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 pseudo-progression, 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 chemioimmunotherapy (followed by autologous stem-cell transplantation or whole-brain radiation) is provided. 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. By genetic engineering, CARs redirect the killing activity of autologous T cells against the B-cell antigen CD19. Given concerns for neurotoxicity and insufficient efficacy due to limited CAR T-cell trafficking across the blood-brain barrier, 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. 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. To confirm these promising findings, prospective trials need...
Table 1: Clinical Characteristics and Outcome

| #  | 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             | —              | —              | PD (-22%)       | —              | —              | Deceased at 4 months because of disease progression |
| 2  | 59  | F   | DLBCL     | Lumboischialgia     | Spinal (meningeal; L4-S2) | None         | Nodal, muscular, bones, peritoneal | PD             | —              | —              | PD (+58%)       | —              | PD (+360%)      | 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 (-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) | None         | Leptomeningeal dissemination | CR (after pseudoprogression) | CR              | CR              | None           | None           | None           | Alive at 6 months |
| 6  | 70  | M   | trFL      | (double-hit)        | Intracerebral (lateral ventricular horn) | None         | Nodal, pleural, bones, soft tissue | —              | —              | —              | 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, pulmoral, hepatic, pancreatic, muscular, bones, soft tissue | PD             | —              | —              | PD (-60%)       | —              | —              | Deceased at 1 month because of disease progression |
| 8  | 35  | F   | DLBCL     | Paraplegia          | Intracerebral (Ri frontal, lateral and 4th ventricle), spinal (extramedullary/extradural; T6-T7) | None | None | PR | —              | —              | None           | —              | —              | —              | Alive at 1 month |
| 9  | 65  | M   | DLBCL     | (double-hit)        | None                | Leptomeningeal dissemination | Bones | SD             | —              | —              | —              | —              | —              | —              | Alive at 2 months |
| 10 | 49  | F   | DLBCL     | None                | Dural               | Leptomeningeal dissemination | Nodal, pulmoral, renal, bones, soft tissue | SD             | —              | —              | —              | —              | —              | Deceased after 10 days because of pneumonia |

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

| # | ICANS highest grade | ICANS day of onset (after CAR T-cell transfusion) | ICANS duration (d) | Neurotoxic symptoms | CRS highest grade | CRS day of onset (after CAR T-cell transfusion) | CRS duration (d) |
|---|---|---|---|---|---|---|---|
| 0 | 0 | n.a. | n.a. | None | 1 | 4 | 8 |
| 1 | 0 | n.a. | n.a. | None | 1 | 3 | 4 |
| 2 | 0 | n.a. | n.a. | None | 1 | 2 | 4 |
| 3 | 0 | n.a. | n.a. | None | 2 | 1 | 7 |
| 4 | 0 | n.a. | n.a. | None | 2 | 1 | 8 |
| 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, (sensor)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.
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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Appendix (continued)

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