Hematology and Oncology Discovery

Review

Chimeric antigen receptor engineered T-cell therapy for central nervous system lymphoma

Tiantian Sun[a,b], **Mi Zhou**[b], **Liang Huang**[b,*]

[a]Department of Hematology, The Seventh Affiliated Hospital, Sun Yat-Sen University, Shenzhen, China
[b]Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

***Correspondence:** lhuang@tjh.tjmu.edu.cn (L. Huang)

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ABSTRACT

Central nervous system lymphoma (CNSL) includes primary and secondary subtypes. It is associated with poor prognosis even after aggressive therapies. Primary CNSL involves mainly the brain, eyes, leptomeninges and spinal cord, without evidence of systemic non-Hodgkin's lymphoma (NHL). Secondary CNSL refers to involvement of the CNS secondary to systemic NHL. Chimeric antigen receptor T (CAR-T) cells are genetically engineered T-cells directed against tumor target antigens. CAR-T-cells have shown encouraging results in treating B-cell malignancies. Clinical data on CAR-T-cells in CNSL treatment are limited, because of concerns regarding the immunoprivileged status of the CNS and the possibility of immune effector cell-associated neurotoxicity syndrome. Clinical trials on CAR-T therapy for CNSL are increasingly being conducted to evaluate its efficiency and safety since CAR-T-cells have been detected in the cerebrospinal fluid from a patient with PMBCL who received CAR-T-cell therapy. Current data suggest that CAR-T-cells are an emerging therapeutic modality for CNSL with clinical benefits and acceptable adverse effects. However, whether CAR-T therapy may be a promising therapeutic avenue remains controversial, because evidence from large-scale randomized clinical trials remains lacking. Herein, we provide a review of existing clinical data on CAR-T-cell therapy for CNSL, discuss the limitations of CAR-T-cells in CNSL treatment and hypothesize strategies to overcome these challenges.

Keywords: Central nervous system lymphoma, Chimeric antigen receptor T-cell, immune effector cell-associated neurotoxicity syndrome

1. INTRODUCTION

Central nervous system lymphoma (CNSL) is an uncommon malignant tumor of the CNS, comprising 1%–6% of CNS tumors [1, 2]. CNSL is divided into primary central nervous system lymphoma (PCNSL) and secondary central nervous system lymphoma (SCNSL). PCNSL is a rare type of diffuse large B-cell lymphoma (DLBCL) originating in the brain parenchyma, spinal cord, eyes or meninges, without evidence of systemic dissemination [3]. It accounts for 3% of primary CNS tumors and 1% of non-Hodgkin's lymphoma (NHL) in adults [4, 5]. The 5-year survival rate for PCNSL is 30.1% [6–8]. Approximately 16%–26% of PCNSL cases do not initially respond to high-dose methotrexate [9, 10], but most patients relapse within 5 years of treatment [6]. SCNSL is defined by CNS involvement secondary to recurrent or progressive systemic lymphoma outside the CNS [11]. It also refers to isolated CNS relapse after primary systemic lymphoma remission [11]. CNS invasion occurs in 10%–30% of DLBCL [11] and 0.2%–0.6% of Hodgkin's lymphoma cases [12–14]. The median survival time after diagnosis of SCNSL is approximately 2–6 months [15–20]. In patients with CNSL, high-dose methotrexate based chemotherapeutic regimens followed by autologous stem cell transplantation (ASCT) or radiotherapy have been found to significantly improve survival rates [10, 11, 21–26]. However, only a minority of patients can achieve long-term progression-free survival (PFS) and overall survival (OS) [11, 20, 27, 28]. Although novel agents such as Bruton tyrosine kinase inhibitors, immunomodulatory drugs, PI3K/AKT/mTOR inhibitors and checkpoint inhibitors have exhibited promising efficacy, the outcomes for these patients remain dismal [29–32]. Novel, efficacious and safe therapies are urgently required for relapsed or refractory (R/R) CNSL.

