STIMULUS REPORT

blood advances

CAR T-cell therapy for secondary CNS DLBCL

Gulrayz Ahmed, Mehdi Hamadani, and Nirav N. Shah

Blood and Marrow Transplant and Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

Key Points

- SCNSL should not preclude patients from receiving CAR T-cell therapy because of concerns regarding ICANS.
- WBRT is not associated with increased ICANS when used as a bridge to CAR T-cell therapy with a short median interval in SCNSL.

Management of secondary central nervous system (SCNS) involvement in relapsed or refractory aggressive B-cell lymphomas remains an area of unmet medical need. We report a single-center retrospective analysis of 7 adult patients with SCNS lymphoma (SCNSL) who underwent chimeric antigen receptor (CAR) T-cell therapy for their refractory disease, and we describe the safety of whole brain radiation therapy (WBRT) as a bridging therapy. Six patients (85.7%) achieved a complete response at day 28, and 1 patient had progressive disease. The median progression-free survival was 83 days (range, 28-219 days), and median overall survival was 129 days (range, 32-219 days). Three patients died as a result of disease progression. Of the 5 patients who received WBRT as bridging therapy, 3 had no immune effector cell–associated neurotoxicity syndrome (ICANS), but 2 patients had grade 1 or grade 3 ICANS. No grade 4 ICANS was reported in this subset of patients. We conclude that SCNSL should not preclude patients from receiving CAR T-cell therapy as a treatment option because of concerns regarding ICANS, and bridging with WBRT is not associated with increased ICANS.

Introduction

Despite recent advances, the management of secondary central nervous system (SCNS) involvement in relapsed or refractory (R/R) aggressive B-cell lymphomas remains an area of unmet medical need because these patients are often excluded from clinical trials.[1,2] Even among patients with isolated SCNS lymphoma (SCNSL), systemic relapse is invariable, and the median survival of these patients is poor (≤6 months).[3-6] The mainstay for treatment of SCNSL remains intravenous high-dose methotrexate, whole brain radiation therapy (WBRT), or high-dose chemotherapy followed by autologous stem cell transplantation. New treatment approaches are indicated for these patients. Anti–CD-19 chimeric antigen receptor (CAR) T-cell therapy is a paradigm-changing option for patients with R/R diffuse large B-cell lymphoma (DLBCL), and there are now 3 treatment products available in the United States that have been approved by the US Food and Drug Administration.[7] The first 2 registrational CAR T-cell studies excluded patients with lymphoma with CNS involvement because of concerns about immune effector cell–associated neurotoxicity syndrome (ICANS), but limited retrospective data along with data from the TRANSCEND trial have shown the feasibility of CAR T-cell therapy in SCNSL.[1,2,7-10] Although in-field systemic radiation has been shown to be safe as a bridging therapy before CAR T-cell therapy, there are no data on the safety of WBRT as a bridging therapy before CAR T-cell infusion.[11,12] Physician groups have concerns regarding increased ICANS because there is only a limited amount of literature that would support the idea of a combination of both modalities. However, mouse models for glioblastoma have shown that the combination of CAR T-cell therapy and radiation therapy has a synergistic effect.[13]

Submitted 17 May 2021; accepted 6 July 2021; prepublished online on *Blood Advances* First Edition 22 September 2021; final version published online 28 December 2021. DOI 10.1182/bloodadvances.2021005292.

Data sharing requests may be submitted to Nirav N. Shah (nishah@mcw.edu).

The full-text version of this article contains a data supplement.

