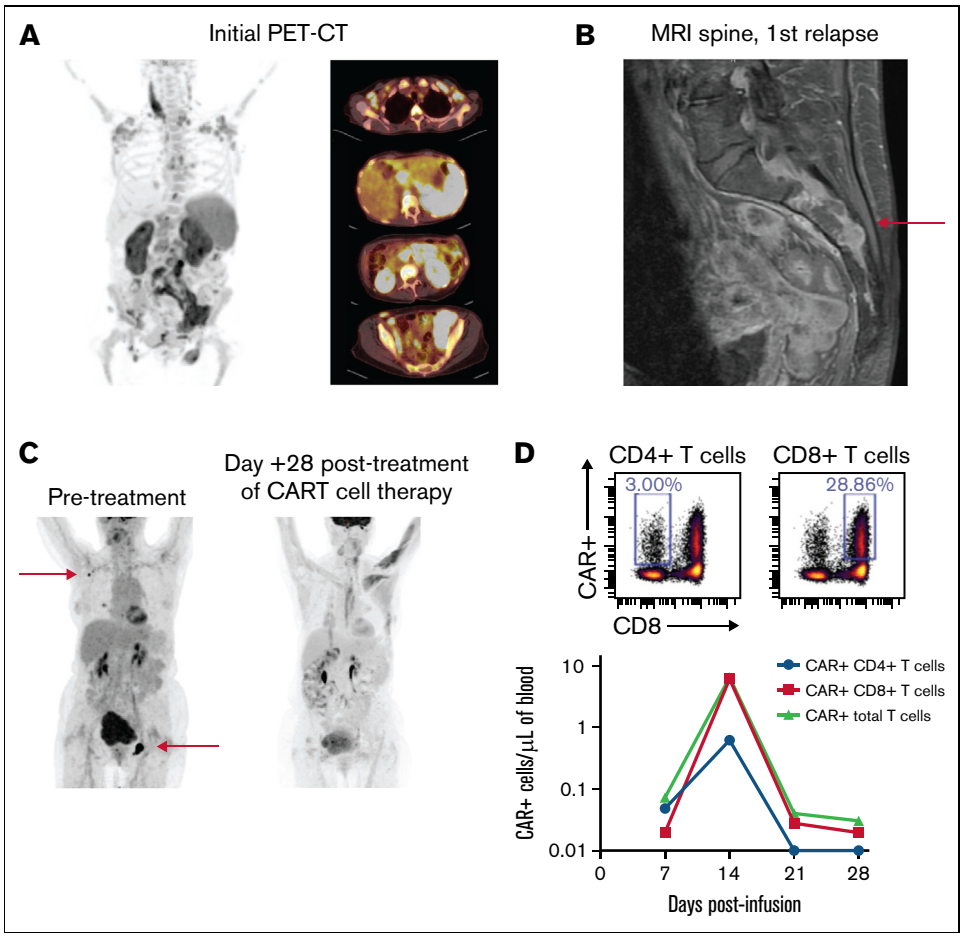

Figure 1. Initial and subsequent imaging of a patient with CNS MCL who achieved remission after brex-cel infusion. (A) Initial PET/CT scan demonstrating MCL within the bilateral cervical, supraclavicular, axillary, mediastinal, iliac, and inguinal regions; mild splenomegaly with diffuse hypermetabolism; bilaterally enlarged kidneys with hypermetabolic cortical thickening; nodular hypermetabolic foci along the large bowel; and diffuse bone marrow space hypermetabolism. (B) Magnetic resonance imaging of the spine at the time of first relapse. The red arrow indicates the presence of enhancing soft tissue posterior to the sacral spine nerve levels 2 and 3. (C) PET/CT scan prior to CAR T therapy and Day +28 after therapy. The red arrows highlight the presence of enlarged hypermetabolic left inguinofemoral and right axillary lymph nodes prior to treatment. These lesions resolved after CAR T therapy. (D) Upper plot shows $CD8^+$ versus CD19 anti-idiotype–positive cells (CD19 anti-idiotype antibody is described in Jena et al[24]) on peripheral blood monocytes gated on live $CD45^+$ $CD3^+$ $CD14^-$ cells via a gating strategy as described previously.[25] $CD4^+$ and $CD8^+$ CAR T-cells are shown on the left and right, respectively. On a log scale, the absolute number of circulating $CD4^+$ (blue), $CD8^+$ (red), and total CD19 CAR T-cells (green) after infusion as measured by flow cytometry over time.

comprising 33% of total events. MTX was halted and after starting weekly intrathecal (IT) cytarabine 50 mg, the CSF WBC rapidly declined. Five weeks later, CSF studies showed no detectable malignant cells. A PET/CT showed no systemic disease. She continued maintenance IT cytarabine 50 mg every 2 weeks.

