blood advances

TO THE EDITOR:

CAR T-cell therapy in mantle cell lymphoma with secondary CNS involvement: a multicenter experience

Gulrayz Ahmed,[1] Aseel Alsouqi,[2] Aniko Szabo,[1] Laura Samples,[3] Mazyar Shadman,[3] Farrukh T. Awan,[4] Alexandra E. Rojek,[5] Peter A. Riedell,[5] Madiha Iqbal,[6] Timothy S. Fenske,[1] Mohamed A. Kharfan-Dabaja,[6] Sawa Ito,[2] and Mehdi Hamadani[1]

[1]Division of Hematology-Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [2]Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; [3]Division of Hematology-Oncology, Department of Medicine, Fred Hutchinson Cancer Center, Seattle, WA; [4]Division of Hematology-Oncology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX; [5]David and Etta Jonas Center for Cellular Therapy, The University of Chicago, Chicago, IL; and [6]Division of Hematology-Oncology, Department of Medicine, Mayo Clinic Florida, Jacksonville, FL

Mantle cell lymphoma (MCL) makes up 5% to 6% of all non-Hodgkin lymphomas.[1,2] The risk of secondary central nervous system (SCNS) involvement in MCL is ~4%, with 0.9% having CNS involvement at diagnosis.[1] The median survival from time of CNS diagnosis was historically <4 months.[1] Limited data have shown that Bruton tyrosine kinase inhibitors can achieve biologically relevant concentrations in CNS and may improve outcomes of patients with MCL with SCNS involvement, relative to conventional chemoimmunotherapies.[3,4]

CD19–directed chimeric antigen receptor T-cell (CAR-T) therapy is a standard option for relapsed/refractory MCL. The ZUMA-2 trial showed favorable efficacy with 67% complete response (CR) rates and a manageable safety profile, leading to Food and Drug Administration approval of brexucabtagene autoleucel.[3,5] Unfortunately, patients with SCNS involvement were excluded. With limited availability of data, additional studies are required to assess safety and efficacy of CAR-T in MCL with SCNS involvement. Here, we report a retrospective experience of 6 US centers of patients with MCL with SCNS involvement receiving CAR-T therapy.

Patients with MCL with SCNS involvement at any point in their disease history and receiving CAR-T therapy between the years 2016 and 2022 were included. This study was approved by institutional review boards of all participating sites. Disease response assessment was done for both systemic and CNS disease. Systemic response was assessed using the Lugano criteria,[6] whereas CNS response was assessed as per International Primary CNS Lymphoma Collaborative Group criteria.[7] Progression-free survival (PFS) and overall survival (OS) for entire cohort, as well as subsets of patients with and without active CNS disease at the time of CAR-T infusion, were assessed. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were collected using the consensus guidelines from American Society of Transplantation and Cellular Therapy.[8] This study was approved by institutional review boards of all participating sites, with Medical College of Wisconsin serving as the primary site for data holding and analysis.

Twelve patients were included with a median age of 72 years (range, 50-82) at CAR-T infusion, and 9 participants (75%) were males. Patient demographics are detailed in Table 1. Eight patients had active CNS disease at the time of CAR-T infusion. Of the 4 patients without CNS disease, 2 had active systemic disease at infusion. The median number of prior therapies was 4 (range, 2-6). Three patients received cranial radiation as bridging therapy with a median interval of 16 days (range, 11-55) before CAR-T infusion. A total of 11 patients received brexucabtagene autoleucel, whereas 1 patient received a CD19/20-directed investigational product. CRS developed in 11 patients (91.67%) and was grade 1 to 2 in all cases (tocilizumab use; n = 9). Ten patients (83.33%) developed ICANS, including 7 (58%) with grade 3 to 4 ICANS (62% and 50% in patients with or without active CNS disease, respectively). Median time to CRS and

Submitted 22 November 2023; accepted 28 April 2024; prepublished online on *Blood Advances* First Edition 3 May 2024. https://doi.org/10.1182/bloodadvances.2023012255.

Data are available on request from the corresponding author, Gulrayz Ahmed (gahmed@mcw.edu).

