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REVIEW ARTICLE

Chimeric Antigen Receptor T-cell Therapies in Lymphoma Patients with Central Nervous System Involvement

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Abstract

Background and objective: CAR T-cell therapy has significantly improved the outcomes of patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). However, most clinical trials excluded patients with central nervous system (CNS) involvement due to uncertain efficacy and safety.

Material and methods: On January 1, 2022, we searched PubMed to identify all published literature associated with current commercial CAR T-cell therapies for B-NHL, including tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), and lisocabtagene maraleucel (liso-cel). Studies that involved patients with either primary or secondary CNS lymphoma, and evaluated response rate, adverse events (AEs), or survival were included and summarized.

Result: Herein, we summarize the results of 11 studies qualified for our inclusion criteria, reporting 58 lymphoma patients with CNS involvement with 44 evaluable for clinical response, 25 for immune effector cell-associated neurotoxicity syndrome (ICANS) and 48 for Cytokine release syndrome (CRS). Objective response was achieved in 62% (16/26) of patients, and CR was achieved in 52% (23/44) of patients. Forty-four percent (11/25) developed ICANS, and 35% (17/48) developed severe ICANS (grade \geq 3). CRS was reported in 63% (15/24) of patients, while severe CRS (grade \geq 3) was reported in 7% (3/42) of patients.

Conclusion: Based on our PubMed literature review, we conclude that CAR T-cell therapy may benefit patients with CNS lymphoma with promising response rates and acceptable AE. However, definite conclusions cannot be drawn until data with a larger sample size is available.

Keywords: CAR T in CNS lymphoma, CNS lymphoma, Chimeric antigen receptors, Lymphoma

1. Introduction

In the past five years, the U.S. Food and Drug Administration (FDA) has approved four chimeric antigen receptor (CAR) T-cell products for relapsed or refractory (R/R) B-NHL treatment beyond the second line of therapy. Tisa-cel, being the first, was approved in August 2017 for R/R LBCL after the JULIET trial [1]. Axi-cel was approved two months later for R/R LBCL and, more recently, for

follicular lymphoma (FL) supported by the ZUMA-1 trial [2]. In July 2021, brexu-cel was approved for mantle cell lymphoma (MCL) after the ZUMA-2 trial [3]. Most recently, the FDA approved liso-cel for LBCL with promising data from the TRANSCEND-NHL-001 trial [4]. Patients with central nervous system (CNS) involvement were excluded from most CAR T-cell clinical trials. The only licensing trial that enrolled patients with CNS lymphoma was TRANSCEND-NHL-001 for liso-cel,

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which included seven patients with secondary CNS lymphoma (SCNSL) [4].

CNS lymphoma comprises primary CNS lymphoma (PCNSL) and SCNSL. PCNSL is a rare and aggressive disease; it accounts for about 2% of all primary brain cancers and 7% of malignant primary brain tumors [5]. PCNSL must be distinguished from SCNSL, defined as CNS lymphoma occurring concomitantly with or as a relapse of systemic lymphoma. Efficacy and toxicity are the two main concerns that led to the exclusion of patients with CNS lymphoma from most CAR T clinical trials. It is unknown how effectively CAR T-cells penetrate the blood–brain barrier (BBB) and whether they increase the risk of immune effector cell-associated neurotoxicity syndrome (ICANS). Tumors are known to compromise the integrity of the BBB, resulting in a vasculature known as the blood–tumor barrier (BTB), which is highly heterogeneous with variable permeability and is generally considered ‘leakier’ than the BBB [6]. The BTB can be beneficial, allowing the entry of immune components and CAR T-cells to attack tumor cells and clear debris. However, BBB disruption can lead to vasogenic edema due to increased movement of water and plasma proteins into the CNS [7]. The systemic inflammation and high levels of circulating cytokines during CAR T-cell therapy can activate endothelial cell damage and further disrupt the BBB, which in turn causes an inflammatory cascade within the CNS, causing severe ICANS.

