blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

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

Tracking no: ADV-2022-008031R1

Khoan Vu (Texas Oncology, United States) Matthew Frank (Stanford University, United States)

Abstract:

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: K.V and M.J.F jointly analyzed the data and wrote the paper

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: emails to the corresponding author

Clinical trial registration information (if any):

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; [2]Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University, Palo Alto, CA

Running Title: CAR T for CNS MCL

Number of tables and figures: 1

Word Count: 1192

Corresponding Author:

Matthew J. Frank, MD, PhD

Assistant Professor of Medicine

Email: mjfrank@stanford.edu

Address: 300 Pasteur Drive, Room H0145

Stanford, CA 94305-5623

Data sharing: Contact the corresponding author for data sharing: franklymatt@gmail.com.

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 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 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 two 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 on peripheral blood demonstrated a CD5-positive, kappa-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 (ATM) 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 (MIPI) 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. Flow cytometry (FC) of the CSF demonstrated a CD5-positive, kappa-restricted B-cell population comprising 33% of all cells, consistent with central nervous systemic (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 2 and 3 levels (Figure 1B). A contemporaneous CT scan did not show systemic disease. She, now with an Eastern Cooperative Oncology Group performance status 2, underwent palliative radiation (4 Gray) 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 two cycles, repeat CSF analysis demonstrated 135 WBC/μL with FC showing persistent malignant cells 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 post-apheresis. The CSF studies just prior to CAR T-cell infusion showed persistent disease. On day +13, she developed a fever of 100.4 °F 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 flow cytometry (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 complete response; day +90 minimal residual disease analysis via Clono-Seq showed no detectable tumor clones.

MCL comprises ~3% of adult NHL cases,[13] and CNS involvement is rare with crude incidence of 4%. When present, prognosis is poor with a median overall survival of 3-6 months.[7,8] Interestingly, CNS relapse in MCL is typically leptomeningeal rather than parenchymal, unlike diffuse large B-cell lymphoma (DLBCL) in which parenchymal involvement is more frequent.[7] Risk factors for CNS relapse include blastoid histology, high Ki-67 expression, high lactate dehydrogenase (LDH), and high-risk International Prognostic Index score.[8,15,16] However, via multivariable analysis, Ki-67 $\geq$30% was the only significant risk factor predicting CNS relapse with a two-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 (e.g. cytarabine, methotrexate) or rituximab reduces risk of CNS relapse.[16]

The treatment for CNS relapse remains challenging. Historical treatment strategies included high-dose methotrexate, high-dose cytarabine, intrathecal 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 multi-center analysis (n = 84), ibrutinib was associated with superior CR rates (42% vs 22%, p=0.02) and 1-year overall survival (59% vs 25%, p=0.011) compared to alternative therapies (eg. high-dose methotrexate 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 a 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, six 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 three 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 high-dose methotrexate. Her CNS disease was initially sensitive to intrathecal 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 elderly 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.

Authorship

K.V and M.J.F. jointly analyzed the data and wrote the paper. The authors have no conflicts of interest to disclose.

1. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *New England Journal of Medicine*. 2020;382(14):1331-1342. doi:10.1056/nejmoa1914347

2. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *The Lancet*. 2021;398(10299):491-502. doi:10.1016/S0140-6736(21)01222-8

3. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *The Lancet*. 2021;398(10297):314-324. doi:10.1016/S0140-6736(21)00933-8

4. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *The Lancet Oncology*. 2022;23(1):91-103. doi:10.1016/S1470-2045(21)00591-X

5. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *New England Journal of Medicine*. 2022;386(7):640-654. doi:10.1056/NEJMOA2116133/SUPPL_FILE/NEJMOA2116133_DATA-SHARING.PDF

6. Jain P, Wang Y, Locke FL, et al. Brexucabtagene autoleucel for relapsed/refractory mantle cell lymphoma: Real-world experience from the United States lymphoma CAR T consortium. *Journal of Clinical Oncology*. 2022;40(16_suppl):e19583-e19583. doi:10.1200/JCO.2022.40.16_SUPPL.E19583

