Outcomes of patients with primary central nervous system lymphoma following CD19-targeted chimeric antigen receptor T-cell therapy

Primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) is a rare but aggressive lymphoma typically confined to the brain, spinal cord, leptomeninges, cerebrospinal fluid and/or vitreoretinal space without systemic involvement.[1,2] Although the prognosis of these patients has improved with evolving treatments,[1] survival is poor for those who do not achieve a complete remission (CR) following first-line treatment (i.e., primary refractory) or those who relapse after autologous stem cell transplantation (ASCT).[3] There is still no consensus on the best salvage treatment for these patients,[3] and different therapeutic strategies have been employed with modest success.[3,4] CD19-targeted chimeric antigen receptor T-cell (CAR T) therapies are approved for systemic relapsed or refractory (R/R) diffuse large B-cell lymphoma.[5-7] However, patients with PCNSL were not included in these pivotal trials, and patients with PCNSL are specifically excluded from the axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel) labels.[8] Since the approval of CAR T in the United States and Europe, 4 small studies (N of patients=5-27) with relatively short follow-up reported on the preliminary activity and toxicity of CAR T in PCNSL.[9-12] Herein we present an analysis of patients with R/R PCNSL who received commercial CAR T-cell therapy between January 2019 to March 2022 using data from the Center of International Blood and Marrow Transplant Research registry.

The study population included consecutive, consenting patients (≥18 years of age) with a diagnosis of R/R PCNSL who received commercially available CAR T-cell therapy (i.e., axi-cel or tisa-cel) during the index period. No patients were excluded based upon age, comorbidity, product type, or completeness of data. Patients from embargoed centers were excluded. The primary endpoint was overall survival (OS) defined as the time from CAR T infusion to death from any cause. Secondary endpoints included overall response rate (ORR) by day 100, progression-free survival (PFS) (defined as the time from CAR T to relapse/progressive disease (PD) or death from any cause, whichever occurs first, cumulative incidence of relapse or progression, non-relapse mortality (NRM), cause of death, cumulative incidence of any grade severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) as defined by the ASTCT criteria[13] at day 30 post CAR T infusion, and neutrophil and platelet recovery. The cumulative incidence function was used to estimate relapse/progression, NRM, CRS, and ICANS, and Kaplan-Meier estimators were used for OS and PFS. The Institutional Review Board at the Medical College of Wisconsin approved this study.

Twenty-four patients meeting the eligibility criteria were analyzed (Table 1). At the time of CAR T infusion, median patient age was 57 years (range, 25-81), the majority were males (67%), and 10 patients (42%) had a Karnofsky performance score <90. The median number of prior therapies was 4 (range, 1-10), including 12 patients (50%) who had undergone a prior ASCT. Bridging therapy was utilized in 5 patients (20%), and 21 patients (88%) had active disease prior to CAR T infusion while 3 patients (12%) were in CR. Tisa-cel and axi-cel were infused in 21 (88%) and 3 (12%) patients, respectively.

Among 23 patients evaluable for response, the ORR was 61% (N=14) by day 100, including 3 patients (13%) with partial response and 11 patients (48%) with CR. The median follow-up from CAR T infusion was 26 months (range, 3-38). The 1- and 2-year OS were 55% (95% CI: 35-75%) and 50% (95% CI: 29-71%), and the 1- and 2-year PFS were 48% (95% CI: 28-69%) and 28% (95% CI: 9-51%), respectively (Figure 1). The cumulative incidence of disease relapse/progression was 72% (95% CI: 47-92%) and the NRM was 0% at two years. The cumulative incidence of neutrophil recovery at one month was 96% (95% CI: 79-100%) and platelet recovery at day 100 was 96% (95% CI: 79-100%). Sixteen patients (66.7%) developed CRS, with a median time to CRS onset of 3.5 days (range, 1-8). All cases of CRS were grade 1 or 2; no patients had grade ≥3 CRS. Eight patients (33%) developed ICANS, with 5 patients (21%) experiencing grade 1 or 2 ICANS and 2 patients who received tisa-cel having grade ≥3 ICANS. The median time to onset of ICANS was six days (range, 1-9). Eleven patients died from disease recurrence or progression (92%), and one patient died from a bacterial infection (8%) after prior disease relapse/progression.