Given the paucity of data for CAR T-cell therapy in CNS lymphoma, we reviewed the current literature assessing the efficacy and safety profile of commercial CAR T products.

2. Methods

2.1. Information source and search strategies

On January 1, 2022, we searched PubMed:

1. For **Axicabtagene ciloleucel** we searched: (((((axicabtagene ciloleucel[Supplementary Concept]) OR (axicabtagene ciloleucel[Title/Abstract])) OR (axicel[Title/Abstract])) OR (Yescarta[Title/Abstract])) OR (KTE-C19[Title/Abstract])) OR (KTEC19[Title/Abstract])

2. For **Tisagenlecleucel** we searched: (((((tisagenlecleucel[Supplementary Concept]) OR (tisagenlecleucel[Title/Abstract])) OR (tisa-cel[Title/Abstract])) OR (KYMRIAHI[Title/Abstract])) OR (CTL-019[Title/Abstract])) OR (CTL019[Title/Abstract])

3. For **Lisocabtagene maraleucel** we searched: (((lisocabtagene maraleucel[Title/Abstract]) OR (liso-cel[Title/Abstract])) OR (Breyanzi[Title/Abstract])) OR (JCAR017[Title/Abstract])

4. For **Brexucabtagene autoleucel** we searched: (((((brexucabtagene autoleucel[Supplementary Concept]) OR (brexucabtagene autoleucel[Title/Abstract])) OR (brexu-cel[Title/Abstract])) OR (Tecartus[Title/Abstract])) OR (KTE-X19[Title/Abstract])) OR (KTEX19[Title/Abstract])

5. Final search: #1 OR #2 OR #3 OR #4.

2.2. Eligibility criteria

Inclusion criteria: (a) Some proportions, or the entirety, of a study population that presented with lymphoma with primary or secondary CNS involvement, regardless of whether patients had active CNS involvement or a history of CNS involvement at the time of CAR T-cell infusion; (b) All patients were treated with one of the four commercial CAR T-cell products.

Exclusion criteria: (a) Studies without original data, including reviews, meta-analyses, clinical trials, letters, commentaries, or editorials; (b) Studies that did not specify any of the following endpoints of interest in patients with CNS involvement: overall response (OR), complete response (CR), partial response (PR), overall survival (OS), progression-free survival (PFS), Cytokine release syndrome (CRS), or ICANS.

2.3. Selection and data collection process

In total, 572 reports were identified in PubMed. Two reviewers independently screened the reports based on the eligibility criteria. Two reviewers independently extracted data pertaining to the first author, publication year, product type, the number of patients with CNS involvement, age, lymphoma type, CNS involvement type (primary vs. secondary), CNS disease status at the time of CAR T-cell infusion ICANS, CRS, response to therapy, survival, and follow-up time. Certain included patients were subgroups in cohort studies that did not specifically provide characteristics of age, prior lines of therapy, and follow-up time in patients with CNS involvement. Any discrepancy in data selection and extraction was resolved by consensus via discussion with a third senior reviewer.

Descriptive statistics were used to summarize the eligible studies.

3. Result

3.1. Study selection

Initially, our literature search yielded 572 records. Screening of titles and/or abstracts resulted