Table 1. Demographics, outcomes, and management of adverse events

Patient ID	Age, sex	Disease location	Systemic disease at time of CAR T-cell treatment	No. of previous lines of therapy	Previous auto-HCT	Bridging WBRT, total dose (cGy) (fractions)	Systemic status before CAR T-cell therapy	Product	Day 28 systemic response	MRD status at day 28	CRS, grade, treatment	ICANS and grade	Treatment of ICANS	Relapse, day of assessment	Current status
1	47, M	LMD	Yes	4	Yes	No	CR	Axi-cel	CR	Negative	Yes, 1, tocilizumab	No	NA	No, day 91	Alive with CR at day 91
							CR (LP negative)*		CR†						
2	**72, F**	**Parenchyma**	**No**	**4**	**No**	**Yes, 2800 (14)**	**PD**	**Axi-cel**	**CR**	**Negative**	**Yes, 1, none**	**Yes, 3**	**Solumedrol pulse and dexamethasone taper**	**No, day 129**	**Alive with CR at day 129**
							SD (MRI after RT)*		**CR (LP and MRI)†**						
3	**42, F**	**Parenchyma**	**No**	**4**	**No**	**Yes, 2340 (13)**	**CR**	**Tisa-cel**	**CR**	**NA**	**Yes, 3, tocilizumab and dexamethasone taper**	**Yes, 1**	**Dexamethasone**	**No, day 219**	**Alive with CR at day 219**
							PR (MRI after RT)*		**CR (MRI)†**						
4	39, F	LMD	Yes	2	No	No	PD	Axi-cel	CR	NA	Yes, 2, tocilizumab and dexamethasone	Yes, 2	Dexamethasone taper	Yes, day 51	Dead as a result of PD, day 109
							PD (LP positive)*		CR (LP)†						
5	**50, M**	**Parenchyma**	**No**	**4**	**Yes**	**Yes, 4000 (20)**	**PD**	**Tisa-cel**	**CR**	**Negative**	**No**	**No**	**NA**	**Yes, day 83**	**Dead as a result of PD, day 133**
							PR (MRI after RT)*		**CR (LP)†**						
6	**72, M**	**Parenchyma**	**No**	**2**	**No**	**Yes, 400 (2)**	**PD**	**Tisa-cel**	**PD**	**NA**	**No**	**No**	**NA**	**Yes, day 28**	**Dead as a result of PD, day 63**
							PD (MRI before RT)*‡		**PD (MRI)†**						
7	**51, M**	**Parenchyma**	**Yes**	**3**	**No**	**Yes, 3000 (18)**	**PD**	**Tisa-cel**	**CR**	**Negative**	**No**	**No**	**No**	**No, day 48**	**Alive with CR, day 48**
							PR (MRI after RT)*		**CR (MRI)†**						

Patients who received WBRT are shown in **bold.**

Auto-HCT, autologous hematopoietic cell transplantation; Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; F, female; LMD, leptomeningeal disease; LP, lumbar puncture; M, male; MRD, minimal residual disease; MRI, magnetic resonance imaging; NA, not applicable or not available; PD, progressive disease; PR, partial response; RT, radiation thereapy; SD, stable disease; Tisa-cel, tisagenlecleucel.

*CNS status before CAR T-cell therapy (assessment study).

†Day 28 CNS response (assessment study).

‡Had PD before CAR T-cell infusion; received 2 Gy × 2 of WBRT; response was assessed after day 28.