Table 1. Patient and disease characteristics

Characteristic	Overall, N = 12	Without active CNS disease at CAR-T infusion, n = 4	Active CNS disease at CAR-T infusion, n = 8
Age at CAR-T infusion (range), y	72 (50-82)	75 (71-82)	71 (50-77)
Race			
Asian	2 (17%)	1 (25%)	1 (12.5%)
White	10 (83%)	3 (75%)	7 (87.5%)
Sex			
Female	3 (25%)	2 (50%)	1 (12.5%)
Male	9 (75%)	2 (50%)	7 (87.5%)
Stage at diagnosis			
III	1 (8.3%)	1 (25%)	0 (0%)
IV	11 (92%)	3 (75%)	8 (100%)
ECOG			
0-1	9 (75%)	4 (100%)	5 (62.5%)
2	2 (16.7%)	0 (0%)	2 (25%)
>3	1 (8.3%)	0 (0%)	1 (12.5%)
Timing of secondary CNS involvement			
Diagnosis	2 (17%)	1 (25%)	1 (12.5%)
Relapse	10 (83%)	3 (75%)	7 (87.5%)
Median number of prior therapy lines (range)	4 (2-6)	4 (4-5)	4 (2-6)
Sites of active CNS Disease at CAR-T infusion			
None	4 (33%)	4 (100%)	0 (0%)
Parenchymal	2 (17%)	0 (0%)	2 (25%)
Leptomeningeal	5 (42%)	0 (0%)	5 (63%)
Both	1 (8.3%)	0 (0%)	1 (13%)
Active systemic disease present at CAR-T infusion	6 (50%)	2 (50%)	4 (50%)
Prior transplant before CAR-T	3 (25%)	1 (25%)	2 (25%)
History of CNS radiation			
No	8 (67%)	3 (75%)	5 (62.5%)
Yes, extracranial stereotactic RT	1 (8.3%)	1 (25%)	0 (0%)
Yes, WBRT or focal stereotactic brain RT	3 (25%)	0 (0%)	3 (37.5%)
Prior BTKi use	11 (92%)	4 (100%)	7 (88%)
Interval between BTKi before CAR-T (range), mo	4 (1-22)	3.0 (2-4)	5 (1-22)
Reasons for discontinuation			
Intolerance	1 (8.3%)	0 (0%)	1 (14%)
PD	6 (50%)	1 (25%)	5 (72%)
Not available/others	4 (33%)	3 (75%)	1 (14%)
Time from last RT to CAR-T infusion (range), d	36 (11-245)	245 (245-245)	16 (11-55)
Bridging therapy prior to CAR-T			
None	6 (50%)	1 (25%)	5 (63%)
BTKi with or without chemotherapy	2 (17%)	2 (50%)	0 (0%)
Extracranial focal stereotactic RT	1 (8.5%)	1 (25%)	1 (13%)
WBRT or stereotactic brain RT	3 (25.5%)	0 (0%)	2 (25%)
Interval between diagnosis and CAR-T infusion (range), d	20 (6-169)	25 (6-90)	20 (7-169)
Type of CAR-T product			
Brexu-cel	11 (92.7%)	4 (100%)	7 (88%)
Investigational	1 (8.3%)	0 (0%)	1 (13%)

BTKi, Bruton tyrosine kinase inhibitor; Brexu-cel, brexucabtagene autoleucel; ECOG, Eastern Cooperative Oncology Group; RT, radiation; WBRT, whole brain radiation.

Table 1 (continued)

Characteristic	Overall, N = 12	Without active CNS disease at CAR-T infusion, n = 4	Active CNS disease at CAR-T infusion, n = 8
Lymphodepletion regimen			
Bendamustine	1 (8.3%)	0 (0%)	1 (13%)
Fludarabine/cyclophosphamide	11 (92.7%)	4 (100%)	7 (88%)

BTKi, Bruton tyrosine kinase inhibitor; Brexu-cel, brexucabtagene autoleucel; ECOG, Eastern Cooperative Oncology Group; RT, radiation; WBRT, whole brain radiation.