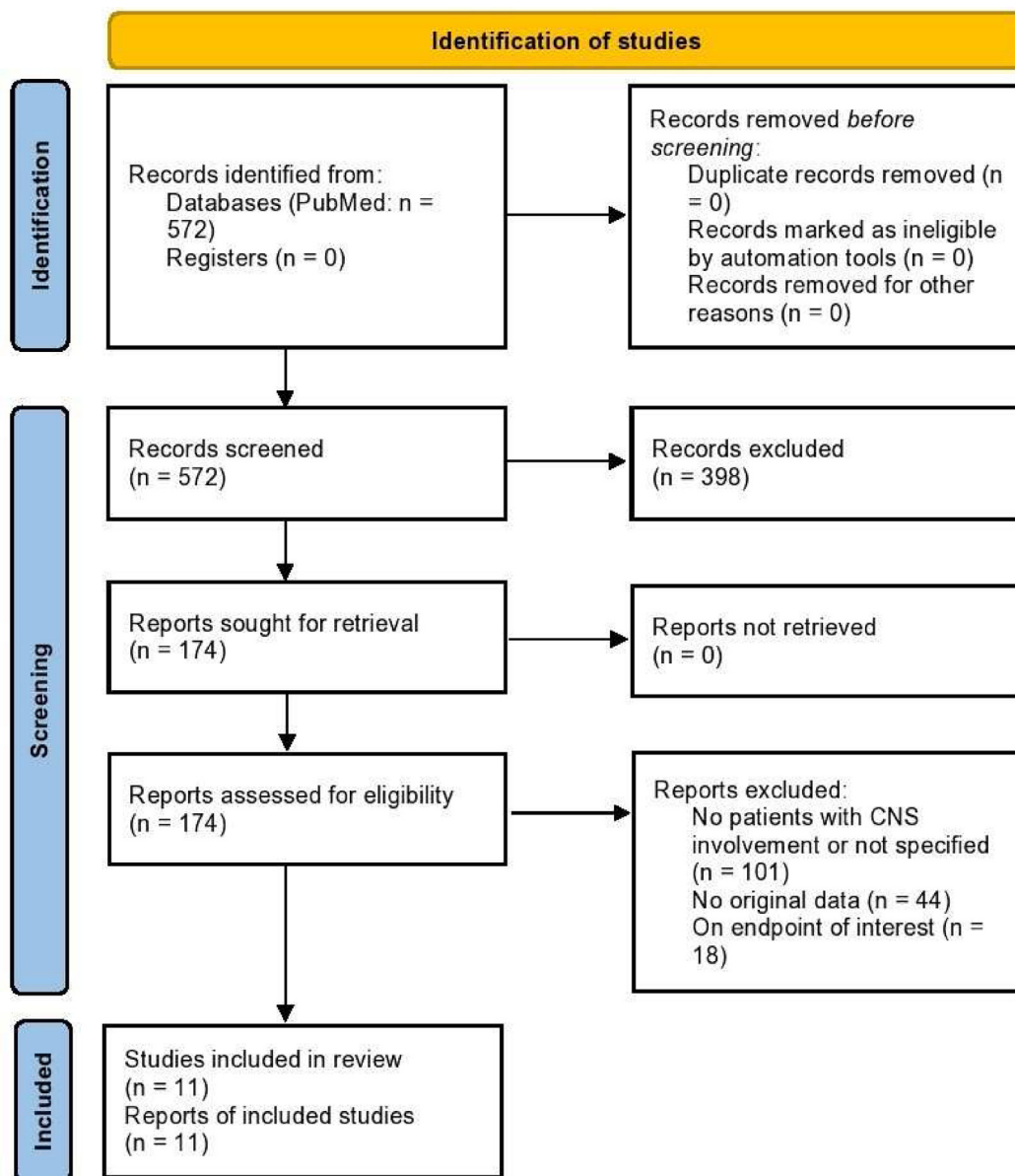


Fig. 1. Flow diagram of the study selection process.

in 398 records being excluded. Full texts of the remaining 174 records were reviewed. Eleven reports met the eligibility criteria [4,8–17]. Detailed selection flow and the reasons for exclusion are shown in Fig. 1.

3.2. Study characteristics

We included 11 studies reporting 58 patients with lymphoma with CNS Involvement (63 cases with 5 duplicate patients). Six of the 11 reports are from cohort studies [4,10,12,13,15,17]. Five records are case series or case reports [8,9,11,14,16]. Two of the studies, including a case series and a retrospective

cohort study, were reported by the same group from the University of California, Los Angeles [10,11]. The case series reported 5 patients with active SCNSL who were treated with axi-cel between October 2017 and January 2020 [11]. The retrospective cohort study involved 53 patients in total treated with axi-cel or tisa-cel between October 2017 and June 2020, among which seven patients had SCNSL prior to (n = 1) or at the time of (n = 6) CAR-T therapy [10]. Given that the retrospective cohort study included all patients diagnosed with R/R LBCL who received axi-cel or tisa-cel over a longer time frame, the five patients reported in the case series were identified as duplicates.

