Neuro-Oncology
25(12), 2239–2249, 2023 | https://doi.org/10.1093/neuonc/noad118 | Advance Access date 4 July 2023

Neurotoxicity and management of primary and secondary central nervous system lymphoma after adoptive immunotherapy with CD19-directed chimeric antigen receptor T-cells

Philipp Karschnia, Isabel C. Arrillaga-Romany, April Eichler, Deborah A. Forst, Elizabeth Gerstner, Justin T. Jordan, Ina Ly, Scott R. Plotkin, Nancy Wang, Maria Martinez-Lage, Sebastian F. Winter, Joerg-Christian Tonn, Kai Rejeski, Louisa von Baumgarten, Daniel P. Cahill, Brian V. Nahed, Ganesh M. Shankar, Jeremy S. Abramson, Jeffrey A. Barnes, Areej El-Jawahri, Ephraim P. Hochberg, P. Connor Johnson, Jacob D. Soumerai, Ronald W. Takvorian, Yi-Bin Chen, Matthew J. Frigault[#], and Jorg Dietrich[#]

All author affiliations are listed at the end of the article

Corresponding Author: Jorg Dietrich, MD, PhD, Department of Neurology, Division of Neuro-Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, USA (Dietrich.Jorg@mgh.harvard.edu).

[#]The senior authors contributed equally to this work

Abstract

Background: Chimeric antigen receptor (CAR) T-cells targeting CD19 have been established as a leading engineered T-cell therapy for B-cell lymphomas; however, data for patients with central nervous system (CNS) involvement are limited.

Methods: We retrospectively report on CNS-specific toxicities, management, and CNS response of 45 consecutive CAR T-cell transfusions for patients with active CNS lymphoma at the Massachusetts General Hospital over a 5-year period.

Results: Our cohort includes 17 patients with primary CNS lymphoma (PCNSL; 1 patient with 2 CAR T-cell transfusions) and 27 patients with secondary CNS lymphoma (SCNSL). Mild ICANS (grade 1–2) was observed after 19/45 transfusions (42.2%) and severe immune effector cell-associated neurotoxicity syndrome (ICANS) (grade 3–4) after 7/45 transfusions (15.6%). A larger increase in C-reactive protein (CRP) levels and higher rates of ICANS were detected in SCNSL. Early fever and baseline C-reactive protein levels were associated with ICANS occurrence. CNS response was seen in 31 cases (68.9%), including a complete response of CNS disease in 18 cases (40.0%) which lasted for a median of 11.4 ± 4.5 months. Dexamethasone dose at time of lymphodepletion (but not at or after CAR T-cell transfusion) was associated with an increased risk for CNS progression (hazard ratios [HR] per mg/d: 1.16, $P = .031$). If bridging therapy was warranted, the use of ibrutinib translated into favorable CNS-progression-free survival (5 vs. 1 month, HR 0.28, CI 0.1–0.7; $P = .010$).

Conclusions: CAR T-cells exhibit promising antitumor effects and a favorable safety profile in CNS lymphoma. Further evaluation of the role of bridging regimens and corticosteroids is warranted.

Key Points

- CD19-directed chimeric antigen receptor T-cells appear safe in central nervous system (CNS) lymphoma, with systemic baseline inflammation being associated with immune effector cell-associated neurotoxicity syndrome.
- CNS response was seen in 69% of cases; lower steroid doses during lymphodepletion and ibrutinib as bridging are associated with outcome.

Importance of the Study

CD19-directed chimeric antigen receptor (CAR) T-cells represent a promising approach for systemic lymphoma; but the safety and efficacy profile for patients with central nervous system (CNS) lymphoma remains elusive. We, therefore, studied our institutional cohort of 17 consecutive patients with primary CNS lymphoma and 27 patients with secondary CNS lymphoma who received CD19-directed CAR T-cells at the Massachusetts General Hospital for active CNS disease. Based on this cohort, we provided evidence that a high CNS response rate of 69% can be achieved, including a large number of complete responses. No CNS-specific side effects other than what has been reported for extra-axial disease were observed; and elevated CRP levels identified patients at risk. Higher doses of dexamethasone at time of lymphodepletion were associated with increased risk of CNS progression, while the use of ibrutinib as bridging therapy seemed to translate into favorable CNS outcomes. CD19-directed CAR T-cells appear as a powerful and safe therapy in CNS lymphoma.

Central nervous system (CNS) lymphoma either refers to a lymphoma that is confined to the brain, meninges, eyes, or spinal cord in the absence of systemic disease at time of initial diagnosis (primary CNS lymphoma, PCNSL) or to metastatic seeding of a systemic lymphoma to the CNS (secondary CNS lymphoma, SCNSL). Individuals with relapsed CNS lymphoma carry a prognosis of less than 12 months even when aggressive treatment (including radio- or chemo-therapy) is provided.[1–4] Innovative and more effective therapeutic approaches are therefore urgently needed.

Chimeric antigen receptors endow an autologous polyclonal T-cell population with MHC-unrestricted antigen specificity. Following viral transduction, incorporation of chimeric antigen receptors redirects the killing activity of T-cells against specific tumor cell targets such as the pan-B-cell antigen CD19. Based on compelling response rates of up to 80%,[5–7] several commercial CAR T-cell products have recently gained approval from the US Food and Drug Administration for treatment of relapsed or refractory diffuse large B-cell lymphoma. However, such therapy carries substantial toxicity burden including neurotoxic symptoms denoted as "immune effector cell-associated neurotoxicity syndrome" (ICANS),[8] which range from mild confusion to potentially fatal brain edema.[9] Given the concern for increased neurotoxicity when the target antigen is present within the CNS as well as impaired CAR T-cell trafficking across the blood-brain barrier, lymphoma patients with primary and secondary CNS involvement were excluded from all but one of the pivotal studies.[7] In one trial that included SCNSL patients, only seven of the 269 patients had active CNS involvement at the time of treatment.[7] As 3 of those patients had complete response, data on response but also on CNS-specific toxicities following CAR T-cell transfusion in the setting of active CNS disease are limited but suggestive of intracranial activity.[10–12]

Here, we present our institutional experience at the Massachusetts General Hospital of CNS lymphoma patients managed with CD19-directed CAR T-cells over a 5-year period. We describe the clinical course following CAR T-cell transfusion and encountered neurotoxic side effects, and their correlation with inflammatory serum markers. Next, we explore the CNS-specific response patterns and predictors of clinical outcomes including bridging therapies and steroid use.

