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Research Article

Systematic Review Reflecting the Magic Role of CART - cell in Central Nervous System with Secondary Lymphomas

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Abstract

Background: Chimeric antigen receptor T (CAR-T) cell therapy is an approved, safe and effective therapy for patients with non-Hodgkin's lymphoma.

Aim: The current study sought to determine if secondary CNS lymphoma patients will safely benefit from CAR T-cell therapy.

Materials and Methods: Two independent raters separately examined PubMed, Web of Science, Embase, and the Cochrane library for all records relating to CAR T-cell therapies (i.e. Axi-cel and Tisa-cel) published prior to May 19, 2022. Included were studies that investigated secondary CNS lymphoma patients treated with CAR T-cell and reported the (Their) effectiveness and safety. Six cohort observational studies were included. A method "(RoB 2.0) tool for observational studies" developed expressly to assess the risk of bias was employed.

Results: Studies were symmetrically distributed, no publication bias. < 20% missing data. (According to current data) CAR-T cell therapy resulted in long-term remission in individuals with secondary CNS lymphoma, according to current data. The results for 872 patients in six trials showed 45 patients with CNS involvement, 827 with no CNS involvement, an ORR in 619 patients (16 of them with CNS involvement) and CR rate in 490 patients (18 with CNS involvement) mean estimate of 73.5% (95% CI, 36.5 - 82%) and 62.5% (95% CI, 39.5 - 64%), respectively. In patients with CNS involvement the CRS "Grade ≥ 3" was 6/45 (30.9%, 21 - 68%) and the ICANS rate was 8/45 (17.7%, 9.8 - 30.2%). The ICU admission was 12/45 (30.31%, 29 - 51%). The progression of the disease/death was reported for 136 patients with BCL from the six selected studies, and reported in one case with CNS involvement. The "progression of the disease/death" pooled "OR" (95% CI) was 14.35% (8.5 - 36.2%).

Conclusion: Patients with secondary CNS lymphoma may benefit from CAR-T cell therapy, with manageable toxicities. As a result, CAR-T cell therapy has the potential to be a therapeutic option for lymphoma patients with CNS involvement. Prospective research with bigger samples and longer follow-up periods are needed.

Keywords: *Efficacy; Safety; CAR; T-Cell; Therapies; Lymphoma; Central Nervous System*

Introduction

Diffuse large B cell lymphoma (DLBCL) represents 22% of newly diagnosed B-cell non-Hodgkin lymphoma (NHL) cases and 30% of all lymphomas in the United States of America [1]. NHL may affect the central nervous system (CNS) by direct involvement (brain, spinal cord, meninges, spinal and cranial nerves), or indirectly by para-neoplastic manifestations [2]. The incidence of CNS involvement reported in the literature ranges from 5 - 20% [3,4]. Primary and secondary CNS lymphomas occur either as a rare subtype of extra-nodal "B-cell" NHL arising primarily from CNS or due to secondary involvement of CNS from systemic disease, respectively [5,6]. Primary CNS lymphomas account for 2% of primary CNS tumors [7,8]. Secondary CNS lymphomas are associated with an aggressive course and poor prognosis and outcomes [6].

Despite considerable cure rates (60 - 70%) with the currently available frontline chemo-immunotherapy, relapse/refractory disease still account for 30 - 40% of case [9-14]. Intra-thecal chemotherapy and high dose methotrexate may reduce the incidence of secondary CNS involvement in high risk patients, however this remains controversial and at a price of significant toxicities [15-19].

Promising adoptive immunotherapeutic, including (CAR) T-cell therapy (Chimeric Antigen Receptor T-cell therapy), have enhanced the armamentarium for relapsed/refractory DLBCL patients, offering efficacious treatment with predictable manageable side effect profile [20-26].

Aim of the Study

The aim of this systematic review and meta-analysis is to evaluate the CAR T-cell therapy in the treatment of lymphoma patients with central nervous system involvement, looking specifically to neurotoxicity, response, cytokine release syndrome, ICU admission, disease progression and death.

Materials and Methods

We published the proposal for this research in the Inter-national "Prospective Register of Systematic Reviews" (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/display-record.php?RecordID=44439786). The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [27].

Search strategy

Our search strategy in study selection of research articles focused on efficacy and safety of CAR T-Cell therapies in lymphoma patients with central nervous system involvement, we searched the literature of "bibliographic electronic databases" such as: Medline-PubMed, Cochrane, Google Scholar, EBSCO, CINAHL, EMBAS. Electronic databases were searched until 1st January 2022. The search terms included: "axicabtagene ciloleucel " OR tisagenlecleucel OR "Kymriah" OR "lisocabtagene maraleucel" OR " "brexucabtagene autoleucel". For Axicabtagene ciloleucel we searched: (((((axicabtagene ciloleucel [Supplementary Concept]) OR (axicabtagene ciloleucel [Title/Abstract])) OR (axi-cel [Title/Abstract])) OR (Yescarta [Title/Abstract])) OR (KTE-C19[Title/Abstract])) OR (KTEC19[Title/Abstract]). For Tisagenlecleucel we searched: (((((tisagenlecleucel [Supplementary Concept]) OR (tisagenlecleucel [Title/Abstract])) OR (tisa-cel [Title/Abstract])) OR (KYMRIAH[Title/Abstract])) OR (CTL-019[Title/Abstract])) OR (CTL019[Title/Abstract]). For Lisocabtagene maraleucel we searched: (((lisocabtagene maraleucel [Title/Abstract]) OR (liso-cel [Title/Abstract])) OR (Breyanzi [Title/Abstract])) OR (JCAR017[Title/Abstract]). 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]). Final search: #1 OR #2 OR #3 OR #4