There are limited data available on outcomes following CAR T for R/R PCNSL. Siddiqi *et al.*[9] reported preliminary results on 5 patients with R/R PCNSL who were treated on a phase I trial evaluating a CD19 CAR T containing a novel CAR construct, demonstrating anti-tumor activity (CR: N=2; stable disease: N=2) and reassuring safety (ICANS grade 3: N=1). Frigault *et al.*[10] also demonstrated promising safety and efficacy outcomes following treatment with tisa-cel in a cohort of 12 patients with highly refractory PCNSL. With a median follow-up of 12 months, 50% of patients achieved a CR and only one grade 3 ICANS was reported. Alcantara *et al.*[11] reported a 6-month OS and PFS of 89% and 44%, respectively, among 9 patients with R/R PCNSL who received

CD19 CAR T (axi-cel: N=2; tisa-cel: N=7). One patient experienced grade 3 CRS and 2 patients had ≥ grade 3 ICANS. Recently, Choquet *et al.*[12] reported retrospective findings on a French cohort of 25 patients with R/R PCNSL who were infused with CD19 CAR T (axi-cel: N=9; tisa-cel: N=16). With a median follow-up of 20.8 months after CAR T infusion, 14 patients (56%) achieved CR at three months, while 16 patients (64%) obtained CR as best response. One-year PFS and OS from CAR T infusion was 46% (95% CI: 29-72%) and 55% (95% CI: 37-82%), respectively. Higher CR rates after CAR T were observed in patients in CR or PR *versus* stable or progressive disease at the time of cell infusion, and in patients receiving axi-cel.

Our analysis represents one of the largest cohorts with the longest follow-up of patients with R/R PCNSL following receipt of commercial CAR T-cell therapy. We show that CAR T cell has activity in PCNSL, as demonstrated by an ORR of 61% and 48% CR rate by day 100 in a heavily treated patient cohort. Despite the responses observed, a minority of patients experienced a durable remission (2-year PFS: 28%). Several factors may influence this modest PFS, including having active disease at the time of cell infusion, immune evasion by the tumor through expression of PD-L1,[14] or the intrinsic aggressive biology of the disease.[1,2] Another explanation for poor PFS may be short persistence of CAR T cells in the CNS. These findings suggest that developing maintenance / consolidation treatment strategies (e.g., use of Bruton tyrosine kinase inhibitors, checkpoint inhibitors) in patients receiving a response after CAR T should be explored in well-designed clinical trials.

While our results appear better than those published in secondary CNS lymphoma following CAR T-cell therapy where the 1-year PFS and OS were 16% (95% CI: 8-30%) and 41% (95% CI: 30-57%), respectively,[15] the efficacy of CAR T in our series seems to be lower compared to the pivotal CAR T trials in systemic lymphoma.[5]

Although the number of patients was small, we did not observe an increase in CAR T-related toxicity in our patients

Table 1. Patients', disease, and CAR T-cell therapy-related baseline characteristics and study outcomes.

Baseline characteristics	Patients N=24
N of centers	12
Age at CAR T infusion in years, median (min-max)	57 (25-81)
Age at CAR T infusion in years, N (%)	
18-64	18 (75)
≥65	6 (25)
Male sex, N (%)	16 (67)
Recipient race, N (%)	
White	20 (83)
African-American	1 (4)
Asian	0 (<1)
Not reported	3 (13)
Recipient ethnicity, N (%)	
Hispanic or Latino	2 (8)
Non-Hispanic or non-Latino	17 (71)
Unknown/not reported	5 (21)
Karnofsky performance score prior to CAR T, N (%)	
90-100	11 (46)
<90	10 (42)
Not reported	3 (13)
HCT-CI, N (%)	
≥3	5 (21)
Site of CNS involvement, N (%)	
Parenchymal involvement	12 (50)
CSF/leptomeningeal involvement	1 (4)
Parenchymal and CSF/leptomeningeal involvement	3 (13)
Not reported	8 (33)
Disease status prior to CAR T infusion (%)	
Complete remission	3 (13)
Not complete remission/active disease	21 (88)