Chimeric antigen receptor (CAR) is a synthetic protein with major components: an antigen-recognition moiety,

a T-cell signaling domain and a costimulatory domain [33, 34]. In cancer immunotherapy, CAR is expressed in genetically modified T-cells that specifically recognize tumor-specific antigens, thereby inducing an acquired antitumor immune response [35, 36]. CAR-T-cell therapy has shown encouraging clinical responses in R/R B cell malignancies by targeting CD19, CD20 or CD22 [37–44]. In 2014, CD19 CAR-T-cells administered intravenously were first detected in cerebrospinal fluid (CSF) from two patients with B-cell lymphoma with CAR-T-associated neurotoxic effects [42], thus suggesting that CAR-T-cells effectively penetrate the CNS. Therefore, a strong biologic rationale exists for treating R/R CNSL with CD19/CD20/CD22-specific CAR-T-cells. However, patients with CNSL have been excluded from most of the major trials because of poor response and the possibility of immune effector cell-associated neurotoxicity syndrome (ICANS) after CAR-T-cell treatment. Given the limited available clinical trial data for patients with CNSL receiving CAR-T-cell therapy, no definitive conclusion has been reached regarding whether CAR-T-cell therapy is a safe, efficacious and long-lasting therapeutic avenue. In this review, we summarize the most important clinical data on CAR-T-cell treatment for CNSL, discuss the potential mechanisms responsible for resistance, and discuss strategies to enhance its efficacy and to optimize its role in the therapeutic armamentarium for CNSL.

2. CLINICAL DATA

2.1 Clinical data on CD19 CAR-T therapy for CNSL

A preponderance of evidence has demonstrated that CD19-targeted CAR-T-cell therapy significantly improves CNSL prognosis. Simultaneously targeting other tumor antigens, including CD20, CD22 and CD70, is also a therapeutic option. To date, CAR-T-cells specific for multiple antigens have been developed, at least three of which have been evaluated in patients with CNSL in clinical trials. Given the rarity and poor prognosis of CNSL, each clinical trial has usually enrolled fewer than twenty patients with R/R CNSL. All the clinical trials described in this review are summarized in **Table 1**.

CD19-targeted receptors are currently the most investigated CAR-T-cell product. The US Food and Drug Administration has approved axicabtagene ciloleucel (Axi-Cel), tisagenlecleucel (Tisa-Cel) and lisocabtagene maraleucel (Liso-Cel) for B-cell malignancies. CD19 CAR-T-cells were successfully applied in SCNSL for the first time in 2017 [47]. A patient with primary refractory DLBCL with CNS involvement has been reported to achieve complete remission (CR) at the site of cerebral lymphoma with Liso-Cel. The remission lasted 12 months, and no CRS or ICANS was observed. CD19 CAR-T-cells were identified in the CSF, thus confirming the ability of these cells to migrate from the periphery into the CNS and subsequently mediate anti-tumor effects.

Tisa-Cel has also shown promising efficacy and manageable adverse reactions in CNSL. Frigault et al. [48] (2019.12) have conducted a retrospective study in eight patients with secondary systemic large B-cell lymphoma with CNS involvement, who were treated with Tisa-Cel. Four patients showed an early response to Tisa-Cel at day +28 (two CRs and two partial responses (PRs)). Two patients died because of disease progression within 30 days after CAR-T-cell infusion. Among the four patients who initially responded to treatment, responses were ongoing in three patients at day +90, and only one patient achieved a second CR with radiotherapy after systemic relapse. No patient experienced grade ≥2 CRS or ICANS. In this cohort, active systemic disease was not a prerequisite for CAR-T-cell expansion and disease response, thus suggesting that sufficient intravenously infused CAR-T-cells reached the CNS by crossing the blood-brain barrier (BBB).

A phase I/II study of Tisa-Cel in patients with relapsed PCNSL has recently been reported [49] (2022.2). A total of twelve patients with relapsed PCNSL received Tisa-Cel treatment, with a median follow up of 12.2 months (range, 3.64–23.5 months). Six patients demonstrated CR, one patient demonstrated PR, and three patients had sustained CR at the end of follow-up. Seven patients developed grade 1 CRS, two patients experienced grade 1 ICANS, three patients had grade 2 ICANS, and one patient presented grade 3 ICANS. CD19 CAR-T-cells were expanded in the peripheral blood and CSF.