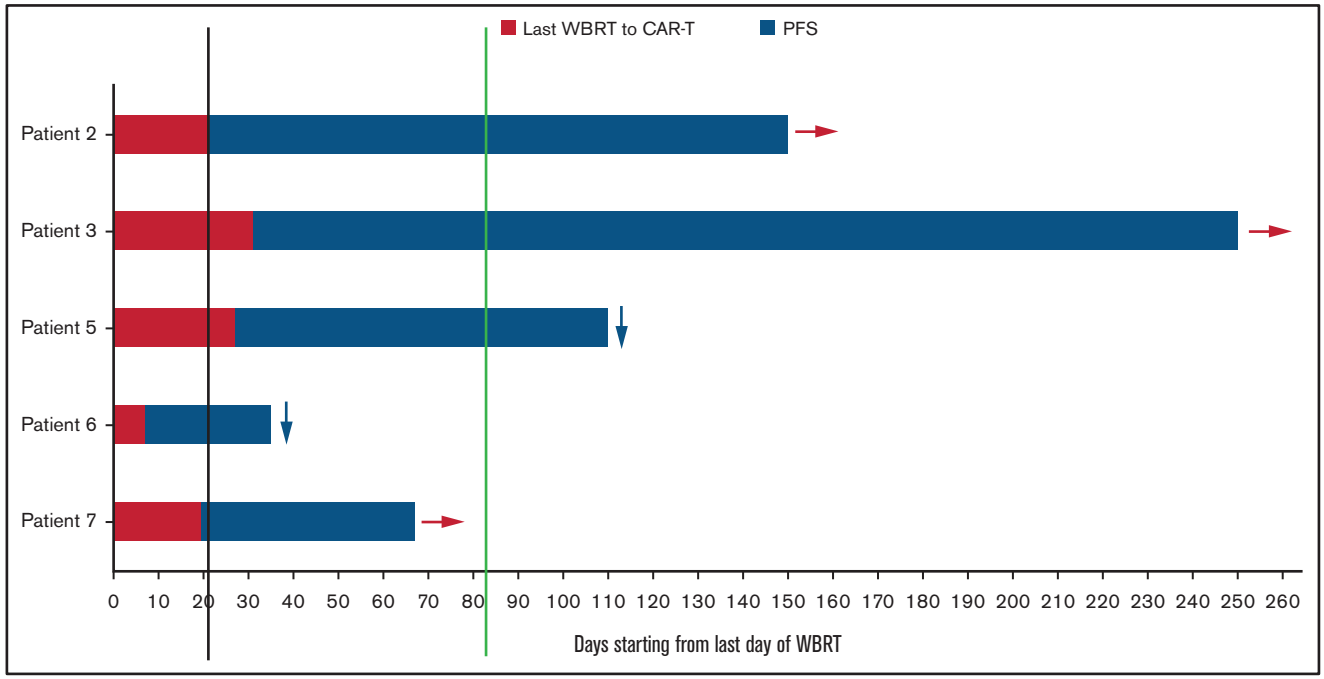

Figure 1. Interval from last WBRT to CAR T-cell therapy and progression-free survival (PFS). PFS is for patients who were bridged with WBRT. Black line, median time (21 days) from last WBRT to CAR T-cell treatment; green line, median PFS (83 days). (→) Ongoing CR; (↓) relapsed.

We report here a single-center retrospective analysis of 7 adult patients with SCNSL who received CAR T-cell therapy for their refractory disease, and we also describe the safety of WBRT as a bridging therapy before T-cell infusion in a subset of patients.

Methods

Data on patient demographics, disease, and CAR T-cell therapy–related variables and patient outcomes were retrieved from the Blood and Marrow Transplant and Cellular Therapy Program Database. Disease and response to treatment were assessed separately for systemic and CNS disease. Results from positron emission tomography scans with Deauville scores of 1, 2, and 3 were considered a complete response (CR), whereas clearing lymphoma cells from the lumbar puncture as indicated and resolution of contrast enhancement within parenchymal lesions on brain magnetic resonance imaging scans were considered a CR for CNS disease (supplemental Table 1). Adverse outcomes of cytokine release syndrome and ICANS were documented by primary care physicians based on consensus guidelines from the American Society of Transplantation and Cellular Therapy for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells.[14] ClonoSEQ assay (Adaptive Biotechnologies) was used to assess minimal residual disease status. The study was approved by Medical College of Wisconsin/Froedtert Hospital Institutional Review Board #5 and conducted according to the Declaration of Helsinki.

