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Toxicities and Response Rates of Secondary CNS Lymphoma After Adoptive Immunotherapy With CD19-Directed Chimeric Antigen Receptor T Cells

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Abstract

Background and Objectives

Secondary CNS involvement in systemic B-cell lymphoma (SCNSL) is difficult to treat and displays dismal clinical outcomes. Chimeric antigen receptor (CAR) T cells emerged as a powerful treatment for systemic lymphoma. We aimed to evaluate whether CAR T cells also represent a safe and effective therapy for SCNSL.

Methods

We retrospectively searched our institutional database for patients with SCNSL treated with CD19-directed CAR T cells.

Results

We identified 10 cases, including 7 patients with intraparenchymal lesions and 3 patients with leptomeningeal disease. CNS staging at 1 month after CAR T-cell transfusion showed disease response (stable disease, partial response, and complete response) in 7 patients (70%), including 2 cases of long-lasting complete response (20%). One patient developed pseudoprogression, which resolved under steroids. Response of CNS disease was associated with systemic 1-month response. With a median follow-up of 6 months, median overall and systemic progression-free survival was 7 and 3 months, respectively. Neurotoxic symptoms occurred in 6 patients, with 3 patients developing severe neurotoxicity (American Society for Transplantation and Cellular Therapy grade ≥3).

Discussion

CAR T cells induce considerable antitumor effects in SCNSL, and CNS response reflects systemic response. Neurotoxicity appears similar to previous reports on patients with lymphoma without CNS involvement. CAR T cells may therefore represent an effective and safe therapy for SCNSL.

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Glossary

CAR = chimeric antigen receptor; **SCNSL** = secondary CNS lymphoma.

Secondary CNS involvement is a devastating complication of systemic lymphoma. Standard therapies remain undefined, but frequently chemoimmunotherapy (followed by autologous stem-cell transplantation or whole-brain radiation) is provided.[1] Still, median survival is less than 6 months. Novel therapeutic strategies are needed.

Chimeric antigen receptor (CAR) T cells represent an innovative cell-based immunotherapy approved as third-line treatment for systemic large B-cell lymphoma.[2] By genetic engineering, CARs redirect the killing activity of autologous T cells against the B-cell antigen CD19. Given concerns for severe neurotoxicity and insufficient efficacy due to limited CAR T-cell trafficking across the blood-brain barrier,[3] patients with systemic lymphoma and CNS involvement (secondary CNS lymphoma, SCNSL) were excluded from pivotal clinical trials. It therefore remains unclear whether CAR T cells represent a safe and effective treatment for SCNSL.[4] We present a retrospective case analysis to describe our institutional real-world experience on response rates and toxicities of CAR T-cell therapy for SCNSL.

Methods

We retrospectively searched our institutional database for patients meeting the following criteria: (1) presence of SCNSL, defined as systemic lymphoma with CNS involvement confirmed per neuroimaging or CSF within 28 days before CAR T-cell transfusion, and (2) lymphoma treatment with CD19-directed CAR T cells (following conditioning lymphodepletion with fludarabine/cyclophosphamide) (Supplementary eFigure 1, links.lww.com/WNL/B907). Clinical metadata were collected with IRB approval and informed consent. Toxicities were graded according to the American Society for Transplantation and Cellular Therapy. Radiographic response was assessed according to Response Assessment in Neuro-Oncology criteria (CNS disease) and Lugano classification (systemic disease). For leptomeningeal disease, CSF clearance from lymphoma cells was evaluated. Uncertainties regarding inclusion and outcome were resolved by interdisciplinary expert consensus. Survival was calculated using Kaplan-Meier analysis and the log-rank test. Relationships between categorical variables were analyzed using the Fisher exact test. The significance level was $p < 0.05$. Anonymized data are available upon qualified request.

Results

We identified 10 patients with SCNSL treated with CAR T cells (Table 1). On MRI, 7 patients had intra-axial lesions, and 3 patients had contrast-enhancing meninges with concurrent CSF findings consistent with leptomeningeal dissemination.

After CAR T-cell transfusion, 6 patients developed CAR T cell–associated neurotoxic symptoms (Table 2), and alternative etiologies (especially disease progression) were ruled out by neuroimaging and CSF analysis. Symptoms were often transient (Figure 1A) and accompanied by temporarily elevated CRP and persistently elevated interleukin-6 serum levels (Supplementary eFigure 2, links.lww.com/WNL/B907). Severe neurotoxicity ≥ grade 3 was observed in 3 patients, including 1 ventilated patient who deceased because of pneumonia on day 10. Notably, 1 patient with leptomeningeal disease of the optic nerve presented with reduced vision of the affected eye 4 days after transfusion (Figure 1B). MRI demonstrated nerve swelling and contrast enhancement, and CAR T cells (but not lymphoma cells) were found in the CSF. Symptoms and MRI affection resolved after steroids, and the event was interpreted as pseudoprogression. Intraparenchymal lesions, leptomeningeal disease, or the number of prior therapies did not predict the occurrence or severity of neurotoxicity (Supplementary eTable 1).