In addition to the databases mentioned above, literature searches were supplemented by i) checking the reference lists of relevant reviews and included papers citations for potentially relevant papers. The titles and abstracts were screened out by two independent

reviewers A.M.E. and O.N. according to the inclusion/exclusion criteria, and studies not fulfilling the criteria were excluded. If it was uncertain that either study met the inclusion/exclusion criteria, they were retained for the next stage. In the second stage, full-text articles were screened out based on inclusion-exclusion criteria again by two independent reviewers A.M.E. and O.N. All records were collected on EndNote, a bibliographic tool used in research to develop personalized databases. Two reviewers independently screened these 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 (active vs resolved), adverse events including ICANS and 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. We summarized the range or median value of the entire cohorts as reference. Any discrepancy in data selection and extraction was resolved by consensus discussion with a third senior reviewer, who is an experienced cellular therapy clinical researcher.

Inclusion and exclusions criteria

Inclusion criteria

Only published studies were included if they met the following inclusion/exclusion: 1) patients with lymphoma and 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, 2) patients were treated with one of the three commercial CAR T-cell products approved by FDA for lymphoma, which include axi-cel, tisa-cel, and Liso-cel, 3) if the studies were published in English language, if in another language English translation was present, 4) only quantitative study design such as RCT or cohorts were included. Research articles written in English articles obtained from new sources and new bases Poses national/international implications. Articles that have been updated, modified, published, printed, or authored between January 1, 2010 and December 31, 2021. We repeated the search method before submitting the paper to find more relevant results.

Exclusion criteria

Studies were excluded if those (they) were: 1) animal studies 2) 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 and secondary data analysis studies such as systematic reviews or meta-analysis along with clinical study protocols, letters, comments, or editorials were excluded. We also omitted any publications published before 2010, articles written in a language other than English, writings translated from other non-scientific sources, articles presented as consensus or expert-based assertions, and articles authored by a single author.

Risk of bias assessment

Each included RCT was assessed for potential risk of Bias using Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [28]. Each trial was assessed on five domains: randomization process, deviation from intended intervention arising from effect to intervention and effect of adhering to intervention (if adherence was studied), missing outcome data, measurement in outcome and selection of reported results. Each domain was assessed as having either low, some or high potential of bias. Final Risk of Bias assessment for each study was combination of assessment on each domain as per instruction given in tool. Assessment of potential risk of bias was made independently by two reviewers A.M.E. and O.N. Discrepancies were resolved through discussion [2].

Observational studies were rated by two independent researchers on the methodological quality using a tool that has been developed by the Agency for Healthcare Research and Quality [29]. Discrepancies were reviewed and resolved by the research team. Juni, Altman, and Egger (2001) have used this adapted tool previously including many other reviews [30]. The tool evaluated the risk of bias in multiple domains: 1) representativeness and description of the cohort 2) the methods utilized to ascertain diagnoses and measure outcomes and

3) whether analyses were appropriate and included consideration of confounding variables. The domains are rated as yes, no, partial, and unclear.

Data extraction

Quantitative data was extracted using a data extraction spreadsheet. Extracted information included study characteristics, study design, sample characteristics, intervention characteristics, and results. The primary outcome was to systematically review the literature and meta-analyze the efficacy and safety of CAR T-Cell therapies in lymphoma patients with central nervous system involvement.

Strategy for data synthesis

We performed meta-analysis using the Review Manager (Revman 5.4.1) software for the efficacy and safety of CAR T-Cell therapies in Lymphoma Patients with Central Nervous System Involvement. For dichotomous data Odds ratios were used as treatment difference. Odds ratios were calculated using the Mantel-Haenzel methods along with generic inverse variance method for comparison. Inconsistency was assessed via the I^2. Moreover, we consolidated descriptive information on intervention characteristics and process outcomes.

Results

Study characteristics

In this systematic review and meta-analysis, six observational studies met the inclusion criteria that explored the efficacy and safety of CAR T-Cell therapies in lymphoma patients with central nervous system involvement. We identified 1445 records from electronic databases, from which 451 duplicated records were excluded before screening. The remaining 994 records were screened, from which 968 were removed as shown in the PRISMA flow diagram of the systematically searched, selected, included studies (Figure 1).

PRISMA flow diagram was adopted from Moher., *et al*. PRISMA group 2009 [31]. We excluded the studies either due to unmet inclusion criteria or existence of one or more exclusion criteria. 25 Studies were retrieved and assessed for eligibility. 19 Reports were excluded: Case report (n = 3), absence of intervention (n = 1), letter to editor (n = 3), absence of CNS involvement (n= 9) or Review Paper (n= 3) (Figure 1).

We chose six observational studies, all conducted in the United States of America. All the selected studies were conducted as "cohort study designs" [6-11]. Three cohort studies were conducted as retrospective cohort [7,8,10], Two as multicenter trials [6,9], and one as cohort analysis [11]. There was one study included in qualitative synthesis and subgroup analysis of "complete response", it was conducted on 12 patients with emphasis on descriptive and no inferential statistics for details about ICANS, CRS, OR, disease progression and overall survival. There was no comparison between groups with different outcomes in terms of topics under study.