Material and Methods

Study Population

Study design and methods of this retrospective study were approved by the Institutional Review Board of the Massachusetts General Hospital. We searched our institutional database for patients with active CNS lymphoma treated with CD19-directed CAR T-cells between 2018 and 2022. Patients were selected based on the following criteria: (1) presence of active CNS lymphoma confirmed by neuroimaging or cerebrospinal fluid (CSF) prior to CAR T-cell transfusion, (2) treatment with CD19-directed CAR T-cells, and (3) at least one follow-up MRI (for parenchymal or radiographic leptomeningeal disease) or CSF (for proven CSF involvement by leptomeningeal disease) to allow response assessment. We collected demographic and clinical information, bridging therapies, serum cytokine levels, radiographic and CSF findings, use of steroids, and clinical outcomes. Baseline assessments including imaging and CSF were taken from pre-transfusion exams as closest to the date of CAR T-cell transfusion as available. To allow detailed analyses of the effects of steroid use, daily dexamethasone doses were noted for each individual patient during bridging, lymphodepletion, CAR T-cell transfusion, and 14 days of follow-up after CAR T-cell transfusion. Bridging was defined as the interval between apheresis to start of lymphodepletion. Steroids were standardized by converting to the corresponding dexamethasone dose (10 mg hydrocortisone to 0.4 mg dexamethasone; 10 mg prednisolone to 1.6 mg dexamethasone). Selected patients in this study have been partly included in previous reports.[11,13]

Toxicity and Response Assessment

For toxicity assessment, ICANS and cytokine release syndrome (CRS) were prospectively graded according to the consensus grading system proposed by the American Society for Transplantation and Cellular Therapy as part of clinical routine.[8] For response assessment, MR imaging of the CNS (and CSF analysis if there was evidence

of involvement) was reviewed at 1 month, 3 months, 6 months, and 1 year after CAR T-cell transfusion when available. CNS disease and response to therapy were evaluated according to the response criteria established by the International PCNSL Collaborative Group whenever possible (IPCG).[14] Response to CAR T-cell therapy was graded as complete response, partial response, stable disease, or progressive disease. Parenchymal disease was graded according to response of the contrast-enhancing lesion on MRI (complete response: complete lesion resolution; partial response: ≥50% decrease of the lesion; stable disease: less than partial response but no progression; progressive disease: >25% increase of the lesion). Leptomeningeal disease was graded per CSF (complete response: negative CSF in the absence of new symptoms; partial response: not recognized in the setting of exclusive leptomeningeal disease, otherwise criteria for parenchymal disease apply; stable disease: less than partial response but no progression; progressive disease: appearance of any new disease site per CSF or imaging). In the absence of baseline CSF disease, patients were not required to repeat CSF evaluation if no interval symptoms that suggest leptomeningeal dissemination developed. Additional retrospective review of the medical records as well as of the imaging findings was performed for the current study to ensure accuracy, and discrepancies were resolved by interdisciplinary expert consensus.

Definition of Endpoints

Patients were followed until death or day of database closure (March 1, 2023). Patients lost to follow-up were censored. Date of recurrence was set as date of MRI or CSF assessment confirming disease progression. CNS-progression-free survival was defined as the time from CAR T-cell transfusion to recurrence or death from any cause. If autopsy did not show CNS disease in deceased patients, individuals were censored on the day of death.

Statistics

Continuous variables were assessed for normal distribution and equal variance using the D'Agostino-Pearson test. For parametric data, differences between 2 groups were tested by the unpaired Student's *t*-test. For non-parametric data, the Mann–Whitney U-test was used. The correlation between dexamethasone doses at the time of bridging, at lymphodepletion, at CAR T-cell transfusion, and during the 14-day follow-up period was estimated utilizing principal component analysis, and loading plots were constructed to visualize the relationships between the individual variables. The diagnostic ability of baseline inflammatory markers to predict ICANS were studied by generating receiver operating curve curves. Continuous data are expressed as mean ± SEM if not indicated otherwise, and range is given. The relationship between categorical variables was calculated using the χ^2-test, and categorical variables are described in absolute numbers and percentages.

For univariate survival analysis stratified by a binary variable (eg, PCNSL vs. SCNSL), Kaplan–Meier survival estimates and log-rank tests were used to assess CNS outcomes. The reverse Kaplan–Meier method was used for calculation of median follow-up. For univariate survival analysis on outcome stratified by continuous variables (eg, varying dexamethasone doses), Cox proportional hazard regression models were computed to estimate hazard ratios (HR) and 95%-confidence intervals (CI). Also, Cox proportional hazard regression models were applied when calculating the combined effects of steroid doses during different clinical intervals on outcome. All statistical analyses were performed using Prism (v9.5.0; GraphPad Software Inc.) and Stata statistical software (v17.0; StataCorp LLC.). The significance level was set at $P \leq .05$. Coded data can be accessed upon qualified request from the authors.

Results

Baseline Patient Characteristics

We identified 45 CAR T-cell transfusions for CNS lymphoma between 2018 and 2022 (Table 1). 17 patients with PCNSL and 27 patients with SCNSL were treated, with one PCNSL patient receiving a second transfusion of CAR T-cells after 16 months due to progressive disease. Patients were treated for the following underlying entities: DLBCL (PCNSL: 18/18 cases, 100%; SCNSL: 19/27 cases, 70.4%), transformed lymphoma (from follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, or mantle cell lymphoma; SCNSL: 7/27 cases, 25.9%), and Burkitt's lymphoma (SCNSL: 1/27 cases, 3.7%). All patients with PCNSL and most patients with SCNSL had failed prior high-dose methotrexate, and each patient had relapsed or refractory disease with a median of 3 (range 1–10) prior therapies. MRI (done at a median of 10 ± 3.2 days prior to CAR T-cell transfusion) or CSF analysis confirmed active CNS disease prior to CAR T-cell transfusion in all patients: Parenchymal involvement was noted in 25 cases (55.6%), leptomeningeal involvement in 8 cases (17.8%), and concurrent parenchymal and leptomeningeal disease in 12 patients (26.7%). Whole-body CT or PET imaging detected active systemic disease in 13 cases (28.9%). Mean time from leukapheresis to CAR T-cell transfusion was 32.0 ± 0.9 days (range 22–53 days). Ibrutinib was most commonly used for bridging therapy to CAR T-cell transfusion (21/36 patients receiving bridging therapy, 58.3%). Steroid doses were weaned off until CAR T-cell transfusion whenever clinically possible. Lymphodepletion was provided as per standard of care using a combination of fludarabine and cyclophosphamide in 44 cases (97.8%) or bendamustine in one SCNSL patient (2.2%). All patients received 1 of the 3 commercially available CAR T-cell products targeting CD19 and incorporating either the costimulatory domain *4-1BB* (tisagenlecleucel, lisocabtagene maraleucel) or *CD28z* (axicabtagene ciloleucel).

There were no differences between patients with PCNSL and SCNSL in regard to demographics, clinical characteristics at time of CAR T-cell transfusion, patterns of CNS involvement, bridging therapies, or mean vein-to-vein time. Notably, only one patient with PCNSL (who relapsed systemically but initially had disease confined to the CNS) but 12 patients with SCNSL had systemic involvement, and baseline serum levels of the inflammatory markers

Table 1. Characteristics of Patients With Central Nervous System (CNS) Lymphoma Treated With CD19-Directed CAR T-Cells. Characteristics are Given for CAR T-Cell Transfusions in Patients With Primary Central Nervous System (CNS) Lymphoma (n = 18), Secondary CNS Lymphoma (n = 27), and Summarized for All Cases (Total; n = 45). Baseline Evaluation was Done at the Date of CAR T-Cell Transfusion ("*at CAR T-cells*")