On first (30-day) staging after CAR T-cell transfusion, we observed CNS response in 7 patients (stable disease: 3 patients; partial response: 2 patients; complete response: 2 patients) (Figure 1C). With a median follow-up of 6 months, median overall and systemic progression-free survival was 7 and 3 months, respectively (Figure 1D). Median CNS progression-free survival was not reached. Ongoing remission lasting 6 and 15 months was noted in both cases of complete CNS response. All 3 patients with progressive CNS disease had systemic progression, and CNS and systemic disease response were associated ($p = 0.018$). Neither the number of prior therapies nor specific lymphoma subtypes were associated with CNS response.

Discussion

We found a remarkable response rate of 70%, and observed 20% sustained complete remissions after CAR T-cell therapy. Our analysis further showed that CNS and systemic response to CAR T cells appear to be closely associated. Although our study is limited by its small sample size and retrospective nature, our observations point towards potent intracranial activity of CAR T cells in heavily pretreated patients as previously suggested.[5,6] To confirm these promising findings, prospective trials need

Table 1 Clinical Characteristics and Outcome

	Demographics and baseline patient characteristics				CNS involvement		Extra-axial involvement	CNS disease outcome (per RANO)			Systemic disease outcome (per Lugano [change in absolute tumor volume])			
#	Age	Sex	Pathology	Neurologic symptoms	MRI findings	CSF findings	PET/CT findings	1-month staging	3-month staging	6-month staging	1-month staging	3-month staging	6-month staging	Current status
1	38	M	DLBCL	None	Dural, intracerebral (temporal)	None	Nodal, pulmonary, muscular	PD	CR (after RT + pembro)	—	PD (−22%)	PR (−28%; after RT + pembro)	—	Deceased at 4 months because of disease progression
2	59	F	DLBCL	Lumboischialgia	Spinal (meningeal; L4-S2)	None	Nodal, muscular, bones, peritoneal	PD	PD (after R + pembro + pola)	—	PD (+58%)	PD (+360%; after R + pembro + pola)	PD (−)	Deceased at 7 months because of disease progression
3	65	M	trFL	Headache	Intracerebral (Ri temporal, B/L occipital)	None	Nodal, pulmonary, hepatic, seminal vesicle	PR	PR	—	PR (−97%)	PR (−99%)	—	Alive at 3 months
4	66	M	DLBCL	None	Intracerebral (L central)	None	Hepatic	SD	—	—	SD (−91%)	—	—	Alive at 1 month
5	51	M	trFL	CN VII palsy and visual deficits	Dural, intracerebral (optic nerve)	Leptomeningeal dissemination	None	CR (after pseudoprogression)	CR	CR	None	None	None	Alive at 6 months
6	70	M	trFL (double-hit)	None	Intracerebral (lateral ventricular horn)	None	Nodal, pleural, bones, soft tissue	—	CR	—	PR (−39%)	PR (−81%)	CR	Alive at 15 months
7	44	F	PTLD	CN VI palsy and headache	Dural/intracerebral (Ri frontal, L parieto-occipital)	None	Nodal, pulmonal, hepatic, pancreatic, muscular, bones, soft tissue	PD	—	—	PD (−60%)	—	—	Deceased at 1 month because of disease progression
8	35	F	DLBCL	Paraplegia	Dural, intracerebral (Ri frontal, lateral and 4th ventricle), spinal (extramedullar/extradural; T6-T7)	None	None	PR	—	—	None	—	—	Alive at 1 month
9	65	M	DLBCL (double-hit)	None	Dural	Leptomeningeal dissemination	Bones	SD	—	—	—	—	—	Alive at 2 months
10	49	F	DLBCL	None	Dural	Leptomeningeal dissemination	Nodal, pulmonal, renal, bones, soft tissue	SD	—	—	—	—	—	Deceased after 10 days because of pneumonia
Total	55 (med.)	M:F 6: 10	6/10 DLBCL	5/10 symptomatic	7/10 intraparenchymal	3/10 positive CSF	8/10 systemic involvement	6/9 CNS response	4/5 CNS response	1/1 CNS response	3/6 response	3/4 response	1/2 response	6-month med. follow-up

Characteristics are given for all patients with SCNSL (n = 10) treated with CD19-directed CAR T cells.
Abbreviations: B/L = bilateral; CN = cranial nerve; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group performance status; F = female; L = left; M = male; med. = median; PD = progressive disease; pembro = pembrolizumab; pola = polatuzumab; PR = partial response; PTLD = posttransplant lymphoproliferative disorder; R = rituximab; RANO = Response Assessment in Neuro-Oncology; Ri = right; RT = radiotherapy; trFL = transformed follicular lymphoma; SD = stable disease (including none progressiveness).
"—" not available for review.