Sample characteristics

All the included studies specified their sample [6-11] (Table 1).

The total sample size of the included patients in the selected studies is 872 patients, 45 of them with CNS involvement. 14 patients had active CNS disease upon receipt of CART cell, 23 had a history of CNS disease but was controlled and 8 had inactive CNS disease at the time of CART cell therapy. The sample size of Lymphoma with CNS ranged from 1 [9] to 21 participants [10]. Mean age of the participants was around 70 years except for one study in which mean age was 52 years [8]. All the six included studies had CNS as secondary involvement [6-11] (Table 1).

In four selected studies male patients were more than female patients [6,7,10,11], except in one study [8]. The gender characteristic was not determined in one study [9]. The study duration in all studies ranged from 1 - 3 years, (minimum of one year [6], maximum of 3

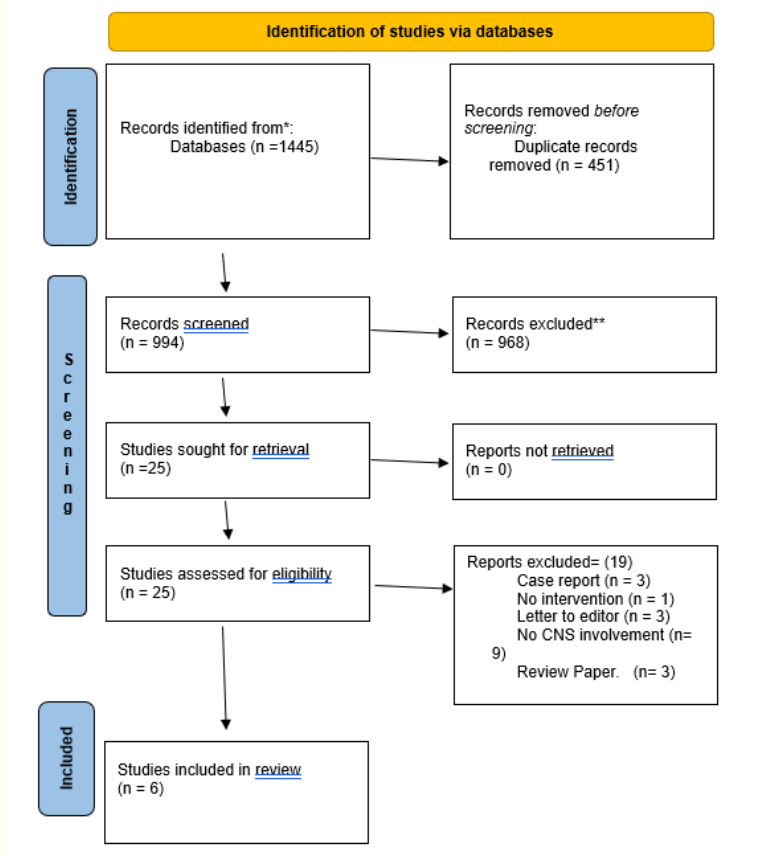

Figure 1: *PRISMA flow diagram. Systematically searching and selecting the included studies. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:https://doi.org/10.1371/journal.pmed1000097 [5]. For more information, visit www.prisma-statement.org. *Medline-PubMed, Cochrane, Google Scholar, EBSCO, CINAHL, EMBAS. **1) animal studies 2) if 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 and secondary data analysis studies such as systematic reviews or meta-analysis along with clinical study protocols, letters, comments, or editorials were excluded. We also omitted any publications published before 2010, articles written in a language other than English, writings translated from other non-scientific sources, articles presented as consensus or expert-based assertions, and articles authored by a single author.*

years and 7 months) [9]. Patients' follow up in all studies was calculated in months using "The Median" and ranged between (7.1 months [8] and 24 months) [11]. In terms of disease severity, three studies were classified as: advanced stage "Stage III/IV in > 50% of patients" [8,10,11] and limited stage "Stage I/II in < 50% of patients" in three studies [6,7,9].

Strati 2020 United States [11]	Holtzman 2021 United States [8]	Nastoupil 2020 United States [10]	**Author**
Cohort analysis	Retrospective cohort	Retrospective cohort	**Design**
Axi-cel	Axi-cel	Axi-cel	**Product**
100	45	298	**Num**
18-85	26–75	21-83	**Age range (years)**
74 (74)	22 (49)	192 (64)	**Male n (%)**
1 year and 5 months	1 year	2 years	**Duration**
24	7.1	12.9	**Median Follow up (Months)**
84 (84)	All high grade	244 (82.4)	**Disease stage III/IV n (%)**
DLBCL	DLBCL	DLBCL	**Histopathological types**
46/46	36.5/49	82/64	**ORR/CR (%)**
6//6	Not reached//15.1	8.3//not reached	**Median Progression-free survival (PFS)//overall survival (OS) in month**
97/68	80/55.5	91/7	**CRS "Any grade/grade ≥3" %**
41/61	56/72	69/31	**Neurotoxicity "Any grade/grade ≥3" %**
NA	14	14 (3-66)	**Median LOS (range)**
64 (64)	36 (80)	170 (62)	**Tocilizumab use n (%)**
44 (44)	24 (53.3)	149 (54)	**Steroid use n (%)**
51%	11%	33%	**Transferred to ICU**
36 (36)	1 (2.2)	97 (32.5)	**Patients progressed and/or Died n (%)**
4 over 8	6 over 8	4 over 8	**Study Quality (NOS)**