CAR T-cell Transfusion for		Primary CNS Lymphoma	Secondary CNS Lymphoma	Total	*P*-value
Overall, *n* (%)		***n* = 18**	***n* = 27**	***n* = 45**	
Demographics	*Age at CAR T-cells (years)*	31.0 ± 0.9	32.7 ± 1.4	32.0 ± 0.9	*.886*
	M:F ratio	1:0.5	1:0.9	1:0.7	*.324*
Clinical characteristics	*KPS at CAR T-cells (median, range)*	80 (50–100)	80 (50–100)	80 (50–100)	*.441*
	ECOG at CAR T-cells (median, range)	1 (0–3)	1 (0–3)	1 (0–3)	*.222*
	Presence of neurologic symptoms	11 (61.1%)	15 (55.6%)	26 (57.8%)	*.712*
Disease entity	*DLBCL*	18 (100%)	19 (70.4%)	37 (82.2%)	***.039**
	Transformed lymphoma[#]	0	7 (25.9%)	9 (20%)	
	Burkitt's lymphoma	0	1 (3.7%)	1 (2.2%)	
Prior therapies	*Median therapy lines (median, range)*	3.5 (2–10)	3 (1–6)	3 (1–10)	***.018**
	HD-MTX	18 (100%)	25 (92.6%)	43 (95.6%)	***.001**
	R-(E)CHOP	1 (5.6%)	24 (88.9%)	25 (55.6%)	
	Ibrutinib	10 (55.6%)	4 (14.8%)	14 (31.1%)	
	TEDDI-R	7 (38.9%)	1 (3.7%)	8 (17.8%)	
	(R-)ICE	1 (5.6%)	4 (14.8%)	5 (11.1%)	
	CNS-directed RT	5 (27.8%)	8 (29.6%)	13 (28.9%)	
	Thiopeta-based ASCT	6 (33.3%)	3 (11.1%)	9 (20.0%)	
Bridging	*Ibrutinib*	11 (61.1%)	10 (37.0%)	21 (46.7%)	*.446*
	HD-MTX	2 (11.1%)	3 (11.1%)	5 (11.1%)	
	Cytarabine	1 (5.6%)	4 (14.8%)	5 (11.1%)	
	CNS-directed RT	1 (5.6%)	5 (18.5%)	6 (13.3%)	
	None	3 (16.7%)	6 (22.2%)	9 (20.0%)	
CNS involvement	*Parenchymal (per MRI)*	13 (72.2%)	12 (44.4%)	25 (55.6%)	*.120*
	Leptomeningeal (per MRI or CSF)	1 (5.6%)	7 (25.9%)	8 (17.8%)	
	Parenchymal and leptomeningeal	4 (22.2%)	8 (29.6%)	12 (26.7%)	
Systemic involvement	*Evidence of systemic disease*	1 (5.6%)	12 (44.4%)	13 (28.9%)	***.005**
Dexamethasone dose (mg/d)	*Bridging*	1.6 ± 0.5	4.9 ± 1.1	3.6 ± 0.7	*.067*
	Lymphodepletion	2.1 ± 0.7	1.7 ± 0.5	1.8 ± 0.4	*.306*
	CAR T-cell transfusion	1.2 ± 0.3	0.4 ± 0.2	0.7 ± 0.2	***.006**
	14 days following CAR T-cells	4.8 ± 1.6	4.2 ± 1.5	4.4 ± 1.1	*.121*
Lymphodepletion	*Fludarabine/cyclophosphamide*	18 (100%)	26 (96.3%)	44 (97.8%)	*.409*
	Bendamustine	0	1 (3.7%)	1 (2.2%)	
Baseline laboratory findings	*CRP (mg/L)*	7.3 ± 2.4	25.6 ± 8.2	18.3 ± 5.2	*.090*
	Ferritin (µg/L)	563 ± 249	1463 ± 344	1103 ± 236	***.010**
	LDH (U/L)	251 ± 25	309 ± 43	285 ± 28	*.509*
CAR T-cell product	*Tisagenlecleucel*	16 (88.9%)	20 (74.1%)	36 (80.0%)	***.019**
	Lisocabtagene maraleucel	0	7 (25.9%)	7 (15.6%)	
	Axicabtagene ciloleucel	2 (11.1%)	0	2 (4.4%)	
	Vein-to-vein time (days)	31.0 ± 0.9	32.7 ± 1.4	32.0 ± 0.9	*.886*

Note that one PCNSL patient also had treatment for systemic disease which he developed years after initial diagnosis. Differences between the groups were analyzed using the unpaired Student's *t*-test (for parametric data) or the Mann–Whitney U-test (for non-parametric data) for continuous variables; and categorical variables were assessed by the χ^2-test. *P* values are given, and asterisks indicate $P \leq .05$.
Abbreviations: *ASCT,* autologous stem cell transplantation; *CAR,* chimeric antigen receptor; *CRP,* C-reactive protein; *CSF,* cerebrospinal fluid; *DLBCL,* diffuse large B-cell lymphoma; *ECOG*, Eastern Cooperative Oncology Group performance status; *F,* female; *HD-MTX,* high-dose methotrexate; *KPS,* Karnofsky Performance Score; *LDH,* lactate dehydrogenase; *M,* male; *MRI,* magnetic resonance imaging; *R-CHOP,* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; *R-EPOCH,* rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; *R-ICE,* rituximab, ifosfamide, carboplatin, and etoposide; *RT*, radiotherapy (including whole brain radiotherapy); *TEDDI-R,* temozolomide, etoposide, doxil, dexamethasone, ibrutinib, and rituximab.
[#]transformed from follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, or mantle cell lymphoma.

C-reactive protein (*CRP*) and *Ferritin* were higher in patients with SCNSL (*CRP* in mg/L for PCNSL vs. SCNSL: 7.3 ± 2.4 vs. 25.6 ± 8.2, $P = .090$; *Ferritin* in µg/L: 563 ± 249 vs. 1463 ± 344, $P = .010$). Also, slightly higher steroid doses were used in PCNSL patients compared to SCNSL at time of CAR T-cell transfusion while no differences were seen during bridging, lymphodepletion, or after CAR T-cell transfusion.

Neurological and Systemic Toxicities Following CAR T-Cell Transfusion

In patients with PCNSL, ICANS symptoms were observed in eight cases (44.4%) with first symptoms detected after a median of 2.5 days (range 0–8 days) (Figure 1A). Although symptoms were often transient with a median duration of 5.5 days (range 1–14 days), 3 cases of high-grade neurotoxicity occurred, including in one patient with grade 4 ICANS who died in the setting of sepsis.

In patients with SCNSL, median onset and duration of neurologic symptoms were similar to PCNSL (onset: 4 days, range 1–14 days; duration: 4.5 days, range 3–25 days). One patient died in the setting of severe neurotoxic symptoms and concurrent sepsis (Figure 1E). Moreover, clinical phenotypes did not differ between PCNSL and SCNSL patients in line with previous reports[9]: ICANS grade 1–2 was characterized by mild encephalopathy (headaches, aphasia, tremor, and confusion) whereas ICANS grade 3–4 resulted in altered mental status or decreased level of consciousness. Seizure prophylaxis with levetiracetam was used in most patients.