Ghafouri et al. [51] (2020.11) subsequently demonstrated the feasibility and safety of Axi-Cel in five R/R NHL patients with CNS invasion, three of whom received bridging therapy. The 28-day post-treatment evaluation showed that three patients attainted CR, one patient had stable disease (SD), and one patient experienced disease progression. Of the four responders (three with CR and one with SD), two died of disease progression, and one died of cardiopulmonary failure within 208 days after administration of CAR-T-cells. The remaining responder who underwent ASCT after CAR-T therapy had sustained remission at the end of follow-up. The median PFS and OS of the four responders were 134.2 days and 155.0 days (range, 86–208), respectively. Two patients experienced grade 1 and grade 2 CRS, and supportive care and tocilizumab were provided, respectively. Two patients had grade 3 or grade 4 ICANS and were well managed with supportive care and steroids.

Siddiqi et al. [50] have reported that patients with PCNSL show good tolerance to another studied CD19 CAR-T-cell product engineered to express epidermal growth factor receptor. These CAR-T-cells can be eliminated through targeting epidermal growth factor receptor in the event of severe CAR-T associated toxicity. Of a total of five patients with PCNSL have received these specfic CD19 CAR-T-cells, three achieved CR, and two had SD on day 28 postinfusion. The durations of response for the three patients with CR were 43 days, 273 days and 520 days. All patients developed no greater than grade 2 CRS, and one patient developed grade 3 ICANS. Tocilizumab and steroids were necessary for two patients

Table 1 | Published studies on CAR-T-cells for treatment of primary and secondary CNS lymphomas.

Author	NCT/ ChiCTR	CAR-T-cell dose	Study design	Study population	Conditioning regimen	Concomitant maintenance	Toxicity	Outcome
Li et al. [44]	ChiCTR-OPN-16008526	CD19 CAR-T-cells ($2.0–7.0\times10^6$/kg, n = 5) CD22 CAR-T-cells ($3.0–7.0\times10^6$/kg, n = 1)	Phase 1 clinical trial	PCNSL-DLBCL (n = 1) SCNSL-DLBCL (n = 4)	Flu/Cy (n = 5)	Radiotherapy PD-1 inhibitor ASCT	Grade 1 CRS (n = 4); Grade 2 CRS (n = 1); Grade 1 NT (n = 1); Grade 4 NT (n = 1)	60-day assessment CR (n = 1) PR (n = 4)
Wu et al. [45]	ChiCTR-OPN-16009847	CD19 CAR-T-cells ($2.0–9.2\times10^6$/kg, n = 13) CD22 CAR-T-cells ($2.6–8.4\times10^6$/kg, n = 13)	Phase 1 clinical trial	PCNSL-DLBCL (n = 4) SCNSL-DLBCL (n = 9)	Dox+BEAM (n = 5) TBC (n = 6) TBCF (n = 2)	Auto-HSCT(n = 13)	Grade 1 CRS (n = 9); Grade 2 CRS (n = 2); Grade 1 NT (n = 2); Grade 3 NT (n = 1)	CR (n = 8) PR (n = 3) PD (n = 2)
Tu. et al. [46]	NCT03125577	CD19 CAR-T-cells 1×10^8; CD70 CAR-T-cells 8.2×10^7	Case report on a patient enrolled in a phase 1 clinical trial	PCNSL-DLBCL (n = 1)	Flu/Cy	None	None	30-day assessment: CR 17-month assessment: CR
Abramson et al. [47]	NCT02631044	CD19 CAR-T-cells NP	Case report on a patient enrolled in a phase 1 clinical trial	SCNSL-DLBCL (n = 1)	Flu/Cy	None	None	1-month assessment: CR
Frigault et al. [48]	NCT04134117	Tisagenlecleucel ($0.6–6.0\times10^8$)	Retrospective cohort study	SCNSL-DLBCL (n = 5) SCNSL-HGBCL (n = 2) SCNSL-PMBCL(n = 1)	Flu/Cy	Ibrutinib (n = 2)	Grade 1 CRS (n = 7); Grade 1 NT (n = 4)	28-day assessment CR (n = 2) PR (n = 2) PD (n = 2) Deceased due to PD (n = 2) 90-day assessment CR (n = 2) PR (n = 1) PD (n = 2)
Frigault et al. [49]	NCT02445248	Tisagenlecleucel ($0.6–6.0\times10^8$)	Phase I/II clinical trial	PCNSL-DLBCL (n = 12)	Flu/Cy	Steroid (n = 4)	Grade 1 CRS (n = 7); Grade 1 NT (n = 3); Grade 2 NT (n = 2); Grade 3 NT (n = 1)	CR (n = 6) PR (n = 1)
Siddiqi et al. [50]	NCT02153580	CD19 CAR-T-cells ($1.15–6.0\times10^8$, n = 7)	Retrospective cohort study	PCNSL-DLBCL (n = 5)	NP	NP	Grade 1 CRS (n = 3); Grade 2 CRS (n = 2); Grade 1 NT (n = 3); Grade 2 NT (n = 1); Grade 3 NT (n = 1)	28-day assessment CR (n = 3) SD (n = 2)