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Ghafouri 2021 United States [7]	Abramson 2020 United States [6]	Jacobson 2020 United States [9]
Retrospective cohort	Multicenter trial	Multicenter trial
Axi-cel	Liso-cel	Axi-cel
53	344	122
18-82	54-70	21-79
31 (58)	174 (65)	NA
2 years 8 months	3 years 7 months	1 year
15.2	18.8	10.4
14 (26)	48 (14)	56 (46)
Relapsed/refractory (R/R) aggressive B-cell lymphomas (aBCL)	DLBCL (51%), High-grade B-cell lymphoma (13%)	DLBCL (43%), tFL (27%), HGBL (14%), and PMBL (7%).
79/64	54/39.5	70/50
7.9/17.7	6.8/21.1	4.5/12
63/6	42/2	93/16
12/19	30/10	70/35
NA	5 (3-22)	16 (7-77)
24 (45)	101 (38)	81 (66)
21 (40)	26 (10)	65 (53)
28.3	0.29%	28%
0 (0)	1 (0.29)	1 (0.8)
5 over 8	6 over 8	4 over 8

Table 1: *Baseline characteristics of the study populations in the included studies in qualitative synthesis.*

Study variables

Diffuse large B cell lymphoma was the main histopathological finding in all studies. and patients as designed, received Axi-cel in five studies "as drug of study intervention", and Liso-cel in one study [6]. Efficacy was measured through predetermined criteria traced by the six studies. Overall response rate and complete response reached 70 - 82% and 50 - 64% respectively [7,9,10]. Median Progression-free survival (PFS) and overall survival (OS) 4.5 - 8.3 months [6,7,9-11] and 6 - 21.1 months [6-9,11] respectively. These findings were for all the patients on these studies. Cytokine Release Syndrome "any grade" occurred at a rate of 42 - 63% in two studies [6,7], and 80 - 97%

in four studies [8-11]. CRS/grade ≥ 3 occurred at rate of 2 - 16% in 4 studies [6,7,9,10] and 55 - 68% in 2 studies [8,11]. Neurotoxicity (ICANS) "any grade" occurred at a rate of 12 - 30% in two studies [6,7], and 41 - 70% in 4 studies [8-11]. ICANS/grade ≥ 3% occurred at rate of 10 - 35% in 4 studies [6,7,9,10] and 61 - 72% in 2 studies [8,11]. Median hospital length of stay (LOS) in days ranged from 5 - 16 in 4 studies [6,8-10]. 0.29% of patients were transferred to ICU due progression of the disease in one study [6], while other studies were as follows: 11 - 33% of patients were transferred to ICU in 4 studies [7-10] and 51% in one study [11]. Number of patients died was one patient in 3 studies [6,8,9], 36 (36%) in one study [11] and 97 (32.5%) in other [10], in terms of total population in all studies. In terms of study quality assessed by New-castle Ottawa Scale, 3 studies were 4/8 [9-11] one study 5/8 [7] and 2 studies 6/8 [6,8]. The excluded study from metanalysis was conducted by Frigault and colleagues [32]. This study was conducted on 12 patients (all of them were CNS positive case) 7 males and 5 females with median age of 63 years (34 - 81 years), FU median time was 12.2 months, CRS was reported in seven patients, ICANS in 5 patients, OR in seven patients, CR in 6 patients with no deaths. The results indicate that CAR T-Cell therapies is efficacious in treatment of Lymphoma patients with CNS. ORs, RRs, CRs, Univariate versus multivariate analysis of the findings presented in details in supplementary table 1.

Author (Year), Country	Objectives	Sample Size	Age	Gender	Study Design	Intervention	Follow up	Results
Abramson, 2020 USA [6]	To assess the activity and safety of liso-cel in patients with relapsed or refractory large B-cell lymphomas	N = 269 n = 6	≥ 63 (54-70) years	Male = 174 (65%) Female = 95 (35%)	Multicenter, multicohort, seamless design	The CAR in liso-cel comprises an FMC63 monoclonal antibody-derived single-chain variable fragment, immunoglobulin G4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3ζ activation domain. To manufacture liso-cel, CD8+ and CD4+ T cells are selected from each patient's leukapheresis Liso-cel cells a median of 3 days (IQR 3–4) after lymphodepleting che- motherapy. The liso-cel–treated set included all patients who received at least one dose of liso-cel. In case a patient received multiple liso-cel doses, the first dose of liso-cel should have been a conforming product, which met specification at the time of product release.	2 Years	Liso-cel can lead to rapid and durable remission, with low incidence of all-grade and severe cytokine release syndrome and neurological events among patients with high-risk aggressive relapsed or refractory large B-cell lymphomas.

