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

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Running heads: CD19 car t for pcnsl

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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] No consensus on best salvage treatment for these patients exists[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, four small studies (N=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 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) with a diagnosis of R/R PCNSL who received commercially available CAR T 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 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, the median patient age was 57 years (range, 25-81), the majority were males (67%), and ten 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 twenty-one 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 2 years. The cumulative incidence of neutrophil recovery at 1 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 6 days (range, 1-9). Eleven patients died from disease recurrence or progression (92%), and 1 patient died from a bacterial infection (8%) but had disease relapse/progression prior.

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 1 trial evaluating a CD19 CAR T containing a novel CAR construct, demonstrating anti-tumor activity (CR; N=2 and 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-months OS and PFS of 89% and 44%, respectively, among 9 patients with R/R PCNSL who received CD19 CAR T (axi-cel, n=2 and tisa-cel; n= 7). One patient experienced grade 3 CRS and two 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 and tisa-cel: N=16). With a median follow-up of 20.8 months after CAR T infusion, 14 patients (56%) achieved CR at 3 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-cells have 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 compared to those published in secondary CNS lymphoma following CAR T 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 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 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 not 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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Table 1. Patient, Disease, and CAR T Related Baseline Characteristics and Study Outcomes

Baseline Characteristics	Patients (N= 24)
N. of centers	12
Age at CAR T infusion, years - median (min-max)	57 (25-81)
Age at CAR T infusion, years (%)	
18 – 64	18 (75)
≥65	6 (25)
Sex–Male (%)	16 (67)
Recipient race (%)	
White	20 (83)
African-American	1 (4)
Asian	0 (<1)
Not reported	3 (13)
Recipient ethnicity (%)	
Hispanic or Latino	2 (8)
Non-Hispanic or non-Latino	17 (71)
Unknown/ Not reported	5 (21)
Karnofsky performance score prior to CAR T (%)	
90-100	11 (46)
<90	10 (42)
Not reported	3 (13)
HCT-CI (%)	
≥3	5 (21)
Site of CNS involvement (%)	
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)
Primary refractory disease (%)	
No	7 (29)
Yes	9 (38)
Not Reported	8 (33)
Elevated LDH prior to infusion (%)	
No	2 (8)
Yes	0 (<1)
Not reported	22 (92)
Bridging therapy (%)	
Yes	5 (21)
Single agent chemotherapy	3 (13)
Monoclonal antibodies	1 (4)
BTKi/IMID	1 (4)

No	15 (63)
Not reported	4 (17)
Number of lines of prior therapies - median (min-max)	4 (1-10)
Time from initial diagnosis to CAR T, months - median (min-max)	36 (10-120)
Types of prior HCTs (%)	
Prior auto-HCT CAR T product (%)	12 (50)
Tisagenlecleucel	21 (88)
Axicabtagene ciloleucel	3 (13)
Year of CAR T (%)	
2019	6 (25)
2020	10 (42)
2021	7 (29)
2022	1 (4)

CAR T: chimeric antigen receptor; 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; CRS: cytokine release syndrome; ICANS:immune effector cell associated neurotoxicity syndrome

Figure legends

Figure 1: Overall survival and Progression-Free Survival

Primary CNS Lymphoma