Results and discussion

For patients in this study, median age was 50 years (range, 39-72 years), and 4 patients (57.1%) were males (see Table 1 for details regarding patient demographics). The median number of previous therapies was 4 (range, 2-4) (detailed treatment regimens are provided in supplemental Table 1). Median lactate dehydrogenase at the time of CAR T-cell therapy was 190 U/L (range, 138-327 U/L) (supplemental Table 1). Five patients had parenchymal involvement and 2 had leptomeningeal disease. WBRT was administered to 5 of the 7 patients at a median dose of 2800 cGy (400-4000 cGy) immediately before CAR T-cell therapy was administered as a bridging therapy with a median interval of 21 days (range, 7-31 days) from the last fraction of radiation to CAR T-cell infusion (Figure 1). All patients received uniform lymphodepletion with fludarabine and cyclophosphamide. Axicabtagene ciloleucel was given at a standard dose of 2×10^6 cells per kg ($n = 3$), and the median number of tisagenlecleucel cells infused was 4×10^8 (range, 3×10^8 to 4.3×10^8) ($n = 4$). Cytokine release syndrome was reported in 4 patients; grade 3 or above was reported in only 1 patient. ICANS was reported in 3 of the 7 patients, and all required medical interventions. Adverse events and their management are described in Table 1. The median follow-up of survivors was 5.1 months (range, 1.6-7.2 months), and at last follow-up, 4 patients were alive. Six patients (85.7%) achieved a CR at day 28, and 1 patient had progressive disease. The median progression-free survival was 83 days (range, 28-219 days), and median overall survival was 129 days (range, 32-219 days). Three patients died as a result of progressive disease. Of the 5 patients who received WBRT as bridging therapy, 3 had no ICANS, but 2 had grade 1 or 3 ICANS. No grade 4 ICANS was reported, and all patients fully recovered with no treatment-related mortalities. No patient received a transplant after CAR T-cell therapy, and no maintenance strategies were used.

SCNSL is associated with poor outcomes and is an disease that should be further investigated.[3,6] ZUMA-1 and JULIET trials, which led to the approval of CAR T-cell therapy for R/R DLBCL, excluded patients with CNS involvement because of concerns regarding

increased ICANS.[1,2] In our patient population, CAR T-cell therapy seemed to be a safe treatment option in SCNSL, with favorable outcomes even among heavily pretreated patients. In their letter to the editor, Abramson et al[9] reported a patient who had relapsed DLBCL with CNS involvement who received lisocabtagene maraleucel with disease remission at 12 months. This led to a case series by Frigault and colleagues[7] of 8 patients who received tisagenlecleucel and showed ongoing CR or partial response at more than 90 days in 3 patients; 1 patient had CR at 180 days. Bennani et al[15] also shared their experience with 17 patients who had similar outcomes compared with patients receiving axicabtagene ciloleucel who had no CNS involvement.[12,15] The TRANSCEND trial included 6 patients with SCNSL of whom 3 achieved a CR.[10] Our outcomes are consistent with results of previously reported studies that had manageable adverse events and no treatment-related mortalities.[7,16,17] Our patients had a median overall survival of 83 days (2.7 months), with 3 patients in CR at more than 90 days.

Our study is limited by its retrospective nature and small sample size, but it demonstrates 2 major findings; first, that having SCNSL should not preclude someone from receiving CAR T-cell therapy as a treatment option because of concerns regarding ICANS. Second, we demonstrate that WBRT as a bridging therapy to CAR T-cell therapy with a short interval (median, 21 days) is associated with no new safety signals or increased ICANS, albeit with limited follow-up. It is possible that radiosensitization may improve CAR T-cell outcomes by enhancing T-cell trafficking into the tumor environment, which was demonstrated with immunotherapy by Dovedi et al.[18] Similarly, recent studies have shown improved progression-free survival and overall response rates in patients receiving CAR T cells with systemic radiation as a bridging therapy when compared with chemotherapy.[12,18,19] In conclusion, we demonstrated the safety of CNS-directed radiation as a bridge to CAR T-cell therapy and provided further evidence that SCNS involvement should not preclude treatment with CAR T cells.

Authorship

Contribution: G.A., M.H., and N.N.S. designed and performed the research, analyzed the data, contributed patients, and wrote, critically reviewed, and approved the manuscript.