7. Cheah CY, George A, Giné E, et al. Central nervous system involvement in mantle cell lymphoma: Clinical features, prognostic factors and outcomes from the European mantle cell lymphoma network. *Annals of Oncology*. 2013;24(8):2119-2123. doi:10.1093/annonc/mdt139

8. Ferrer A, Bosch F, Villamor N, et al. Central nervous system involvement in mantle cell lymphoma. *Annals of Oncology*. 2007;19:135-141. doi:10.1093/annonc/mdm447

9. Frigault MJ, Maus M v., Dietrich J, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood*. 2019;134(11):860-866. doi:10.1182/BLOOD.2019001694

10. Siddiqi T, Wang X, Blanchard MS, et al. CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma. doi:10.1182/bloodadvances.2020004106

11. Ahmed G, Hamadani M, Shah NN. CAR T-cell therapy for secondary CNS DLBCL. *Blood Advances*. 2021;5(24):5626-5630. doi:10.1182/bloodadvances.2021005292

12. Alcantara M, Houillier C, Blonski M, et al. CAR T-cell therapy in primary central nervous system lymphoma: the clinical experience of the French LOC network. *Blood*. 2022;139(5):792-796. doi:10.1182/BLOOD.2021012932

13. National Comprehensive Cancer Network. B-Cell Lymphomas (Version 4.2022). Accessed June 28, 2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

14. Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. *Journal of Clinical Oncology*. 2016;34(11):1256-1269. doi:10.1200/JCO.2015.63.5904

15. Conconi A, Franceschetti S, Lobetti-Bodoni C, et al. Risk factors of central nervous system relapse in mantle cell lymphoma. *Leukemia and Lymphoma*. 2013;54(9):1908-1914. doi:10.3109/10428194.2013.767454/SUPPL_FILE/DISCLOSURE.ZIP

16. Chihara D, Asano N, Ohmachi K, et al. Ki-67 is a strong predictor of central nervous system relapse in patients with mantle cell lymphoma (MCL). *Annals of Oncology*. 2015;26:966-973. doi:10.1093/annonc/mdv074

17. Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *New England Journal of Medicine*. 2013;369(6):507-516. doi:10.1056/nejmoa1306220

18. Trněný M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): A phase 2, randomised, multicentre trial. *The Lancet Oncology*. 2016;17(3):319-331. doi:10.1016/S1470-2045(15)00559-8

19. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA)

and the French oculo-cerebral lymphoma (LOC) network. *European Journal of Cancer*. 2019;117:121-130. doi:10.1016/J.EJCA.2019.05.024

20. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. *Blood Advances*. 2018;2(13):1595-1607. doi:10.1182/BLOODADVANCES.2017014845

21. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. *Annals of Oncology*. 2019;30(4):621-628. doi:10.1093/ANNONC/MDZ032

22. Bernard S, Goldwirt L, Amorim S, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. *Blood*. 2015;126(14). doi:10.1182/blood-2015-05

23. Rusconi C, Cheah Cy, Tucker D, Eyre TA, Klener P, Giné E. Ibrutinib compared to immuno-chemotherapy for central nervous system relapse of mantle cell lymphoma: a report from Fondazione Italiana Linfomi (FIL) and European Mantle Cell Lymphoma Network (EMCLN) [abstract]. *Eur Hematol Assoc*. Published online 2020. Accessed February 22, 2022. https://library.ehaweb.org/eha/2020/eha25th/295049/chiara.rusconi.ibrutinib.compared.to.immuno-chemotherapy.for.central.nervous.html?f=menu=6

24. Jena B, Maiti S, Huls H, et al. Chimeric Antigen Receptor (CAR)-Specific Monoclonal Antibody to Detect CD19-Specific T Cells in Clinical Trials. *PLoS ONE*. 2013;8(3). doi:10.1371/JOURNAL.PONE.0057838

25. Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. *Nature Medicine*. 2021;27(8):1419. doi:10.1038/S41591-021-01436-0

Figure 1 caption

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) MRI 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.[21]) 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.

Figure 1