ICANS onset was 3 (range, 0-8) and 6 days (range, 2-8), respectively. All patients with ICANS also had grade 1 to 2 CRS. Eight patients with ICANS had elevated ferritin (median, 958 ng/mL) and C-reactive protein (median, 11.89 mg/dL). Elevated lactate dehydrogenase at lymphodepletion (n = 7; P = .29), Eastern Cooperative Oncology Group performance status (P = .43), leukemic phase (n = 2; P = .47), and marrow involvement (n = 3; $P \geq .99$) were not associated with ICANS. Management of ICANS included systemic corticosteroids (n = 10), intrathecal steroids (n = 1), intrathecal chemotherapy (n = 1), and anakinra (n = 3). Among patients with or without active CNS involvement, rates of CRS (87.5% vs 100%) or ICANS (87.5% vs 75%) were similar. The median follow-up of survivors was 16.7 months (range, 13.4-33.7), and at last follow-up, 6 patients were alive. Six patients relapsed; 2 had CNS relapse, and 3 had systemic relapse, whereas 1 had both CNS and systemic relapse.

Best systemic response at 1 month after CAR-T therapy was CR (n = 11 [92%]), whereas 1 patient had partial response. At 3 months after CAR-T therapy, 11 patients (92%) had CR, whereas 1 patient had progressive disease (PD). Similarly, best CNS response at 1 month after CAR-T therapy was CR in 11 patients (92%), whereas 1 patient had stable disease. At 3 months, 11 patients (92%) continued to remain in CR, whereas 1 patient had PD. We further assessed the responses of patients who had active CNS disease vs patients with no active CNS disease. Objective response rates (ORRs) for CNS response in patients with active CNS disease at 1-month and 3-month time points were 100% (n = 8) and 88% (n = 7; 1 patient had PD), respectively. For patients with no active CNS disease, the ORR was 100% (n = 4) at 1- and 3-month time points for both CNS and systemic responses. Two patients without active CNS disease experienced a relapse, 1 with CNS and the other with systemic disease. Figure 1 summarizes clinical course of all patients.

The 6- and 12-month PFS for the overall cohort were 58% (95% confidence interval [CI], 36-94) and 33% (95% CI, 15-74), respectively, with an OS of 83% (95% CI, 65-100) and 67% (95% CI, 45-99). Among patients with active CNS disease, the 6- and 12-month PFS were 50% (95% CI, 25-100) and 25% (95% CI, 7.5-83) respectively, whereas the OS was 75% (95% CI, 50-100) and 63% (95% CI, 37-100). Finally, in patients without active CNS disease at CAR-T infusion, the 6-month and 12-month PFS were 75% and 50%, respectively, whereas the OS for similar time intervals was 100% and 75%, respectively. Twelve-month nonrelapse mortality rate for the overall cohort was 10% (95% CI, 0.43-38). Cumulative incidence of relapse at 12 months was 50% (95% CI, 19-75) for the overall cohort and 50% (95% CI, 11-80) in patients with active CNS disease.

Our study continues to build on the efficacy of anti-CD19 CAR-T therapy in patients with MCL with SCNS involvement. Our results are in line with the 2 prior studies with respect to ORRs and CR rates.[9-11] The