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Table 1 | Continued

Author	NCT/ ChiCTR	CAR-T-cell dose	Study design	Study population	Conditioning regimen	Concomitant maintenance	Toxicity	Outcome
Ghafouri et al. [51]	NP	Axicabtagene Ciloleucel	Retrospective cohort study	SCNSL-DLBCL (n = 2) SCNSL-HGBCL (n = 2) SCNSL-PMBCL (n = 1)	NP	NP	Grade 1 CRS (n = 1); Grade 2 CRS (n = 1); Grade 3 NT (n = 1); Grade 4 NT (n = 1)	28-day assessment CR (n = 3) SD (n = 1) PD (n = 1) 208-day assessment Deceased due to PD (n = 4) CR (n = 1)

Abbreviations: NCT: national clinical trial identifier. ChiCTR: Chinese clinical trial register. PCNSL: primary central nervous system lymphoma. SCNSL: secondary central nervous system lymphoma. DLBCL: diffuse large B-cell lymphoma. HGBCL: high-grade B-cell lymphoma. PMBCL: primary mediastinal B-cell lymphoma. Flu: fludarabine. Cy: cyclophosphamide. DOX: doxorubicin. TBC: thiotepa, busulfan, cyclophosphamide. TBCF: thiotepa, busulfan, cyclophosphamide, fludarabine. BEAM: carmustine, etoposide, cytarabine, melphalan. AST: autologous stem cell transplantation. Auto-HSCT: autologous hematopoietic stem cell transplantation. NP: not provided. CRS: cytokine release syndrome. NT: neurotoxicity. CR: complete response. PR: partial response. PD: progressive disease.
Study design, study population, route of CAR-T-cell delivery, antigens, toxicity, patient outcome, and NCT/ChiCTR are indicated.
Maximum CRS and NT were graded according to ASTCT [23]. Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy. ChiCTR: Chinese clinical trial register. CNS: central nervous system. CR: complete response. CRS: cytokine release syndrome. NCT: national clinical trial identifier. NT: neurotoxicity. PD: progressive disease. PR: partial response.

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with severe toxicity, which was reversible and tolerable. Exploratory analyses revealed the presence of CAR-T-cells in the CSF in the absence of systemic lymphoma.

To our knowledge, Xu et al. [52] have conducted the largest clinical trial to date exploring the efficacy and safety of CD19 CAR-T-cell therapy for R/R B-cell acute lymphoblastic leukemia (ALL) with CNS invasion. Severe CRS (grade ≥3) and ICANS (grade ≥3) were observed in 9 (18.8%) and 11 patients (22.9%), respectively. All treatment-associated toxicity symptoms were controllable. CAR-T-cells performed better in CNS than in BM. This study has provided strong evidence supporting the therapeutic potential of CD19 CAR-T-cells in CNS.

2.2 Clinical data on dual CAR-T therapy for CNSL

Despite major advances in CD19 CAR-T therapy in clinical trials, the rates of long-term PFS for patients with R/R CNSL are low. Consequently, dual CAR-T-cells (separate infusions of two different CAR-T-cell products) have been increasingly used in patients with CNSL to improve poor outcomes.

Tu et al. [46] have reported a patient with R/R PCNSL receiving CD19 and CD70 CAR-T-cell infusion, who achieved CR after 1 month. The patient sustained CR for more than 17 months without experiencing CRS or ICANS. Both CD19 and CD70 CAR-T-cells were detectable at the 10th month after infusion.