Seven weeks later, her CSF studies demonstrated CNS relapse with 23 WBC/µL despite. PET/CT also showed systemic relapse with enlarged left inguinofemoral and right axillary lymph nodes (Figure 1C). She started twice weekly IT triple therapy with methotrexate 12 mg, cytarabine 50 mg, and hydrocortisone 50 mg. One week later, she underwent leukapheresis for standard-of-care brex-cel. After standard fludarabine/cyclophosphamide lymphodepletion, brex-cel was infused 19 days postapheresis. The CSF studies just prior to CAR T-cell infusion showed persistent disease. On day +13, she developed a fever of 38°C consistent with grade-1 CRS. Infectious workup was negative, and she defervesced without interventions. These symptoms were associated with CD19 CAR T-cell expansion as measured by FC (Figure 1D). On day +14, she developed slurred speech, lethargy, visual hallucinations, and intermittent headaches, without abnormalities seen on CT and MRI brain imaging; an electroencephalogram was not performed. For grade-2 ICANS and concurrent grade-1 CRS, tocilizumab 450 mg IV, dexamethasone 10 mg every 6 hours for 5 days (followed by a 5-day taper), and anakinra 100 mg every 6 hours (between days +17 to +21 after persistent grade-2 ICANS) were given. Her neurologic symptoms resolved in 8 days on day +22, associated with a reduction in CD19 CAR T-cells (Figure 1D). Day +28 and day +90 PET/CT scans and CSF analysis were consistent with a CR; day +90 minimal residual disease analysis via clonoSEQ showed no detectable tumor clones.

MCL comprises ~3% of adult non-Hodgkin lymphoma cases,[13,14] and CNS involvement is rare with a crude incidence of 4%. When present, prognosis is poor with a median overall survival of 3 to 6 months.[7,8] Interestingly, CNS relapse in MCL is typically leptomeningeal rather than parenchymal, unlike DLBCL in which parenchymal involvement is more frequent.[7] Risk factors for CNS

relapse include blastoid histology, high Ki-67 expression, high lactate dehydrogenase, and high-risk International Prognostic Index score.[8,15,16] However, via multivariable analysis, Ki-67 ≥ 30% was the only significant risk factor predicting CNS relapse with a 2-year cumulative incidence of 25.4%.[16] CNS prophylaxis for MCL is not the standard of care since there is no convincing evidence that high-dose antimetabolites (eg, cytarabine, methotrexate) or rituximab reduces risk of CNS relapse.[16]

The treatment for CNS relapse remains challenging. Historical treatment strategies included MTX, high-dose cytarabine, IT chemotherapy, and radiotherapy. Ibrutinib and lenalidomide can induce durable response in MCL,[17,18] and each has demonstrated efficacy in relapsed/refractory CNS lymphoma.[19-21] Ibrutinib has demonstrated CNS activity in CNS-relapsed MCL.[22,23] In a retrospective multicenter analysis (n = 84), ibrutinib was associated with superior CR rates (42% vs 22%, $P = .02$) and 1-year overall survival (59% vs 25%, $P = .011$) compared with alternative therapies (eg, MTX or cytarabine, ifosfamide) in patients with CNS-relapsed MCL.[23]

Recent studies have shown the safety and efficacy of CAR T-cell therapy in primary and secondary CNS DLBCL.[9-12] In a single-center retrospective analysis of 5 patients with primary CNS DLBCL treated with anti-CD19 CAR T-cell therapy, 3 achieved a CR, and 2 had stable disease.[10] This study demonstrated that CAR T cells can traffic to the CNS space. In a single-center retrospective analysis of 7 patients with secondary CNS lymphoma, 6 patients (85.7%) achieved a CR at day 28 with median progression-free survival of 83 days (range, 28-219 days).[11] ICANS occurred in 3 patients. In summary, these studies show that CNS involvement should not preclude patients from receiving CAR T-cell therapy.

In our patient's case, she developed leptomeningeal CNS relapse that did not initially respond to ibrutinib and MTX. Her CNS disease was initially sensitive to IT cytarabine but relapsed quickly with CNS and systemic disease. After brex-cel infusion, this patient achieved a CR in both CNS and extra-CNS compartments. To our knowledge, this is the first reported case of brex-cel used in an older patient with CNS-relapsed MCL. This case provides further support to the growing literature reporting the safety and efficacy of CAR T-cell therapy in CNS lymphoma, including MCL.

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ORCID profiles: K.V., 0000-0002-2166-4346; M.J.F., 0000-0002-2356-3354.

Correspondence: Matthew J. Frank, 300 Pasteur Dr, Room H0145, Stanford, CA 94305-5623; email: mjfrank@stanford.edu.

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