Holtzman, 2020 USA [8]	Ghafouri, 2021 USA [7]
To evaluate a single-center analysis of ICANS after CAR T-cell therapy in R/R LBCL	To evaluate the safety and efficacy outcomes of real-world patients with R/R aBCL receiving the commercial CD19-directed CAR-T cell products axi-cel and tisagenlecleucel, at a large tertiary academic center, with a focus on the DHL/THL cohort
N = 45 n= 2	N=53 n= 7
60 years (26-75)	63 years (18-82)
Male= 22 (49%) Female = 23 (51%)	Male = 31, (58%) Female = 22 (48%)
Cohort Study	Retrospective Cohort Study
Axi-cel	Axi-cel Tisa-cell
10.4 Months	15.2 months
Among the axi-cel–treated patients, grade ≥ 3 cytokine release syndrome and neurotoxicity occurred in 7% and 31%, respectively. Nonrelapse mortality was 4.4%. Best overall and complete response rates in infused patients were 82% (95% CI, 77% to 86%) and 64% (95% CI, 58% to 69%), respectively. At a median follow-up of 12.9 months from the time of CAR T-cell infusion, median progression-free survival was 8.3 months (95% CI, 6.0 to15.1 months), and median overall survival was not reached.	Early efficacy of CAR-T therapy is agnostic to baseline patient- and disease-related characteristics, but there may be certain features that predict for inferior longer-term outcomes. While our series suggest DHL/THL is a predictor for less durable response to CAR-T therapy, patient numbers limit the strength of these conclusions and additional study is warranted.

Nastoupil., 2020 USA [10]	Jacobson, 2020 USA [9]
To report clinical outcomes with axi-cel in the standard-of-care (SOC) setting for the approved indication	To describes the efficacy and safety correlates and outcomes in aggressive B-cell non-Hodgkin lymphoma in part based on durable remission rates of approximately 40% in a clinical trial population
N = 298 n= 21	N= 120 n = 1
60 (21-83)	60 (21-79)
Male = 192 (64%) Female = 106 (36%)	No Information
Cohort study	Retrospective Cohort
Axi-cel	Axi-cel
13.8 Months	10.4 Months
9 individuals reported major depression: 5 (10.2%) in usual care and 4 (9.1%) in PST group. 23 individuals met the criteria for minor depression: 18 (36.7%) in usual care group and 15 (34.1%) in PST.	overall survival (OS) was NR; 1-year OS was 67% (95% CI, 59% to 77%). Although response rates were similar in the ZUMA-1–eligible and ZUMA-1–ineligible groups (70% v 68%), there was a statistically significant improvement in CR rate (63% v 42%, P = .016), DOR (median, NR v 5.0 months; P = .014), PFS (median, NR v 3.3 months; P = .020), and OS (1-year OS, 89% v 54%; P < .001) in patients who were ZUMA-1 eligible.

Strati., 2020 USA [11]	To report the results from a cohort analysis of 100 patients with relapsed or refractory LBCL treated at our institution with standard of care axi-cel, and describe the clinical, neuroradiologic, and electroencephalographic correlates of ICANS	N=100 n = 8	60 (18-85)	Male = 74 (74%) Female = 26 (26%)	Cohort Study	Axi-cel	Not Given	Of 100 patients included in the study, 68 (68%) developed ICANS of any grade and 41 (41%) had grade ≥3. Median time to ICANS onset was 5 days, and median duration was 6 days. ICANS grade ≥3 was associated with high peak ferritin (P = .03) and C-reactive protein (P = .001) levels and a low peak monocyte count (P = .001) within the 30 days after axi-cel infusion. Magnetic resonance imaging was performed in 38 patients with ICANS and revealed 4 imaging patterns with features of encephalitis (n = 7), stroke (n = 3), leptomeningeal disease (n = 2), and posterior reversible encephalopathy syndrome (n = 2). Abnormalities noted on EEG included diffuse slowing (n = 49), epileptiform discharges (n = 6), and nonconvulsive status epilepticus (n = 8). Although reversible, grade ≥3 ICANS was associated with significantly shorter progression-free (P = .02) and overall survival (progression being the most common cause of death; P = .001).

Supplementary Table 1: *Characteristics of included studies (Objectives, intervention and results).*

Risk of bias assessment

The assessment of risk of bias is presented in table 2. Overall, risk of bias was relatively low with regards to the data (focused on in this review) that were the focus of this review. The most common methodological problems related to justification of sample size, the use of self-selecting samples, blinding of researchers, and sample characteristics. No study justified their sample size in terms of power calculations. This may mean that analyses were underpowered in some cases, leading to inflated type II error rates. Attempts at blinding researchers or interviewers to participants' status were rarely undertaken, which may have introduced rater bias and expectancy effects.

In terms of methodological issues, no study involving group comparisons attempted to match groups on key socio-demographic variables (e.g. age, gender, ethnicity, socio-economic status). Hence confounding variables are likely to have biased group comparisons. Missing data appeared minimal (i.e. < 20%) for a large proportion of studies, and in cases where missing data was apparent, appropriate details were provided in terms of how this was managed (e.g. use of imputation strategies to minimize bias). Finally, the analytic techniques adopted were appropriate in most studies (Table 2).