To date, CD 19 specific and CD22 specific CAR-T therapies in CNSL have been evaluated in two clinical trials. In 2020, Li et al. [44] reported on four patients with R/R SCNSL and one patient with R/R SCNSL receiving CAR19 and CAR22 T-cell cocktail therapy and follow-up for 6–16 months. In the 2nd month after infusion of CAR19 and CAR22 T-cells, CR and PR were achieved in one and four patients, respectively. PD was observed in three patients at the 3rd month, and relapse occurred in one patient at the 8th month; the remaining patient received CAR-T-cell infusion after ASCT, and remission lasted for 14 months. The median PFS was only 3 months. No patient experienced greater than grade 2 CRS. Grade 1 and grade 4 ICANS were observed in one patient each. ICANS was completely reversible by glucocorticoid and plasma exchange. All patients had CAR-T-cell expansion in CSF. CAR-T-cells targeting a single antigen were effective, but the reasponse was not durable for patients with CNSL. Hence, Wu et al. [45] have explored the efficacy, perisitence and safety of CD19/22 CAR-T-cells administered after ASCT in four patients with PCNSL and nine patients with SCNSL, including two patients with CR at enrollment. Among the remaining 11 patients, 6 attained CR, and 3 attained PR within 3 months; the median duration of response was 14.03 months. The overall response rate and complete remission rate were 81.81% and 54.55%, respectively. The estimated 1-year PFS and OS rates were 74.59% and 82.50%, respectively. Two patients did not respond to this therapy and died because of PD, with a median survival time of 2.33 months. No patient experienced grade 3 or 4 CRS, and only one patient experienced grade 3 ICANS. The novel treatment with sequential CD19/22 CAR-T-cell therapy after ASCT for patients with CNSL appeared to have encouraging long-term efficacy with controllable adverse effects.

3. POSSIBLE MECHANISMS UNDERLYING THE EFFECTS OF CAR-T- CELL THERAPY FOR CNSL

The BBB is an important physiological barrier that separates the CNS from the peripheral circulation, and regulates cellular and molecular exchange between the blood vessels and brain parenchyma. It is a crucial obstacle in the delivery of drugs into the CNS [53]. Moreover, the selective properties of the BBB and the blood-CSF barrier strictly limit the entry of immune cells into the CNS [53]. Recently, impressive clinical regression of CNS tumors has been achieved with engineered CAR-T-cells in many clinical trials. After systemic administration, CAR-T-cells traffic to the CSF and mediate anti-tumor effects without direct neurotoxicity [54]. The exact mechanism through which CAR-T-cells cross the BBB remains unclear.

3.1 Endothelial activation and BBB disruption

Peripheral inflammation mediates BBB disruption through multiple pathways [53]. Gust et al. [55] have revealed that in CAR-T therapy-associated ICANS, high levels of IL-6, IFN-γ and TNF-α activate endothelial cells, thus increasing BBB permeability. A patient with fatal neurotoxicity has presented endothelial activation and multifocal vascular disruption in the brain. Preclinical data have demonstrated that CAR-T-cells delivered intraventricularly are detectable in the peripheral blood of mice for more than 300 days, even without detectable lymphoma [56]. Single-cell RNA sequencing analysis has indicated that CD19 expressed in human and mouse brain mural cells is highly important for the integrity of the BBB [57]. Administration of CD19-specific CAR-T-cells can cause BBB disruption and pericyte depletion in mice lacking B cells [57]. CAR-T-cells have been postulated to penetrate the BBB, enter the CNS, and mediate anti-tumor effects through activating endothelial cells and disrupting the BBB. The detailed pathophysiology remains poorly understood.

3.2 The cerebroventricular environment enhances CAR-T-cell potency

CAR-T-cell delivery into resection cavities or administration into the CSF are feasible in glioblastoma [58]. Regional intraventricular (ICV) injection of CAR-T-cells for CNSL has not yet been conducted. In a murine lymphoma model, Wang et al. [56] have observed that CAR-T-cells infused ICV not only eradicate CNSL, but also migrate to the periphery, home to systemic tumors and expand in vivo, thus completely eliminating systemic lymphoma. They have further found that CAR-T-cells exposed to the CSF in the ICV environment exhibit superior anti-lymphoma activity and memory function [56],

thus suggesting that the cerebroventricular environment may improve the efficacy of CAR-T-cells. However, similar phenomena have not yet been confirmed in immunocompetent animal models.

4. CURRENT CHALLENGES AND POTENTIAL STRATEGIES FOR CAR-T-CELL THERAPY IN CNSL

Although several studies have reported the anti-tumor effects of CAR-T-cells, the rates of long-term PFS in patients receiving CAR-T-cell treatment remain low. Morever, the concurrent toxicity limits clinical applications. A summary of possible reasons for the poor efficacy of CAR-T-cells is as follows.