However, the relative frequency for ICANS tended to be higher among SCNSL patients with 18 cases (66.7%) experiencing neurotoxic symptoms of any grade (Figure 1B). ICANS was closely associated with CRS as all patients with ICANS grade 3–4 also had CRS (Figure 1C); and fever ≥ 38°C of early onset (within 3 days after CAR T-cell transfusion) often preceded neurotoxic symptoms in both PCNSL and SCNSL patients. In line with an increased inflammatory burden following CAR T-cell transfusion, patients with SCNSL had a substantial and more prolonged increase in serum levels of CRP compared to PCNSL patients (Figure 1D). Baseline *CRP* (at time of CAR T-cell transfusion) but not *Ferritin* or *LDH* predicted ICANS of any degree (AUC: 0.720, $P = .013$). A serum *CRP* level of > 4.9 mg/L yielded a sensitivity of 69.2% (CI: 50–84) and a specificity of 68.4% (CI: 46–85) to identify patients who later developed ICANS in the entire cohort (Figure 1F–G). Importantly, the *CRP* cutoff of > 4.9 mg/L discriminated patients with ICANS also when applied exclusively in PCNSL or SCNSL patients (PCNSL: χ^2: 3.7, $P = .001$; SCNSL: χ^2: 5.2, $P = .001$). In turn, the mere presence of systemic disease *alone* was neither associated with CRS (χ^2: 1.2; $P = .275$) nor ICANS (χ^2: 1.0; $P = .322$).

Patterns and Rates of CNS Response

Disease staging following CAR T-cell transfusion was available in all patients. Radiographic response to CAR T-cell transfusion was seen in both patients with parenchymal and leptomeningeal involvement (Figure 2A, B). CNS response was seen in 31 cases (31/45 cases, 68.9%), including 18 cases showing a complete response (40.0%) (Figure 2C, D). While most patients reached their best response after a median of 1 month (PCNSL: 29 days, range 4–190 days; SCNSL: 28 days, range 7–122 days), selected individuals continued to have regressing disease with a complete response being reached as late as 6 months after CAR T-cell transfusion even in the absence of additional antitumor therapies. This was accompanied by symptom stabilization or improvement in individuals who presented with baseline neurologic abnormalities, while disease progression was associated with symptom deterioration. Among individuals in which complete response was achieved following CAR T-cells, patients remained free of CNS disease for a median of 11.4 ± 4.5 months. After a median follow-up of 12.0 ± 5.6 months, a total of 33 patients had progressed within the CNS and median CNS-progression-free survival was 2.0 ± 0.7 months (Figure 2E). This includes progressive disease in 14 patients with PCNSL (77.8%) and 18 patients with SCNSL (66.7%). There was no difference in the response patterns or in the median CNS-progression-free survival between patients with PCNSL and SCNSL (median CNS-PFS: 3.5 vs. 2.0 months, HR 0.83, CI 0.4–1.8; $P = .652$).

Pseudoprogression characterized by an increase of T2/fluid-attenuated inversion recovery (FLAIR)-hyperintense signal or contrast-enhancement from known CNS lesions was radiographically suspected on early MRI in 4 cases of PCNSL (22.2%) and 4 cases of SCNSL (14.8%), but remained clinically mostly indolent and improved without antitumor therapies except for use of steroids. Notably, one SCNSL patient developed severe ICANS presenting with seizures and coma 4 days after CAR T-cell transfusion. MRI showed extensive edema surrounding a decreasing contrast-enhancing lesion within the left basal ganglia which was interpreted as pseudoprogression. After high-dose steroids, the patient substantially improved and radiographic changes resolved. Unfortunately, the patient ultimately deceased 4 days later from fungal sepsis in the absence of lymphoma as confirmed by autopsy (Figure 2F). On a cautionary note, we cannot exclude the possibility that some cases which received treatment for presumed progression were in fact experiencing pseudoprogression given that no tissue-based diagnosis was pursued. Nevertheless, the usual aggressive clinical course of patients with presumed progression generally argues against pseudoprogression.

Association of Clinical Variables With CNS Outcome: The Role of Steroids, Bridging Therapies, and Involvement Patterns

Steroids were commonly used to ameliorate clinical symptoms of progressive disease until CAR T-cell transfusion, but were tapered down whenever possible as it has been hypothesized that corticosteroids may negatively impact the desired antitumor effect of CAR T-cells (Figure 3A, Table 1). We, therefore, recorded the daily dexamethasone dose (or equivalent) at different intervals around CAR T-cell transfusion to delineate their specific effects on CNS response. Here, we noted an exponential increase in hazard ratio for CNS progression for each additional mg/d of dexamethasone *during lymphodepletion* as predicted by univariate Cox proportional hazard regression