Table 1. Results of individual studies.

Studies	Product	No.	Median Age (yr)	Histological Type	Prior Lines of Therapy	Primary/Secondary CNS Involvement	CNS Disease upon CAR-T Infusion	ICANS	CRS	Response	Survival	Follow-up
Ghafouri [11]	Axi-cel	5	58.5 (28.3–76.4)	DLBCL: 2 HGBCL: 2 PMBCL: 1	2.4 (1–4)	SCNSL	Active	Grade 3: 1 Grade 4: 1 No NT: 3	Grade 1: 1 Grade 2: 1 No CRS: 3	CR: 3 SD: 1 PD: 1	Median PFS: 155 Ds 134.2 Ds Median OS: 155.0 Ds	155 Ds (86–208 Ds)
Ghafouri [10]	Axi-cel: 6 Tisa-cel: 1	7	63 (46–76)	DLBCL	≥4: 5	SCNSL	Active: 6 Resolved: 1	ICANS: 4 Severe: 2	Grade 1–2: 4	CR: 4	Median EFS: 4.4 M Median OS: 8.8 M	15.2 M ^a
Holtzman [12]	Axi-cel	2	(26–75) ^a	The cohort included DLBCL, tFL, and PMBCL	NP	SCNSL	Resolved	No NT: 2	NP	NP	NP	(3–9.9 M)
Abbasi [8]	Axi-cel	2	66 (55–77) ^a	DLBCL	(2–4)	NP	NP	NP	NP	CR: 2	PFS _{≥5} OS _{≥5} Ms	≥5 Ms
Jacobson [13]	Axi-cel	1	(21–79) ^a	The cohort included DLBCL, HGBL, PMBL, tFL, tMZL, tCLL, and T-cell/histiocyte rich.	NP	NP	NP	NP	NP	OR	NP	10.4 M ^a
Kittai [14]	Axi-cel	1	50	DLBCL	3	SCNSL	Resolved	Grade 4	Grade 1	CR	CR at day 345	345 Ds
Nastoupil [15]	Axi-cel	21	(21–83) ^a	The cohort included DLBCL, tFL, and PMBCL	(2–11) ^a	NP	NP	Grade _{≥3} : 7 ^e	Grade _{≥3} : 3 ^e	CR: 9 ^e PR: NP	44% PFS at 12 Ms 56% OS rate at 12 Ms	(3.9–21.6) Ms ^a
Strati [17]	Axi-cel	8	(18–85) ^a	LBCL	NP	SCNSL	Resolved	Grade _{≥3} : 5	NP	NP	NP	NP
Novo [16]	Axi-cel	1	62	DLBCL	3	SCNSL	Active	Not graded ^c	Grade 2	CR	PFS _{≥12} Ms	≥12 Ms
Frigault [9]	Tisa-cel	8	50 (17–79)	DLBCL: 5 HGBCL: 2 PMBCL: 1	5 (3–6)	SCNSL	Active	No NT: 4 Grade 1: 3 ^b	Grade 1: 7 No CRS: 1	CR: 3 PR: 1 PD: 4	NP	≤6 Ms
Abramson [4]	Liso-cel	7	(54–70) ^a	The cohort included DLBCL, HGBCL, PMBCL, and FL.	(2–4) ^a	SCNSL	NP	Grade 3: 2	Grade 1–2: 2	CR: 3 ^d	NP	18.8 M ^a

Axi-cel, axicabtagene ciloleucel; Liso-cel, lisocabtagene maraleucel; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; tMZL, transformed marginal zone lymphoma; tCLL transformed lymphocytic leukemia; NP, not provided; tFL, transformed follicular lymphoma; FL, follicular lymphoma; LBCL, large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; CRS, cytokine release syndrome; CR, complete response; R: partial response; SD: stable disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; Ms, months; Ds, days; SCNSL, secondary central nervous system lymphoma.; NT: neurotoxicity.