Authors	Unbiased selection	Selection minimizes baseline differences in demographic factors	Sample size calculated	Validated method for ascertaining clinical status or participant group	Blind outcome assessment	Adequate follow-up period	Adequate handling of missing data	Appropriate analytic methods
Abramson, 2020 [46]	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Ghafouri, 2021 [47]	Yes	No	No	Yes	No	Yes	Yes	Yes
Holtzman., 2020 [48]	Yes	Yes	No	Yes	N/A	Yes	Yes	Yes
Jacobson 2020 [49]	Yes	No	No	Yes	N/A	Yes	Unclear	Yes
Nastoupil 2020 [50]	Yes	No	No	Yes	N/A	N/A	Yes	Yes
Strati 2020 [51]	Yes	No	No	Yes	N/A	N/A	Yes	Yes

Table 2: *Risk of bias assessment of the included studies. N/A= Not Applicable.*

Meta-analysis

The aim of the included studies was to explore the efficacy and safety of CAR T-Cell therapies in lymphoma patients with and without central nervous system involvement. Studies were synthesized quantitatively through fixed effect meta-analysis where five studies were available for single outcome. Studies were synthesized quantitatively through a random effect meta-analysis. Random effect meta-analysis assumes that variation between studies or heterogeneity is not only because of random error, also known as random variation (e.g. sampling error) but studies have inherent difference primarily due to difference in methodologies and test accuracy. In this review, included studies varied greatly in their laboratory methodologies and molecular studies. These variations are accounted by τ^2 in random effect

meta-analysis. Heterogeneity was minimum among the included studies indicating that the difference between the studies was primarily the result of random error within studies. Chi-square indicates that studies are homogenous between studies $I^2 = 0$, df = 3 (p = .040). Results of meta-analysis indicate that overall effect size favors therapies in Lymphoma Patients without Central Nervous System Involvement (no CNS) in comparison to Lymphoma with CNS (Figure 2).

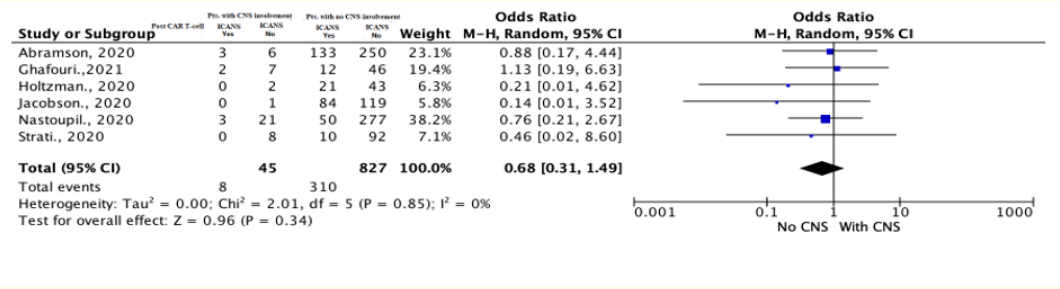

Figure 2: *Forest plot of the random-effects meta-analysis of the association between CNS-No CNS efficacy and safety. CI: Confidence Interval; OR: Odds Ratio, ICANS: Immune Effector Cell Associated Neurotoxicity.*

We conducted subgroup analysis to compare the findings between the CNS negative population (n = 827) included in the studies and those patients who had CNS involvement (n = 45). We measured the efficacy and the safety through pre-determined parameters discussed in the selected studies; ORR (overall response rate), CR (complete response), CRS (cytokine release syndrome), ICANS, ICU admission and progression of disease or death. The ORR (overall response rate) was reported for 619 patients with BCL from the six selected studies, and reported among 16/45 patients with CNS involvement. ORR (overall response rate); the pooled "OR" (95% CI) was 73.5% (36.5 - 82%) (Figure 3), and The CR (complete response) was reported for 490 patients with BCL from the six selected studies, the pooled "CR" rate (95% CI) was 62.5% (39.5 - 64%) (Figure 4). The CRS "Grade ≥ 3" was reported for 144 patients with BCL from the six selected studies and reported among 6/45 patients with CNS involvement. and at "Grade ≥3", the CRS was 30.9% (95% CI, 21 - 68%) (Figure 5). The ICANS rate in patients with CNS involvement was 8/45 and was 310/827 in patients without CNS involvement. The ICU admission was reported for 204 patients with BCL from the six selected studies and reported among 12/45 patients with CNS involvement. ICU admission; the pooled "OR" (95% CI) was 30.31% (29 - 51%) (Figure 6). The progression of the disease/death was reported for 136 patients with BCL from the six selected studies, and reported in one case with CNS involvement. The "progression of the disease/death"; the pooled "OR" (95% CI) was 14.35% (8.5 - 36.2%) (Figure 7).

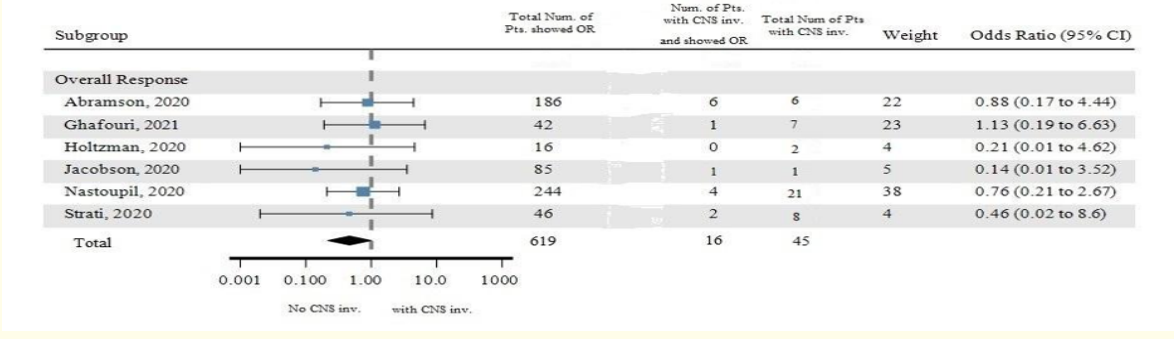

Figure 3: *Subgroup analysis forest plot of the random-effects meta-analysis of the association between efficacy and safety of CAR-T cell therapy. CI: Confidence Interval; OR: Odds Ratio. Overall response, $Tau^2 = 0.00$; $Chi^2 = 1.89$, df = 4 (P=0.81); $I^2 = 0\%$ Test of overall effect: Z = 0.96 (P = 0.31).*