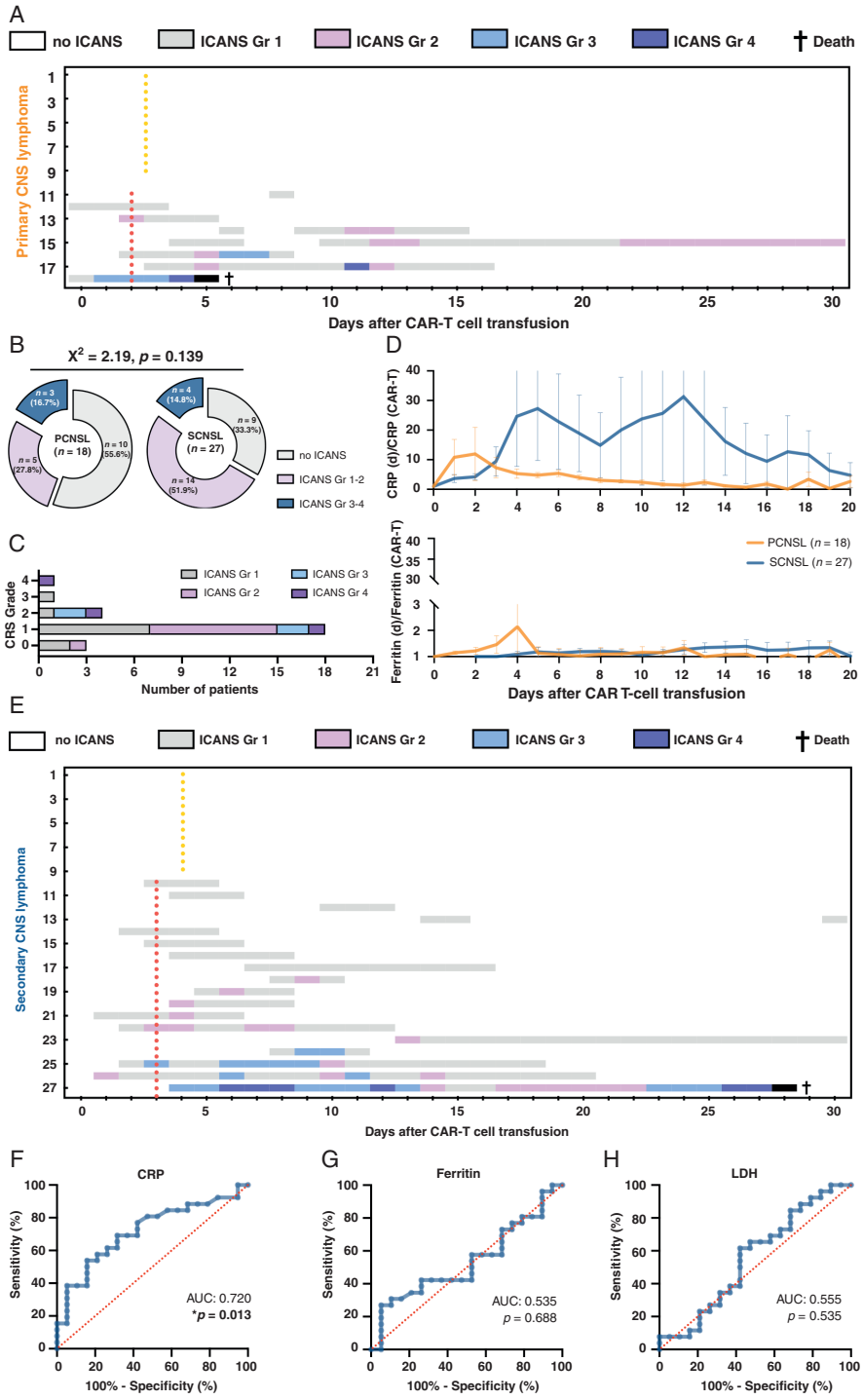

Figure 1. Neurotoxicity following CD19-directed chimeric antigen receptor (CAR) T-cell therapy for central nervous system lymphoma. (**A**) Kinetics of immune effector cell-associated neurotoxicity syndrome (ICANS) for 30 days after each CAR T-cell transfusion for PCNSL (n = 18). Each row represents one patient, and the highest grade of ICANS recorded *per* day is color-coded. Median time to first fever ≥ 38°C for patients with no ICANS (yellow dotted line) and ICANS grade 1–4 is indicated (red dotted line). (**B**) Distribution of ICANS between patients with PCNSL and SCNSL. (**C**) Number of patients with each grade of cytokine release syndrome (CRS) and neurotoxicity. (**D**) Serum levels of the acute-phase proteins C-reactive protein (CRP; upper panel) and Ferritin (lower panel) in relationship to serum levels at CAR T-cell transfusion. Ratio is shown for patients with PCNSL (orange) and SCNSL (blue) for 20 days after CAR T-cell transfusion. Note the profound increase in CRP levels among SCNSL patients. Median ratio and SEM are given. (**E**) Kinetics of ICANS for 30 days after each CAR T-cell transfusion for SCNSL (n = 27). Each row represents one patient, and the highest grade of ICANS recorded *per* day is color-coded. Median time to first fever ≥ 38°C for patients with no ICANS (yellow dotted line) and ICANS grade 1–4 is indicated (red dotted line). (**F–H**) Receiver operating curve curves for the prediction of ICANS by serum levels of CRP (F), Ferritin (G), and lactate dehydrogenase (LDH; H) at CAR T-cell transfusion.

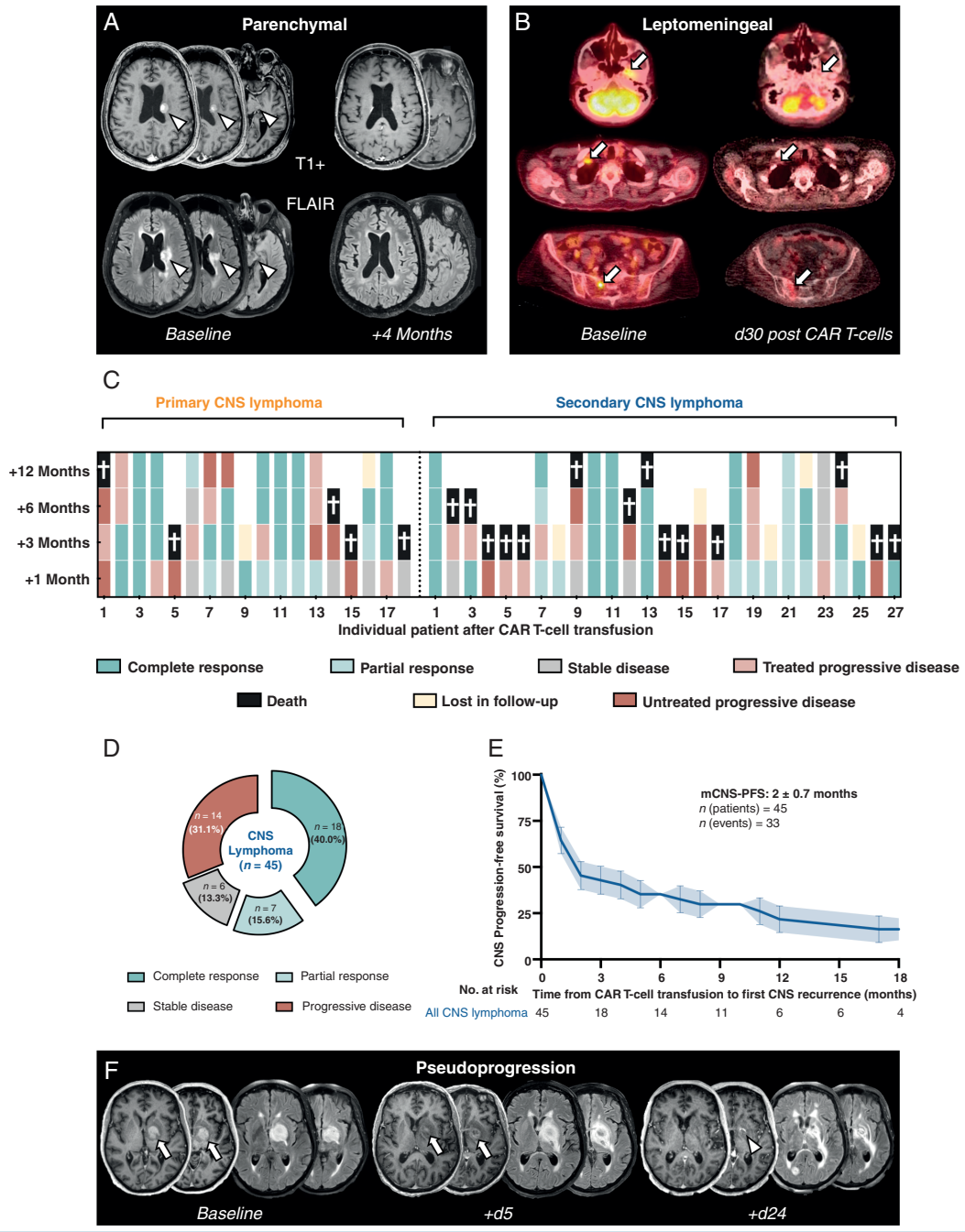

Figure 2. Response of central nervous system (CNS) lymphoma following chimeric antigen receptor (CAR) T-cell therapy. (**A**) Axial brain MRI of the brain with contrast-enhanced T1–weighted (T1+; upper panel) and fluid-attenuated inversion recovery (FLAIR; lower panel) sequences before CAR T-cell transfusion and after 4 months. Complete resolution of a left periventricular lesion (arrowheads) is seen. (**B**) Whole-body FET-PET before and 30 days after CAR T-cell transfusion. Areas of avid metabolism (arrows) are seen at the left foramen ovale (upper panel), the right brachial plexus (middle panel), and the right S1 nerve root (lower panel); suggestive of leptomeningeal involvement by lymphoma. No abnormal metabolism is detected after CAR T-cell transfusion. (**C**) Response of PCNSL (left) and SCNSL (right) at staging exams 1 month, 3 months, 6 months, and 1 year following CAR T-cell therapy. Each column represents one patient, and disease response is color-coded. (**D**) Distribution of best response in all patients with CNS lymphoma. (**E**) Kaplan–Meier estimates of CNS-progression-free survival after CAR T-cell transfusion in patients with primary or secondary CNS lymphoma (n = 45). Points indicate deceased or censored patients, light shading indicates SEM. (**F**) Axial brain MRI of a patient with pseudoprogression before, 5 days after, and 24 days after CAR T-cell transfusion. For all timepoints, contrast-enhanced T1-weighted (left in each panel) and FLAIR sequences (right in each panel) are given. Note the interval increase in FLAIR-hyperintense edema early after CAR T-cell transfusion while contrast-enhancement is reduced.