^a The range or median value of the entire cohort.

^b One patient was not evaluable due to disease progression.

^c Although not graded, patient presented with aphasia, difficulties following commands, and disorientation concerning for ICANS. A mild right hemiparesis was also reported.

^d Six patients were included in the efficacy-evaluable set.

^e Eighteen out of 21 patients were evaluated for response and CRS, and 16 patients were evaluated for ICANS, calculated from the patient number and percentage in Table.

Among the 58 patients, axi-cel was administered to 42, tisa-cel was administered to nine, and one received liso-cel. Although we planned to include brexu-cel, we could not find any reports on brexu-cel administered in patients with CNS lymphoma. Thirty-four patients had SCNSL, while information regarding primary versus SCNSL was not provided for the remaining 24. Fifteen patients had active CNS disease at the time of CAR T-cell infusion. Twelve patients had resolved CNS lymphoma at the time of infusion. CNS disease status was not provided for 31 patients.

3.3. Results of individual studies

Detailed information pertaining to the studies included in this analysis is shown in [Table 1](#). Baseline patient demographic and clinical characteristics are displayed in [Table 2](#).

3.4. Response

Among 11 studies, nine evaluated response to CAR T-cell therapies in patients with CNS involvement, including 48 patients [4,8–11,13–16]. In total, 44 out of 48 patients from the nine studies were evaluated for response. Objective response was achieved in 62% (16/26), and CR was achieved in 52% (23/44) of patients.

Table 2. | Baseline patient demographics and clinical characteristics.

Patient Characteristics	Values
Number	n = 58
Age	17–85 ^a
Gender (male/female)	5/4 (information available for 9 patients)
Histological Type	DLBCL: 13 HGBCL: 4 PMBCL: 2 LBCL, NOS: 8 NP: 31
Prior Lines of Therapy	1–11 ^b
PCNSL vs SCNSL	SCNSL: 34 NP: 24
CNS Disease at Time of CAR-T Infusion	Active: 15 Resolved: 12 NP: 31
CAR T-cell Product	Axi-cel: 42 Tisa-cel: 9 Liso-cel: 7

Axi-cel, axicabtagene ciloleucel; Liso-cel, lisocabtagene maraleucel; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; LBCL, large B-cell lymphoma; NOS, not otherwise specified; NP, not provided; PCNSL, primary CNS lymphoma; SCNSL, secondary CNS lymphoma.

^a The youngest patient with CNS lymphoma in this review was 17 years old [9]. However, the upper limit was determined by the range of an entire study, which included both patients with CNS involvement and patients without CNS disease [17].

^b Information not provided in some studies.

Objective response rates in patients treated with axi-cel, tisa-cel, and liso-cel were 90% (9/10), 50% (4/8), and 43% (3/7), respectively. Complete response rates were 57% (16/28), 38% (3/8), and 43% (3/7) for axi-cel, tisa-cel, and liso-cel, respectively. The pivotal clinical trial for liso-cel, TRANSCEND NHL 001, compared objective response rate (ORR) and CR rate in patients with and without SCNSL. Six out of seven patients with CNS involvement were evaluated for response. ORR was 50% (95% CI: 11.8–88.2%) for patients with CNS involvement with no significant difference compared to 73.2% (95% CI: 67.3–78.6%) in patients without CNS involvement. CR rate was 50% (95% CI: 11.8–88.2%) in patients with CNS involvement and 53.2% (95% CI: 46.8–59.5%) in patients without CNS involvement [4]. Nastoupil et al. also compared the CR rate at 12 months in patients treated with axi-cel, which was reported as 50% and 65% in patients with and without a CNS involvement history, respectively ($p = 0.21$) [15]. In 14 patients with active CNS involvement at the time of CAR T-cell infusion, ORR was achieved in 64% (9/14) of patients, and CR was achieved in 50% (7/14) of patients [9,11,16]. In 28 patients with unclear remission status of CNS involvement at the time of CAR T infusion, ORR and CR were achieved in 70% (7/10) and 54% (15/28) of patients, respectively [4,8,13–15]. Only 10 patients were involved in calculating the ORR rate because patients with CNS involvement in the cohort study by Nastoupil et al. were reported for CR only [15].