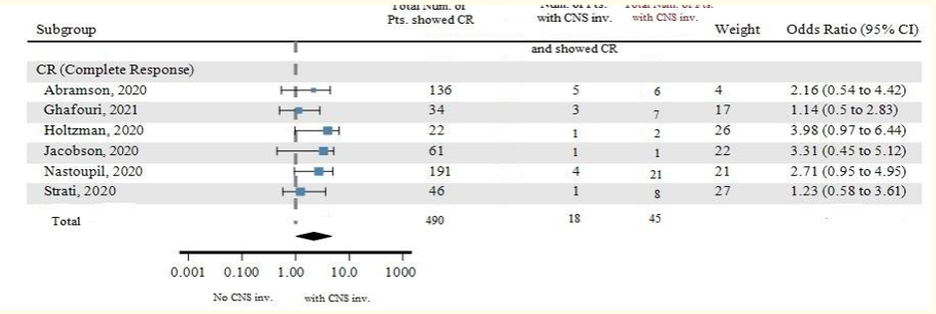

Figure 4: *Subgroup analysis forest plot of the random effects meta-analysis of the association between efficacy and safety of CAR T cell therapy. CI: Confidence Interval, OR: Odds Ratio, Complete response, Tau² = 0.00; Chi² = 1.91, df = 5 (P = 0.11); I² = 0% test of overall effect: Z = 0.96 (P = 0.46).*

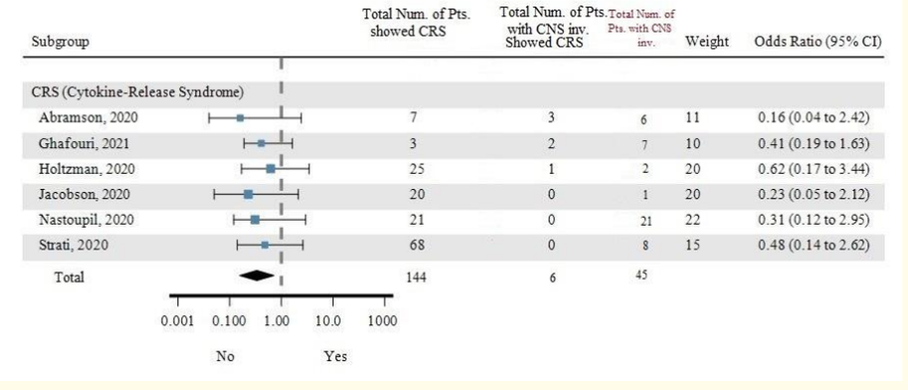

Figure 5: *Subgroup analysis forest plot of the random-effects meta-analysis of the association between efficacy and safety of CAR-T cell therapy. CI: Confidence Interval; OR: Odds Ratio. CRS, Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.56); I² = 0% Test of overall effect: Z = 0.96 (P = 0.07).*

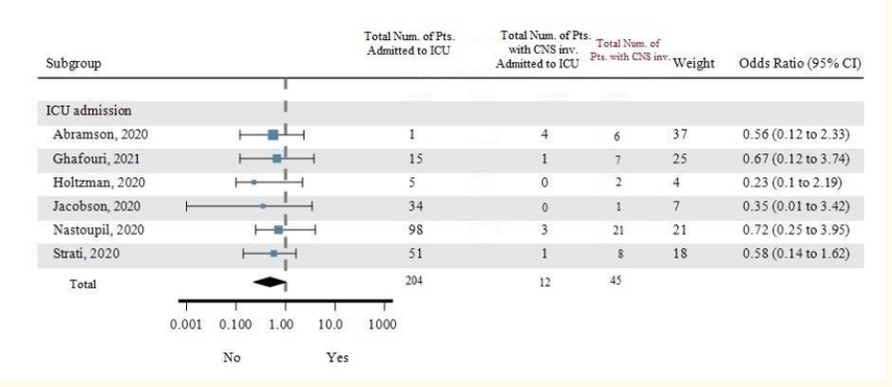

Figure 6: *Subgroup analysis forest plot of the random-effects meta-analysis of the association between efficacy and safety of CAR-T cell therapy. CI: Confidence Interval; OR: Odds Ratio. ICU admission, Tau² = 0.00; Chi² = 2.05, df = 6 (P = 0.52); I² = 0% Test of overall effect: Z = 0.96 (P = 0.17).*