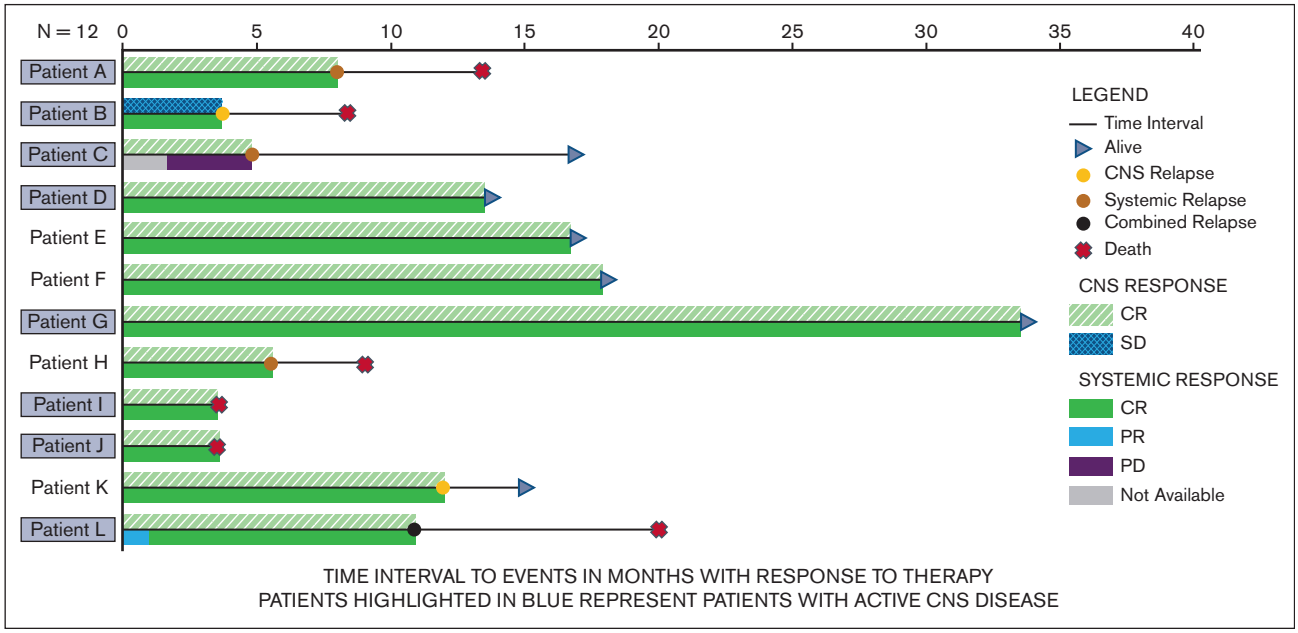

Figure 1. Clinical course of patients. PR, partial response; SD, stable disease.

US Lymphoma CAR-T Consortium study included 16 patients with SCNS involvement and reported an ORR of 81%, with CR rates of 75% in patients with active CNS disease.[9] Ryan et al[10] reported an ORR of 86% in patients with active CNS disease (n = 7) with CR rates of 28.6%. In our cohort, the ORR was 100%, with 92% achieving a CR at the 1-month interval. The US Lymphoma CAR-T Consortium study did not report SCNS specific outcomes, but Ryan et al[10] reported a 12-month PFS of 36% and OS of 71% in patients with active CNS disease, which was slightly higher than that reported in our case series (25% and 63%, respectively). As far as adverse events of CRS and ICANS are concerned, we had no patients with grade ≥3 CRS, consistent with the data from the US Lymphoma CAR-T Consortium study and Ryan et al.[10] Interestingly, similar to Ryan et al,[10] we also report an increased signal of ICANS (10 out of 12 patients; with 7 having grade ≥3) irrespective of the presence or absence of active CNS disease at the time of CAR-T infusion (71% vs 67%). Notable differences in PFS and OS benefit is evident between patients with and without active CNS disease at the time of CAR-T infusion in our analysis, which suggests that controlling CNS disease before infusion could lead to better outcomes in this population.

In this retrospective study, anti-CD19 CAR-T therapy showed encouraging response rates in patients with MCL with and without active CNS disease at infusion, with a reasonable safety profile and manageable adverse events. The risk of CNS relapse unfortunately is high in such patients. Limitations of this study include the retrospective nature and small sample size with broad confidence intervals, although our data provide meaningful insight on CAR-T response in patients with MCL with SCNS involvement. Increased frequency of ICANS remains a concern and a topic worthy of further study.

Contribution: G.A., A.A., and M.H. conceptualized the study; G.A. designed the protocol, collected and analyzed the data, and wrote the manuscript; A.S. conducted data analysis; A.A., L.S., M.S., F.T.A., A.E.R., P.A.R., M.I., T.S.F., M.A.K.-D., and S.I. contributed patients and critically reviewed the manuscript; and all authors approved the final version of the manuscript.