modeling (Figure 3B). Interestingly, no associations for dexamethasone dose *during bridging*, *at CAR T-cell transfusion*, or *during 14 days after CAR T-cell transfusions* were found. This observation was also retained when evaluated on multivariate analysis, and an HR increase of 1.16 (CI 1.0–1.3; $P = .031$) was predicted per each mg/d of dexamethasone provided during lymphodepletion. Notably, dexamethasone doses at the different intervals were all correlated with each other on principal component analysis (by calculating loadings, that is, a numerical estimation of correlation between multiple variables ranging from –1 to 1), suggesting the presence of confounders (eg, more aggressive disease) on dexamethasone dose (loadings on principal component analysis for daily dexamethasone dose: at bridging—0.78/ at lymphodepletion—0.82/ at CAR T-cell transfusion—0.72/14 days after CAR T-cell transfusion—0.39). As only dexamethasone doses *during lymphodepletion* were of importance regarding CNS outcome, this argues against the assumption that higher steroid doses are simply a surrogate marker for tumors with an inherently worse prognosis due to more aggressive growth or proximity to critical brain regions. When we stratified patients into groups according to dexamethasone doses *during lymphodepletion*, we found that a cutoff between 6 and 8 mg/d dexamethasone translated into less favorable CNS outcome compared to patients with only a minimal dose of 0–1 mg/d of dexamethasone (0–1 mg/d vs. 8 mg/d: 4 vs. 1 month, HR 0.11, CI 0.1–1.0, $P = .047$) (Figure 3C).

Given the aggressive nature of active CNS lymphoma, bridging therapies with chemotherapy, radiotherapy, or immunotherapy were warranted in 36 cases (80%; PCNSL: 15/18 patients, 83.3%; SCNSL: 21/27 patients, 77.8%). As such, the necessity of bridging therapy per se seemed to designate more aggressive disease as characterized by somewhat shorter CNS-progression-free survival (2 vs. 6.5 months, HR 1.58, CI 0.5–4.6; $P = .399$). Optimal bridging strategies until CAR T-cell transfusion await evaluation, and ibrutinib has been speculated to enhance T-cell function and persistence.[15,16] We indeed found that the use of ibrutinib (alone or in combination with other therapies) was associated with prolonged CNS-progression-free survival compared to other bridging therapies without ibrutinib (5 vs. 1 month, HR 0.28, CI 0.1–0.7; $P = .010$) (Figure 3D). Interestingly, there was no specific response duration when comparing patients with parenchymal or leptomeningeal involvement; however, shorter CNS-progression-free survival was noted when concurrent parenchymal and leptomeningeal disease was present at CAR T-cell transfusion (1 vs. 2 months, HR 3.15, CI 1.1–8.7; $P = .027$) which may therefore indicate more advanced disease (Figure 3E). Although response duration was favorably affected, initial response patterns did not differ between ibrutinib from other bridging therapies (Figure 3F).

Discussion

CAR T-cell therapy revolutionized the treatment of systemic lymphomas; however, fewer than 150 CAR T-cell patients with CNS involvement have been reported so far.[12] Here, we characterize 45 unique cases of CD19-directed CAR T-cell therapy for primary and secondary CNS lymphoma.

We were able to show a substantial CNS response rate of about 70% in both PCNSL and SCNSL, including complete response in about 40% of this heavily pretreated population. Individuals with complete response frequently experienced long-lasting remission sustained over months, and radiographic and CSF response was documented not only for patients with leptomeningeal disease but also with solid parenchymal lesions. Our findings therefore suggest that CAR T-cells effectively cross the blood-brain barrier and exhibit potent antitumor effects even in the absence of systemic disease. These encouraging observations are corroborated by studies from Alcantara et al.[17] and Siddiqi et al.[18] who reported complete responses in 56% and 60% of PCNSL patients, respectively. Moreover, we previously detailed on CSF findings for a subset of PCNSL patients (which were also included in the present study) who were recruited for a phase I/II trial on the use of tisagenlecleucel for PCNSL at our institution.[11] RNA profiling allowed the detection of considerable CAR-RNA within the CSF, supporting the notion of CAR T-cell activity within the CNS. Similar data on CAR T-cell trafficking, as well as disease response, have been described for secondary CNS lymphoma,[10,13,19] and preliminarily also for primary brain tumors or brain metastases.[20,21] Given the potentially promising therapeutic effects of CAR T-cells in patients with CNS lymphoma, prospective phase II trials (with or without randomization) comparing CAR T-cells to other salvage therapies in this unique patient population are warranted. Such trials will also need to incorporate a predefined clinical assessment to analyze the longitudinal symptom profile including cognitive complaints.

While we observed neurotoxic symptoms in only about 40% of PCNSL patients, more than 65% of SCNSL patients experienced neurotoxicity of any grade. This was accompanied by a profound increase in serum levels of *CRP* among patients with SCNSL. Neurotoxicity was closely associated with clinical symptoms of systemic inflammation giving rise to CRS in all individuals with ICANS grade 3–4. Thus, it appears that systemic inflammation rather than the mere presence of CNS disease translates into increased risk for neurotoxicity. In line with this assumption, clinical symptoms of neurotoxicity did not differ from what has been described for CAR T-cell patients without CNS involvement.[9] Accordingly, we were able to confirm that baseline serum levels of *CRP* level may serve to identify patients at particular risk as early as of time of CAR T-cell transfusion. Although MRI of the neuroaxis in the setting of neurotoxicity is primarily utilized to exclude alternative explanations for the observed symptoms, pseudoprogression might be a common imaging finding. Moreover, tumor inflammation-associated neurotoxicity has been recently suggested as a unique entity in patients treated with CAR T-cells for CNS disease and recognition of this response pattern will be relevant in future studies utilizing CAR T-cells in CNS lymphoma.[22] A high level of suspicion is therefore indicated to delineate such inflammatory changes from true disease progression as management differs. This comes with major implications for controlled