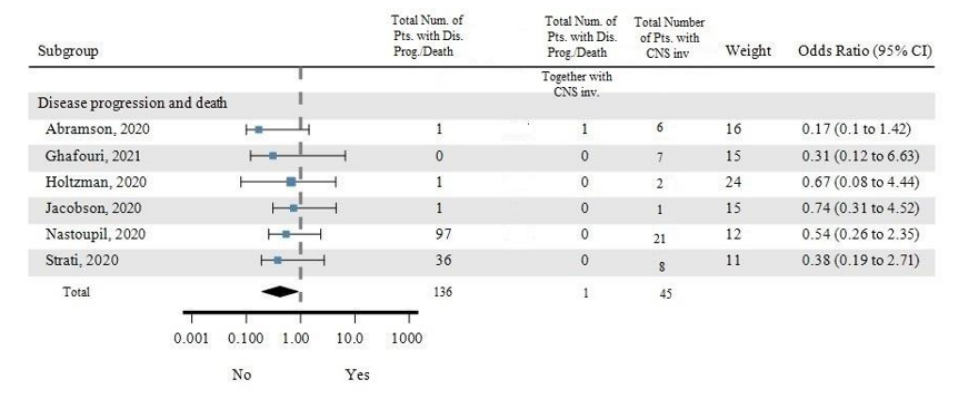

Figure 7: *Subgroup analysis forest plot of the random-effects meta-analysis of the association between efficacy and safety of CAR-T cell therapy. CI: Confidence Interval; OR: Odds Ratio. Disease progression and death, $Tau^2 = 0.00$; $Chi^2 = 1.19$, $df = 3$ ($P = 0.62$); $I^2 = 0\%$ Test of overall effect: $Z = 0.96$ ($P = 0.49$).*

Publication bias

Finally, we consider the potential impact of publication bias in the literature examined in these meta-analyses. For the outcome, funnel plot is showing each study plotted by study precision and result are presented in figure 8 visual inspection of these funnel plots suggests that across the outcome, studies were symmetrically distributed. That is, we found no evidence for publication bias in literature included in the present meta-analyses. Given that no indication of publication bias was found, no adjustments were needed according to trim-and-fill analysis in all analyses (Figure 8).

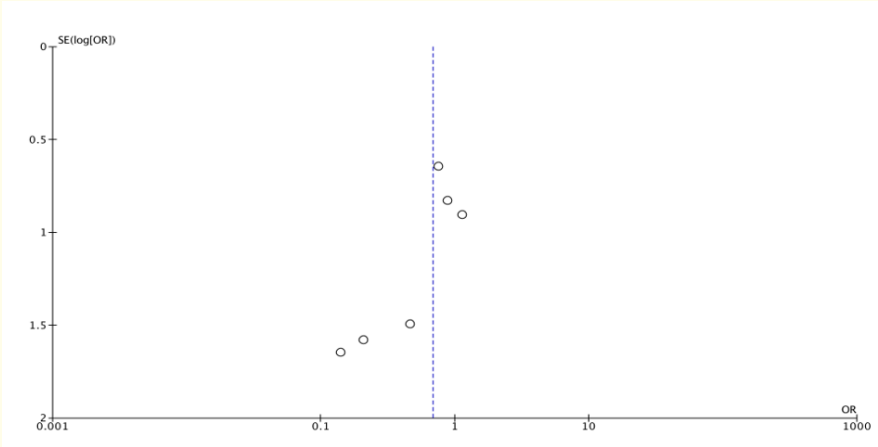

Figure 8: *Funnel plot to assess publication bias in the included studies.*

Discussion

CAR T-cell therapy is associated with distinct toxicities such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), on-target-off-target toxicities, and extended cytopenia [33]. To our knowledge this is the first systematic review and meta-analysis looking into the efficacy and safety of CAR T-Cell therapies in lymphoma patients with central nervous system involvement. The efficacy and safety of CAR T-cell therapy have improved significantly since the inception of this new therapeutic modality [34]. The initial constructs showed limited efficacy and significant toxicities [35-37]. With ICANS being one of the significant side effects of CART cell, the registration studies of the commercially available products avoided the inclusion of lymphoma patients with CNS disease [38,39,45]. Currently with data emerging about the feasibility of CART cell in patients with CNS involvement, more and more patients with CNS involvement are being treated with this modality. A recent study reported on 55 patients with ALL and CNS involvement showed that this modality is safe and not associated with higher CNS toxicity profile in patients with CNS involvement [40]. Another retrospective analysis of lymphoma patients with CNS involvement showed acceptable toxicity [42].

We restricted this systematic review and meta-analysis to studies that reported on both patients with and without CNS involvement, case reports, letters to editor and studies that did not report both patients with and without CNS involvement were excluded [41-44].

Of the 872 patients from the six included trials, 45 patients had CNS involvement (ICANS). Looking into the OS, PFS, ICANS, CRS and ICU admission rate of patients with versus those without CNS involvement, no statistically significant difference was seen.

In general, all the reported studies addressing the use of CAR-T cell in patients with CNS lymphoma showed acceptable safety profile, comparable to the safety profile in patients with no CNS involvement. The efficacy needs longer follow up and a higher number of patients for the data to mature, but in general the archived responses do not seem sustainable [45].

Conclusion

Our study along with several other reports show that it is safe to use CART cell in patients with CNS involvement, even in patients with active CNS disease at the time of infusion. Collaborative groups are planning prospective trials to address this question. The reported literature may suffer from reporting bias; however, the procedure seems to be safe for a group of patients that has (have) no other approved therapeutic options. Different CART cell constructs may have different toxicity/efficacy profiles and unfortunately none of them were compared in head to head prospective trials. Ideally, every construct should be assessed separately, and hopefully in the future, safer constructs and constructs with better CNS efficacy will be introduced for this group of patients in need.

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