3.5. ICANS

Nine studies evaluated patients for ICANS [4,9–12,14–17]. In total, 25 patients were evaluated for ICANS of any grade, among which 11 developed ICANS. Forty-eight patients were evaluable for grade ≥ 3 ICANS, which was reported in 17 patients. The incidence of ICANS and ICANS \geq grade 3 were 44% (11/25) and 35% (17/48), respectively. Nastoupil et al. compared the incidence of grade ≥ 3 ICANS in patients with and without CNS involvement; 43% versus 30%, respectively ($p = 0.45$) [15]. Abramson et al. did a similar comparison. The incidence of ICANS of any grade was 29% (2/7) and 30% (78/262) in patients with and without SCNSL ($p = 0.95$), and the incidence of grade ≥ 3 ICANS was 29% (2/7) and 10% (25/262) in patients with and without SCNSL ($p = 0.10$) [4]. Strati et al. reported that among 41 patients in the entire cohort who developed severe ICANS, five had a prior history of SCNSL ($p = 0.27$) [17]. Among patients treated with axi-cel, 67% (6/9) developed ICANS of any grade, and 44% (14/32) developed severe ICANS [11,12,14–17]. Among

patients treated with tisa-cel, 43% (3/7) of patient developed ICANS of any grade, and no patient developed severe ICANS [9]. Only one study in our review evaluated ICANS incidence in patients treated with liso-cel. Two out of seven patients had ICANS (both were grade 3) [4]. Among patients with active CNS involvement at the time of CAR T-cell infusion, 50% (7/14) of patients developed ICANS, and 15% (2/13) developed ICANS \geq grade 3. The incidence of ICANS in patients with resolved CNS involvement was 50% (2/4), and the incidence of severe ICANS was 50% (6/12). Eight more patients were included in the analysis of severe ICANS because these patients were from a cohort study that only recorded patients with grade ≥ 3 ICANS [17]. The incidence of ICANS in patients with unknown CNS disease status at the time of CAR T infusion was 29% (2/7), and the incidence of severe ICANS in this subset was 39% (9/23). Sixteen more patients were involved in the analysis of severe ICANS because these patients were from a cohort study that only recorded patients with grade ≥ 3 ICANS [15].

3.6. CRS

Seven studies evaluated patients for CRS [4,9–11,14–16]. CRS was reported in 63% (15/24) of patients. However, grade ≥ 3 CRS was reported only in 7% (3/42) of patients. Nastoupil et al. did not specify the number of patients evaluated for CRS. However, based on the number of patients who developed grade ≥ 3 CRS ($n = 3$) and the percentage (17%), it is presumed that 18 out of 21 patients were evaluated for severe CRS [15]. Among patients treated with axi-cel, 58% (4/7) developed CRS of any grade, and 16% (4/25) developed severe CRS. Eighty-eight percent (7/8) of patients treated with tisa-cel developed CRS of any grade, while no patient developed severe CRS. Among patients treated with liso-cel, 29% (2/7) developed CRS of any grade, and no patient had severe CRS. We did not include the seven patients in the cohort study conducted by Ghafouri because it was unclear which patients received axi-cel and tisa-cel [10]. Nastoupil et al. also compared the incidence of severe CRS in patients with and without CNS involvement, which was reported as 17% versus 6%, respectively ($p = 0.12$) [15]. The incidence of CRS of any grade was reported by Abramson et al. as 29% (2/7) and 42% (111/262), respectively, in patients with and without SCNSL ($p = 0.47$). The incidence of grade ≥ 3 CRS was 0% and 2% (6/262) in patients with and without SCNSL in the same study [4]. No significant difference was detected between the two subsets.