Table 2 Toxicities After CAR T-Cell Transfusion for Secondary CNS Lymphoma

	ICANS				CRS		
#	Highest ICANS grade	Day of onset (after CAR T-cell transfusion)	Duration (d)	Neurotoxic symptoms	Highest CRS grade	Day of onset (after CAR T-cell transfusion)	Duration (d)
1	0	n.a.	n.a.	None	1	4	8
2	0	n.a.	n.a.	None	1	3	4
3	0	n.a.	n.a.	None	1	2	4
4	0	n.a.	n.a.	None	2	1	7
5	2	3	3	Visual deficits and delirious	2	1	6
6	2	3	12	Dysgraphia and somnolent	2	1	8
7	2	17	7	Aphasia, apraxia, dysgraphia, and somnolent	2	3	4
8	3	9	22	Paraphasia and soporose	1	3	1
9	3	3	17	Apraxia, (sensory) aphasia, and soporose	2	2	5
10	4	2	9	(Motor) aphasia and coma	3	1	10
Total	2 (median)	3 ± 2 (median)	10.5 ± 3 (median)	6/10 Symptomatic	2 (median)	2 ± 0.4 (median)	5.5 ± 0.8 (median)

Abbreviations: CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; n.a. = not applicable.
Characteristics of ICANS and CRS (highest grade according to the American Society for Transplantation and Cellular Therapy, day of onset after CAR T-cell transfusion, duration) and neurologic symptoms are given for all patients with SCNSL (n = 10) treated with CD19-directed CAR T cells.

to delineate how CAR T cells compare to other therapies (including chemoimmunotherapy or radiotherapy). Notably, suspicion is indicated when assessing therapeutic response because pseudoprogression may occur.

Following CAR T-cell transfusion, we observed (transient) neurotoxic symptoms, which were similar in frequency and presentation to previous reports of patients with lymphoma without CNS involvement.[3] CNS disease thus does not appear to be associated with more severe neurotoxicity and should not prevent patients from receiving CAR T cells. Neither pretreatment burden nor prior CNS-directed radiotherapy in particular predisposed to more severe neurotoxicity, albeit preexisting brain damage and blood-brain barrier disruptions were previously linked to neurotoxicity.[7] Collectively, CAR T cells may represent an effective and safe therapy for SCNSL and therefore warrant further evaluation.