Baseline characteristics	Patients N=24
Primary refractory disease, N (%)	
No	7 (29)
Yes	9 (38)
Not reported	8 (33)
Elevated LDH prior to infusion, N (%)	
No	2 (8)
Yes	0 (<1)
Not reported	22 (92)
Bridging therapy, N (%)	
Yes	5 (21)
Single agent chemotherapy	3 (13)
Monoclonal antibodies	1 (4)
BTKi/IMID	1 (4)
No	15 (63)
Not reported	4 (17)
N of lines of prior therapies, median (min-max)	4 (1-10)
Time from initial diagnosis to CAR T in months, median (min-max)	36 (10-120)
Types of prior HCT, N (%)	
Prior auto-HCT	12 (50)
CAR T product, N (%)	
Tisagenlecleucel	21 (88)
Axicabtagene ciloleucel	3 (13)
Year of CAR T, N (%)	
2019	6 (25)
2020	10 (42)
2021	7 (29)
2022	1 (4)

N: number; CAR T: chimeric antigen receptor T-cell therapy; HCT-CI: hematopoietic stem cell transplantation-comorbidity index; CNS: central nervous system; CSF: cerebrospinal fluid; LDH: lactate dehydrogenase; BTKi/IMID: Bruton tyrosine kinase/immunomodulatory imide drugs.

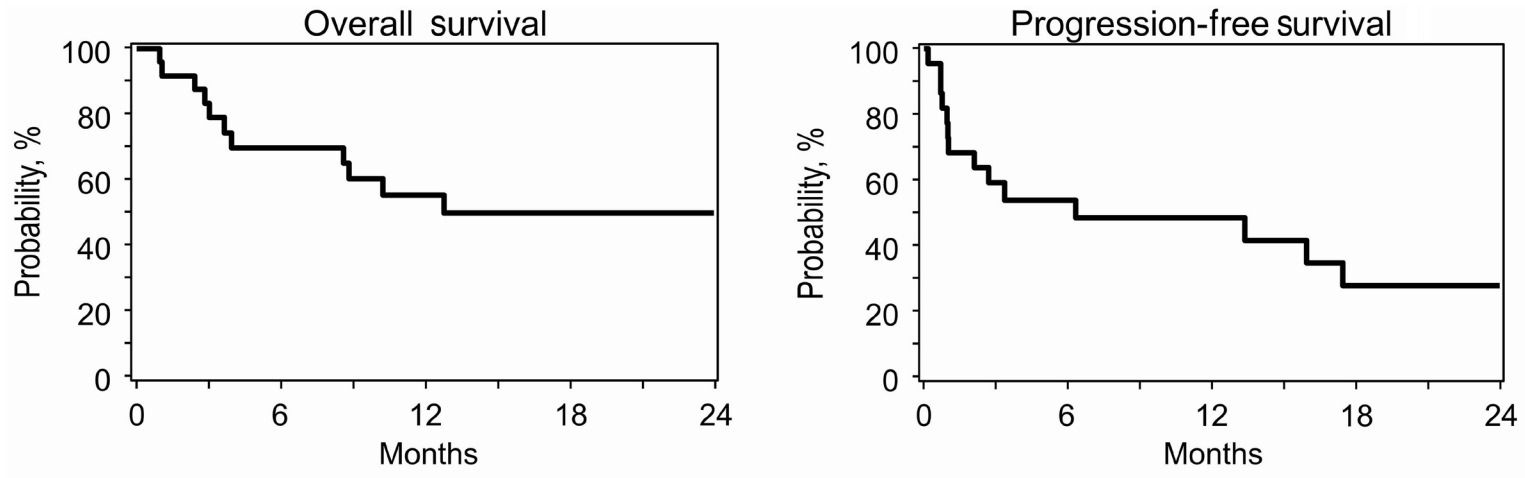

Figure 1. Overall survival and progression-free survival in primary central nervous system lymphoma.

with R/R PCNSL (grade ≥3 CRS: 0%; grade ≥3 ICANS: 8%) compared to reported data in patients with systemic lymphoma with CNS involvement (grade ≥3 CRS: 16%; grade ≥3 ICANS: 44%)[15] or without CNS involvement (grade ≥3 CRS: 2-13%; grade ≥3 ICANS: 10-28%).[5-7] In our cohort, the presence of CNS disease before the administration of CAR T did not appear to result in more frequent or more severe ICANS. This may reflect the fact that the majority of patients received tisa-cel, a CAR T construct with a 4-1BB co-stimulatory domain that is associated with lower rates of ICANS.[6] Limitations of our study include having a small number of patients and patient selection bias. The CIBMTR registry only includes data on patients who received CAR T cells and not on patients who were intended for CAR T. Specifically, in our cohort there was limited information about the details of prior treatments, the administration of bridging therapy, and certain disease characteristics (e.g., disease response) at the time of CAR T infusion, thus making it difficult to assess tumoral status before CAR T infusion with response and survival.