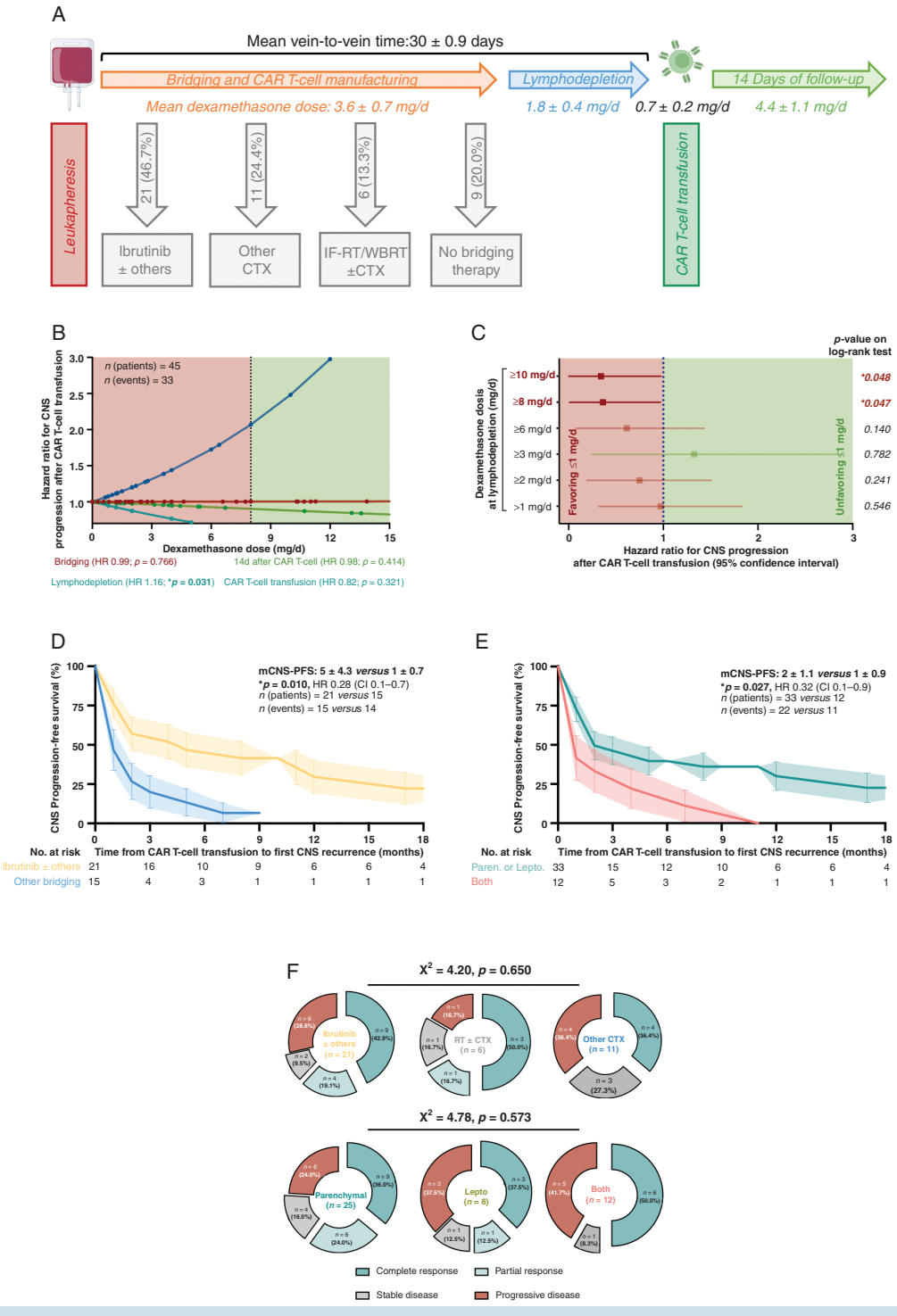

Figure 3. Predictors of outcome for central nervous system (CNS) disease. (**A**) Overview of corticosteroid use and bridging therapies at intervals around chimeric antigen receptor (CAR) T-cell transfusion. CTX, chemotherapy; IF-RT, Involved-field radiation therapy; WBRT, whole brain radiotherapy. (**B**) Hazard ratios for CNS progression were calculated for each individual dexamethasone dose (in mg/d) at different intervals among all CNS lymphoma patients undergoing CAR T-cell transfusion ($n = 45$). The binary prognostic cutoff of 8 mg/d dexamethasones during lymphodepletion calculated with step-wise log-rank tests (Figure 3C) is indicated. An exponential hazard increase can be seen for higher dexamethasone doses during lymphodepletion. (**C**) Univariate analysis using log-rank tests comparing patients with different amounts of daily dexamethasone doses during lymphodepletion to patients with 0–1 mg/d dexamethasone during lymphodepletion. Note that an association with worse outcomes was seen for dexamethasone doses ≥ 8 mg/d. Hazard ratio ± 95% confidence interval. (**D–E**) Kaplan–Meier estimates of CNS-progression-free survival after CAR T-cell transfusion for the use of ibrutinib when bridging has been provided (D; $n = 36$) and for different forms of CNS involvement (E; $n = 45$). Points indicate deceased or censored patients, light shading indicates SEM. (**F**) Distribution of best response patterns for various bridging therapies (upper panel) and different forms of CNS involvement (lower panel).

clinical trials as pseudoprogression will need to be carefully excluded to avoid underestimation of the true CAR T-cell effects.

Whereas selected reports suggest that corticosteroids jeopardize the beneficial antitumor properties of CAR T-cells,[23] other studies failed to detect such an association and the role of corticosteroids remains therefore puzzling.[24] In our cohort, we found an exponential risk increase for CNS progression when higher dexamethasone doses were administered *during lymphodepletion* (but not earlier or later during the clinical course). A cutoff between 6 and 8 mg/d dexamethasone stratified patients into those at risk for CNS progression after CAR T-cell transfusion; however, it appears important to note that the relationship between steroids and outcome was predicted to be exponential in nature rather than a simple dichotomous cutoff. Based on 48 patients with B-cell lymphoma, Hirayama et al.[25] postulated that lymphodepletion with cyclophosphamide and fludarabine prior to CAR T-cell transfusion may induce a pro-inflammatory cytokine profile augmenting CAR T-cell effects which in turn translates into improved PFS. These findings appear to support not only the mindset that dexamethasone should be avoided whenever clinically possible, but also highlight that the interval of lymphodepletion possibly represents a time point of unique vulnerability to corticosteroids (potentially by suppressing pro-inflammatory cytokines). Notably, the use of corticosteroids may represent an additional risk factor for other acute complications as both of our patients who deceased in the setting of high-grade neurotoxicity had concurrent sepsis (potentially exacerbated by treatment with high-dose steroids).[26]

Ibrutinib use was associated with a more favorable CNS outcomes compared to the use of other bridging regimens when bridging therapy was deemed clinically necessary. While initial response was similar to other bridging therapies, the time to CNS progression was substantially longer in patients treated with ibrutinib. Using a human xenograft model, Fraietta et al.[15] showed improved CAR T-cell engraftment when treatment with concurrent ibrutinib was provided. Similar observations have been reported in individuals with chronic lymphocytic leukemia[16,27]; however, we cannot rule out that our findings on ibrutinib bridging have been subjected to confounding (eg, by less severe disease) given the retrospective nature of our study. Also, different CAR T-cell products may carry distinct risk and response profiles which will need to be prospectively assessed.[28] As we were bound to clinical trial regulations, we were unable to identify our findings with respect to CAR T-cell products or further details on outcomes of systemic disease.

Collectively, CD19-directed CAR T-cells exhibit encouraging antitumor properties in patients with primary and secondary CNS lymphoma. Neurotoxic symptoms may occur, but appear to reflect effects from systemic inflammation rather than the presence of CNS disease itself. Corticosteroids should be used cautiously, particularly during lymphodepletion. Bridging therapies may synergistically affect CAR T-cell therapy, and ibrutinib or other BTK inhibitors might be promising candidates to further boost the success of CAR T-cells. Further prospective phase II studies in this regard are warranted.