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Disclosure

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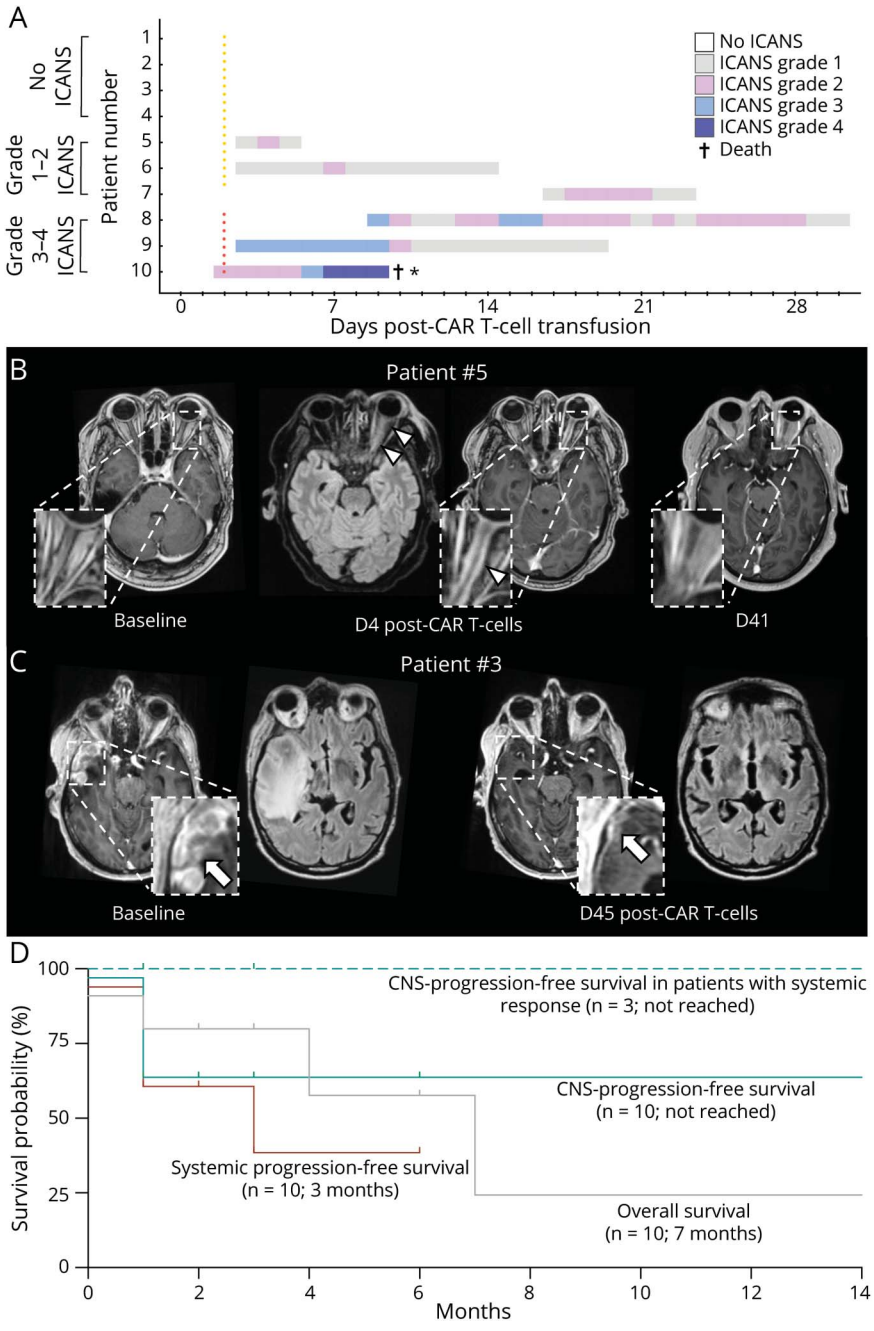
Figure Toxicities and Outcome After CAR T-Cell Therapy for Secondary CNS Lymphoma



(A) Kinetics of immune effector cell-associated neurotoxicity syndrome (ICANS) through 30 days after transfusion of CD19-directed CAR T cells (n = 10). Each row represents one patient, each column a single day after CAR T-cell transfusion, and the highest ICANS grade (graded according to American Society for Transplantation and Cellular Therapy recommendations) on each day is color coded. Note that the patient number matches the individual patient number provided in the tables. Median time to fever ≥38°C for patients with grade 0–2 ICANS (yellow dotted line) and grade 3–4 ICANS (red dotted line) is indicated. *Patient #10 with ICANS grade 4 deceased because of a pulmonary infection. (B and C) Axial MRI of the brain with contrast-enhanced T1-weighted sequences from patients with lymphoma involvement of the left optic nerve (B) and of the right temporal lobe (C; arrows). In the patient with optic nerve affection (B), note the pseudoprogression characterized by nerve swelling (arrowheads) particularly on FLAIR-weighted imaging (left image in the middle panel) preceding complete response. In the patient with temporal lobe affection (C), note the substantial edema before CAR T-cell transfusion on FLAIR-weighted imaging (right image on each panel). (D) Kaplan-Meier estimates of overall survival, CNS progression-free survival, and systemic progression-free survival for our entire cohort (n = 10). Numbers in brackets indicate median survival times. In the subgroup of patients with systemic response (n = 3; dashed line), favorable systemic response was reflected by the CNS response.

received research funding, speaker honoraria, and serves on the speakers bureau of AMGEN, MSD Sharp & Dohme, Novartis, Roche, KITE/Gilead, Bristol-Myers Squibb, Astellas, Mologen, and Miltenyi. J.-C. Tonn has received consultant/speaker honoraria from BrainLab and Carthera and royalties from Springer Publisher Intl. W. G. Kunz and L. von Baumgarten report no disclosures. M. Subklewe has received industry research support from Amgen, Gilead, Miltenyi, MorphoSys, Roche, and Seattle Genetics and has served as a consultant/advisor to Amgen, BMS, Celgene, Gilead, Pfizer, Novartis, and Roche. She sits on the advisory boards of Amgen, Celgene, Gilead, Janssen, Novartis, Pfizer, and Seattle Genetics and serves on the speakers' bureau at Amgen, Celgene, Gilead, Janssen, and Pfizer. Go to Neurology.org/N for full disclosures.

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