Conflict-of-interest disclosure: M.S. reports consulting, advisory board, steering committee, or data safety monitoring committee fees from AbbVie, Genentech, AstraZeneca, Janssen, BeiGene, Bristol Myers Squibb (BMS), MorphoSys/Incyte, Kite Pharma, Eli Lilly, Mustang Bio, Fate Therapeutics, Nurix, and Merck; research funding from Mustang Bio, Genentech, AbbVie, BeiGene, AstraZeneca, Genmab, MorphoSys/Incyte, and Vincerx; stock options in Koi Biotherapeutics; and employment with BMS (spouse). F.T.A. has provided consultancy to Genentech, AstraZeneca, AbbVie, Janssen, Pharmacyclics, Gilead Sciences, Kite Pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, BeiGene, Johnson & Johnson, Dava Oncology, BMS, Merck, Cardinal Health, ADC Therapeutics, Epizyme, Caribou Biosciences, Cellectar Biosciences, Loxo Oncology, and Adaptive Biotechnologies, and received research funding from Pharmacyclics. P.A.R. has served as a consultant and/or advisory board member for AbbVie, Novartis, BMS, ADC Therapeutics, Kite/Gilead, Sana Biotechnology, Nektar Therapeutics, Nurix Therapeutics, Intellia Therapeutics, CVS Caremark, Genmab, BeiGene, Janssen, and Pharmacyclics; received honoraria from Novartis; and research support from BMS, Kite Pharma, Novartis, MorphoSys, CRISPR Therapeutics, Calibr, Xencor, Fate Therapeutics, AstraZeneca, Genentech, and Tessa Therapeutics. T.S.F. reports providing consultancy to Adaptive Biotechnologies, AstraZeneca, BeiGene, Kite (Gilead), Lilly/Loxo, Pharmacyclics (AbbVie), and Seagen, and speaking for AstraZeneca, BeiGene, Kite (Gilead), Sanofi, Seagen, and TG Therapeutics. M.H. reports research support/funding from ADC Therapeutics, Spectrum Pharmaceuticals, and Astellas Pharma; consultancy fees from ADC Therapeutics, Omeros, CRISPR, BMS, Kite, AbbVie, Caribou, and Genmab; and speaker's bureau fees from ADC Therapeutics, AstraZeneca, BeiGene, Kite, DMC Inc, Genentech, Myeloid Therapeutics, and CRISPR. The remaining authors declare no competing financial interests.

ORCID profiles: G.A., 0000-0001-6873-9571; A.A., 0000-0001-9112-9034; A.S., 0000-0002-8129-0614; L.S., 0000-0003-2680-0244; F.T.A., 0000-0003-1813-9812; A.E.R., 0000-0003-1615-1447; M.A.K.-D., 0000-0001-7394-5185; S.I., 0000-0002-6076-0234; M.H., 0000-0001-5372-510X.

Correspondence: Gulrayz Ahmed, Division of Hematology and Oncology, Medical College of Wisconsin, 9200 W. Wisconsin Ave, Milwaukee, WI 53226; email: gahmed@mcw.edu.

References

1. 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. *Ann Oncol*. 2013;24(8):2119-2123.
2. Kröger K, Siats J, Kerkhoff A, et al. Long-term survival of patients with mantle cell lymphoma after total body irradiation, high-dose chemotherapy and stem cell transplantation: a monocenter study. *Cancers*. 2023;15(3):983.
3. McLaughlin N, Wang Y, Inwards DJ, et al. Outcomes in mantle cell lymphoma with central nervous system involvement. *J Clin Oncol*. 2021;39(Suppl 15):e19527.
4. Rusconi C, Cheah CY, Eyre TA, et al. Ibrutinib improves survival compared with chemotherapy in mantle cell lymphoma with central nervous system relapse. *Blood*. 2022;140(17):1907-1916.
5. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342.
6. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
7. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;23(22):5034-5043.
8. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
9. Wang Y, Jain P, Locke FL, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in standard-of-care practice: results from the US lymphoma CAR T consortium. *J Clin Oncol*. 2023;41(14):2594-2606.
10. Ryan CE, Zon RL, Redd R, et al. Clinical efficacy and safety of chimeric antigen receptor T-cell therapy for mantle cell lymphoma with secondary central nervous system involvement. *Br J Haematol*. 2023;203(5):774-780.
11. Vu K, Frank MJ. CAR T-cell therapy for mantle cell lymphoma with central nervous system relapse. *Blood Adv*. 2023;7(3):375-378.