Conflict-of-interest disclosure: N.N.S. received honoraria and/or travel support from Incyte, Celgene, Eli Lily, and Miltenyi Biotec, served on scientific advisory boards for Eli Lily, Kite Pharma, Celgene, Legend, Epizyme, Seattle Genetics, and TG therapeutics, holds equity ownership in Exelixis and Geron, and received institutional research support for clinical trials from Miltenyi Biotec. M.H. received research support from Takeda Pharmaceuticals and Spectrum Pharmaceuticals, served as a consultant for Incyte, ADC Therapeutics, Pharmacyclics, Omeros, AbGenomics, Verastem, TeneoBio, and Kite Pharma, and served on the Speaker's Bureau for Sanofi Genzyme, AstraZeneca, and Beigene. The remaining author declares no competing financial interests.

ORCID profiles: G.A., 0000-0001-6873-9571; M.H., 0000-0001-5372-510X; N.N.S., 0000-0002-4336-1071.

Correspondence: Nirav N. Shah, Division of Hematology and Oncology, Medical College of Wisconsin, 9200 W. Wisconsin Ave, Milwaukee, WI 53226; e-mail: nishah@mcw.edu.

References

1. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med.* 2019;380(1):45-56.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
3. Hollender A, Kvaloy S, Lote K, Nome O, Holte H. Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis. *Eur J Cancer.* 2000;36(14):1762-1768.
4. Bollen EL, Brouwer RE, Hamers S, et al. Central nervous system relapse in non-Hodgkin lymphoma. A single-center study of 532 patients. *Arch Neurol.* 1997;54(7):854-859.
5. Tomita N, Kodama F, Kanamori H, Motomura S, Ishigatsubo Y. Secondary central nervous system lymphoma. *Int J Hematol.* 2006;84(2):128-135.
6. El-Galaly TC, Cheah CY, Bendtsen MD, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. *Eur J Cancer.* 2018;93:57-68.
7. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood.* 2019;134(11):860-866.
8. Ramos CA. The CNS can be a safe space for CARs. *Blood.* 2019;134(11):845-846.
9. Abramson JS, McGree B, Noyes S, et al. Anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. *N Engl J Med.* 2017;377(8):783-784.
10. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet.* 2020;396(10254):839-852.
11. Sim AJ, Jain MD, Figura NB, et al. Radiation therapy as a bridging strategy for CAR T cell therapy with axicabtagene ciloleucel in diffuse large B-cell lymphoma. *Int J Radiat Oncol Biol Phys.* 2019;105(5):1012-1021.
12. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood Adv.* 2020;4(13):2871-2883.
13. Weiss T, Weller M, Guckenberger M, Sentman CL, Roth P. NKG2D-based CAR T cells and radiotherapy exert synergistic efficacy in glioblastoma. *Cancer Res.* 2018;78(4):1031-1043.

14. 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.

15. Bennani NN, Maurer MJ, Nastoupil LJ, et al. Experience with axicabtagene ciloleucel (axi-cel) in patients with secondary CNS involvement: Results from the US Lymphoma CAR T Consortium [abstract]. *Blood.* 2019;134(suppl_1). Abstract 763.

16. Siddiqi T, Wang X, Palmer J, et al. CD19-targeting CAR-T cell therapy in CNS lymphoma [abstract]. *Blood.* 2019;134(suppl_1). Abstract 4075.

17. Ghafouri S, Timmerman J, Larson S, Mead MD. Axicabtagene ciloleucel CAR T-cell therapy for relapsed/refractory secondary CNS non-Hodgkin lymphoma: comparable outcomes and toxicities, but shorter remissions may warrant alternative consolidative strategies? *Bone Marrow Transplant.* 2021;56(4):974-977.

18. Dovedi SJ, Cheadle EJ, Popple AL, et al. Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. *Clin Cancer Res.* 2017;23(18):5514-5526.

19. Qu C, Ping N, Kang L, et al. Radiation priming chimeric antigen receptor T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma with high tumor burden. *J Immunother.* 2020;43(1):32-37.