3.7. Survival

Six studies provided survival data of patients with CNS involvement [8,10,11,14–16]. The cohort study conducted by Ghafouri et al. involved seven patients with CNS lymphoma, including the five in the case series. The median PFS and OS were 4.5 and 8.8 months, respectively, while the median PFS and OS of the entire cohort were 7.9 and 17.7 months, respectively [10]. Nastoupil et al. compared the PFS and OS rates in patients with and without CNS lymphoma, and no significant difference was noticed. PFS rate was 44% and 47% in the two subsets, respectively ($p = 0.23$), and OS rate was 56% and 69% ($p = 0.21$) [15]. The patient with Richter syndrome (RS) and SCNSL reported by Kittai et al. maintained CR until the end of follow-up, which was 345 days after CAR T-cell infusion [14]. Similarly, the patient with DLBCL and SCNSL in the case report by Novo et al. remained in CR 12 months after CAR T-cell infusion [16]. In the case series by Abbasi et al., both patients with CNS involvement sustained CR until the end of follow-up, which was at least 5 months [8].

4. Discussion

Among the 11 studies included in the review, two compared the response to CAR T-cell therapy in patients with and without CNS involvement, which included seven and 21 patients with CNS lymphoma, respectively [4,15]. No significant difference was noted in either study. Nastoupil et al. compared the PFS and OS rates in patients with CNS lymphoma ($n = 21$) and without CNS lymphoma ($n = 277$) and demonstrated no significant difference [15]. However, Ghafouri et al. argued that early response to CAR T-cell therapy might not be durable given the fact that the majority of responders to CAR T-cell therapy relapsed within 5 months. They suggested that patients in this subset might benefit from early maintenance or consolidation therapies with allogeneic HCT [11].

Three out of 11 studies investigated whether CNS involvement increased the risk of ICANS and/or severe ICANS [4,15,17]. All 3 studies demonstrated no increased risk of ICANS and/or severe ICANS that was statistically significant. Besides, no evidence demonstrated an increased incidence of CRS, either.

When we started this review, we planned to evaluate the efficacy and safety of all four CAR T-cell therapies available for B-NHL, including axi-cel, tisa-cel, liso-cel, and brexu-cel. However, we could not find any reports regarding brexu-cel treating

patients with CNS lymphoma. Brexu-cel is indicated for relapsed or refractory mantle cell lymphoma, for which CNS involvement is uncommon. The crude incidence of CNS involvement is 4.1%, with 0.9% having CNS involvement at diagnosis. Further investigation is warranted to evaluate CAR-T therapy candidacy in this subset of patients.

We also planned to compare the outcomes of patients with PCNSL vs. SCNSL. However, eight out of 11 studies focused on SCNSL [4,9–12,14,16,17], and the rest did not specifically report if patients had PCNSL or SCNSL [8,13,15]. On January 27, 2022, we searched ClinicalTrials.gov, and found five ongoing clinical trials investigating CAR-T therapy treating PCNSL (ClinicalTrials.gov Identifier: NCT04443829, NCT04134117, NCT04608487, NCT04464200, and NCT03484702). Emerging data from ongoing clinical trials will be the best answer to the topic of this manuscript.

We recognize many inherent limitations to our review. A meta-analysis is beyond the scope of this single database review of 58 heterogeneous patients. Patients received one of three commercial CAR T products without uniform trial eligibility criteria, such as bridging chemoimmunotherapy. Ten out of 11 studies were retrospective with variable follow-up times and AE grading systems. Nevertheless, our review best summarizes the current experience using CAR T therapy for patients with CNS lymphoma.

5. Conclusion

Patients with CNS B-NHL treated with axi-cel, tisa-cel or liso-cel demonstrated comparable efficacy and safety profile to the data reported in the pivotal trials in patients without CNS involvement.

Conflict of interest

Authors declare no conflict of interest.

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