In conclusion, in this CIBMTR registry study of CAR T-cell therapy in patients with R/R PCNSL, we observed anti-tumor efficacy and no higher toxicity to that observed in patients with systemic lymphoma with or without CNS involvement. Despite a majority of patients experiencing an objective response to CAR T cells, most responses were not durable. These findings should be confirmed in larger prospective studies. Furthermore, clinical trials designed to evaluate the efficacy and safety of CAR T as consolidation therapy in patients with chemosensitive disease to first-line therapy should be considered.

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https://doi.org/10.3324/haematol.2024.285613

Received: April 19, 2024.
Accepted: August 28, 2024.
Early view: September 5, 2024.

Disclosures

SM reports honoraria from Roche, Gilead, Janssen, and Servier, and research funding from Roche. SG reports honoraria from BMS and

Sanofi, and serves on the Speaker's Board for Kite Pharma and Pfizer. PRG has provided consultancy services to Kite/Gilead Pharma and Bristol Myers Squibb (BMS), and served on the Advisory Boards of Pharmacyclics LLC, ADC Therapeutics, Cellectar Biosciences, Ono Pharma, CRISPR therapeutics, IPSEN Biopharma, and Regeneron Pharmaceuticals. HM reports honoraria from Mustang Bio and Bavarian Nordic. AS reports grant funding from Kite Pharma and has provided consultancy services to CRISPR Therapeutics. CU reports honoraria from Takeda and Blueprint. CSS has served as a paid consultant for Kite Pharma, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics, Ipsen Biopharmaceuticals and GSK, and has received research funds for clinical trials from Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme, Cargo Therapeutics, Affimed and NKARTA. MH reports research support / funding from Takeda Pharmaceutical Company, ADC Therapeutics, Spectrum Pharmaceuticals, and Astellas Pharma, consultancy from ADC Therapeutics, Omeros, CRISPR, BMS, Kite, Abbvie, Caribou, and Genmab, and Speaker's Bureau from ADC Therapeutics, AstraZeneca, BeiGene, Kite, DMC Inc., Genentech, Myeloid Therapeutics, CRISPR, and Autolus. CJL received honoraria and / or consultancy and / or research funding from Incyte, Sanofi, Fresenius Kabi, BMS, Kite, and Kadmon. None of the other authors have any conflicts of interest to disclose.

Contributions

MAJ and MH are responsible for data collection and assembly. MAJ, KWA and MH analyzed the data. SM prepared the first draft. All authors are responsible for the study concept and design, and interpretation of data, helped revise the manuscript, and approved the final version for publication.

Funding

The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID); HHSH250201700006C from the Health Resources and Services Administration (HRSA); and N00014-20-1-2705 and N00014-20-1-2832 from the Office of Naval Research; Support is also provided by Be the Match Foundation, the Medical College of Wisconsin, the National Marrow Donor Program, and from the following commercial entities: Actinium Pharmaceuticals Inc.; Adienne SA; Allovir Inc.; Amgen Inc.; Angiocrine Bioscience; Astellas Pharma US; bluebird bio, Inc.; Bristol Myers Squibb Co.; Celgene Corp.; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co. Ltd.; ExcellThera; Fate Therapeutics; Gamida-Cell Ltd.; Genentech Inc; Incyte Corporation; Janssen/Johnson & Johnson; Jazz Pharmaceuticals Inc.; Kiadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Legend Biotech; Magenta Therapeutics; Merck Sharp & Dohme Corp.; Millennium, the Takeda Oncology Co.; Miltenyi Biotec Inc.; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncoimmune Inc.; Orca Biosystems Inc.; Pfizer Inc.; Pharmacyclics, LLC; Sanofi Genzyme; Stemcyte; Takeda Pharma; Vor Biopharma; Xenikos BV.

Data-sharing statement

For original data, please contact the Corresponding Author.

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