Keywords:

CNS lymphoma | chimeric antigen receptor | CAR T-cells | neurotoxicity | response

Funding

Nothing to report. No unpublished papers cited.

Acknowledgments

The authors thank all patients who contributed to the results of the study. We appreciate the support of the excellent nurses, staff, and providers of the Cellular Immunotherapy Program and the Massachusetts General Hospital Cancer Center. Figure 3 has been created with the help of BioRender.com.

Conflict of Interest statement

P. Karschnia—No disclosures. **I. C. Arillaga-Romany**—No disclosures. **A. Eichler**—No disclosures. **D. A. Forst**—No disclosures. **E. Gerstner**—No disclosures. **J. T. Jordan**—Consulting income from Recursion pharmaceuticals, Alexion Pharmaceuticals, Navio Theragnostics, Shepherd Therapeutics. Equity from Navio Theragnostics, Shepherd Therapeutics, The Doctor Lounge. Royalties from Elsevier. **I. Ly**—Consultancy: SpringWorks Therapeutics; Grant Funding: Department of Defense, Neurofibromatosis Therapeutic Acceleration Program. **S. R. Plotkin**—No disclosures. **N. Wang**—No disclosures. **M. Martinez-Lage**—No disclosures. **S. F. Winter**—No disclosures. **J. C. Tonn**—No disclosures. **K. Rejeski**—Research Funding and Travel Support: Kite/Gilead; Honoraria: Novartis; Consultancy, Honoraria: BMS/Celgene. **L. von Baumgarten**—No disclosures. **D. P. Cahill**—No disclosures. **B. V. Nahed**—No disclosures. **G. M. Shankar**—No disclosures. **J. S. Abramson**—No disclosures. **J. A. Barnes**—No disclosures. **A. El-Jawahri**—No disclosures. **E. P. Hochberg**—No disclosures. **P. C. Johnson**—Consulting: Seagen, ADC Therapeutics, AstraZeneca; Research Funding: AstraZeneca, Medically Home. **J. D. Soumerai**—No disclosures. **R. W. Takvorian**—No disclosures. **Yi-Bin Chen**—No disclosures. **M. J. Frigault**—Consulting: BMS, Novartis, Kite, Arcellx, Iovance, Cytoagents. **J. Dietrich**—Consulting: Amgen, Unum Therapeutics, Novartis.

Authorship statement

Study concept & design: PK, KR, MJF, JD. Data collection: PK, MML, MF, JD. Data analysis & interpretation: PK, JD. Statistics: PK, JD. Manuscript drafting: PK, MJF, JF. Manuscript revising: PK, ICAR, AE, DAF, EG, JTJ, IL, SRP, NW, MML, SFW, JCT, KDR, LVB, DPC, BVH, GMS, YBC, JSA, JAB, AEJ, EPH, PCJ, JDS, RWT, YBC, MJF, JD.

Affiliations

Department of Neurology, Division of Neuro-Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA (P.K., I.C.A-R., A.E., D.A.F., E.G., J.T.J, I.L., S.R.P., N.W., S.F.W., J.D.); Department of Neurosurgery, Section for Neuro-Oncology, Ludwig-Maximilians-University, Munich, Germany (P.K., J-C.T., L.vB.); German Cancer Consortium (DKTK), Partner Site Munich, Germany (P.K., J-C.T., K.R.); Department of Pathology, Division of Neuropathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA (M.M-L.); Department of Medicine III, Section for Cellular Immunotherapy, Ludwig-Maximilians-University, Munich, Germany (K.R.); Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA (D.P.C., B.V.N., G.M.S.); Department of Medicine, Hematology, and Oncology Division, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA (J.S.A., J.A.B., A.E-J., E.P.H., P.C.J., J.D.S., R.W.T.); Department of Medicine, Cellular Immunotherapy Program, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA (Y-B.C., M.J.F.)

References

1. Ferreri AJM, Doorduijn JK, Re A, et al; International Extranodal Lymphoma Study Group (IELSG). MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): An international, single-arm, phase 2 trial. *Lancet Haematol.* 2021;8(2):e110–e121.
2. Ferreri AJ, Cwynarski K, Pulczynski E, et al; International Extranodal Lymphoma Study Group (IELSG). Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: Results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol.* 2016;3(5):e217–e227.
3. Ferreri AJM, Cwynarski K, Pulczynski E, et al; IELSG32 study investigators. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. *Leukemia.* 2022;36(7):1870–1878.
4. Langner-Lemercier S, Houillier C, Soussain C, et al. Primary CNS lymphoma at first relapse/progression: Characteristics, management, and outcome of 256 patients from the French LOC network. *Neuro Oncol.* 2016;18(9):1297–1303.
5. 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.
6. 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.
7. 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.
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. Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. *Blood.* 2019;133(20):2212–2221.
10. Karschnia P, Rejeski K, Winkelmann M, et al. Toxicities and response rates of secondary cns lymphoma after adoptive immunotherapy with CD19-directed chimeric antigen receptor T cells. *Neurology.* 2022;98(21):884–889.
11. Frigault MJ, Dietrich J, Gallagher K, et al. Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: A phase 1/2 clinical trial. *Blood.* 2022;139(15):2306–2315.
12. Cook MR, Dorris CS, Makambi KH, et al. Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: A meta-analysis of 128 patients. *Blood Adv.* 2023;7(1):32–39.
13. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood.* 2019;134(11):860–866.
14. Abrey LE, Batchelor TT, Ferreri AJ, et al; International Primary CNS Lymphoma Collaborative Group. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol.* 2005;23(22):5034–5043.
15. Fraietta JA, Beckwith KA, Patel PR, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. *Blood.* 2016;127(9):1117–1127.
16. Long M, Beckwith K, Do P, et al. Ibrutinib treatment improves T cell number and function in CLL patients. *J Clin Invest.* 2017;127(8):3052–3064.
17. 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.
18. Siddiqi T, Wang X, Blanchard MS, et al. CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma. *Blood Adv.* 2021;5(20):4059–4063.
19. Ahmed G, Hamadani M, Shah NN. CAR T-cell therapy for secondary CNS DLBCL. *Blood Adv.* 2021;5(24):5626–5630.
20. Karschnia P, Teske N, Thon N, et al. Chimeric antigen receptor T cells for glioblastoma: Current concepts, challenges, and future perspectives. *Neurology.* 2021;97(5):218–230.
21. Xu T, Karschnia P, Cadilha BL, et al. In vivo dynamics and anti-tumor effects of EpCAM-directed CAR T-cells against brain metastases from lung cancer. *Oncoimmunology.* 2023;12(1):2163781.
22. Mahdi J, Dietrich J, Straathof K, et al. Tumor inflammation-associated neurotoxicity. *Nat Med.* 2023;29(4):803–810.
23. Strati P, Ahmed S, Furqan F, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. *Blood.* 2021;137(23):3272–3276.
24. Liu S, Deng B, Yin Z, et al. Corticosteroids do not influence the efficacy and kinetics of CAR-T cells for B-cell acute lymphoblastic leukemia. *Blood Cancer J.* 2020;10(2):15.
25. Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. *Blood.* 2019;133(17):1876–1887.
26. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. *J ImmunoTher Cancer.* 2022;10(5):e004475.
27. Gauthier J, Hirayama AV, Purushe J, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood.* 2020;135(19):1650–1660.
28. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med.* 2022;28(10):2145–2154.