4.1 Low CAR-T-cell persistence

The short lifespan of CAR-T-cells critically impairs the efficacy of CAR-T therapies [59–61]. CAR construction, ex vivo manipulation and T-cell exhaustion may contribute to the low persistence of CAR-T-cells.

Compared with murine CAR-T-cells, humanized CAR-T-cells show enhanced persistence and diminished T-cell depletion, owing to lower immunogenicity and less antigen-independent tonic signaling [62–64]. CD28-CAR enhances T-cell effector funtion but has limited effects on durability, whereas 4-1BB-CAR and ICOS-CAR exhibit opposite functions [65–69]. Drent et al. [70] have shown that, in contrast to a single 4-1BB domain in CAR, CAR-T-cells with both CD28 and 4-1BB domains have superior efficacy and persistence. Beyond improvements in the design of CAR-T-cells, CAR-engineered NK cells and macrophages have been found to have anti-tumor effects [71–74] and thus are likely to be promising strategies for CNSL treatment. However, experience with CAR-NK cells and CAR-macrophages is restricted mainly to preclinical investigations. Dual targeting CAR-T-cells are also a novel therapy for CNSL [44–46].

The type of T-cells used for infusion critically affects the success of CAR-T therapy. Previous chemotherapeutic strategies containing clofarabine or doxorubicin may result in lymphopenia or lead to poor quality of the final CAR-T-cell products. Improved persistence and efficacy of CAR-T-cell treatment can be achieved with early lineage cells with enriched T-cell populations [75, 76]. Before CAR-T-cell infusion, the most common lymphodepleting chemotherapy regimen containing cyclophosphamide (Cy), fludarabine (Flu), and bendamustine (Ben) was used to eradicate regulatory T-cells (Tregs) and other immunosuppressive cells, thus increasing CAR-T-cell expansion and prolonging their persistence [77, 78]. Hirayama et al. [79] have used high dose cy-flu lymphodepletion for patients with aggressive B-NHL and found that patients with favorable cytokine profiles have longer PFS. Therefore, enhancing the efficacy of CAR-T-cell therapy is more dependent on biological effects steming from lymphodepletion therapy than on the intensity of lymphodepleting treatments. Adequate lymphodepletion is essential for obtaining optimal clinical benefits from CAR-T-cell treatment.

The tumor microenvironment impairs T-cell function and number, thereby influencing the persistence of CAR-T-cells in tumors [80–82]. CAR-T-cells also progressively languish under persist chronic antigen exposure [83]. In an acute myeloid leukemia model, the PI3K/AKT pathway leads to low persistence of CD33-specific CAR-T-cells, whereas PI3K inhibitor treatment increases the durability and prolongs the efficacy of CAR-T-cells [84]. Exhausted T-cells overexpress inhibitory receptors, such as Programmed Cell Death Protein 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [85–87]. Thus, increased anti-tumor effects have been observed in brain tumor models when a PD1-directed domain was incorporated into CARs or CAR-T-cells were used in combination with checkpoint-blocking antibodies [88]. PD1 inhibitors have been demonstrated to prolong the action of CAR-T-cells and enhance their anti-tumor efficacy in B-cell lymphoma and ALL [89, 90]. Blockade of TIM-3 or CTLA-4 has been hypothesized to improve the efficacy of CAR-T therapy. In addition, many studies have revealed the anti-lymphoma effects of Bcl-2 CAR-T-cells and confirmed the rationale for combining CAR-T-cells and Bruton tyrosine kinase inhibitors/PI3K inhibitors/HDAC inhibitors/rituximab [91–99]. To date, combination therapy for blockade of multiple immune checkpoints/targeted agents and CAR-T-cells for CNSL has not been reported. Thus, further studies remain needed to confirm the efficacy and safety of different combination therapies.

4.2 The delivery route of CAR-T-cells

The traditional delivery route of CAR-T-cells is intravenous administration. To improve treatment efficacy, CD19 CAR-T-cells were first administered ICV to NOD-scid IL2R γ-/- mice with CNS and/or systemic lymphoma [56]. The ICV-administered CAR-T-cells eradicated CNSL more efficiently than IV infused CAR-T-cells [56]. Agarwalla et al. [100] have recently generated an implantable multifunctional alginate scaffold for T-cell engineering and release (MASTER), which provides a new control interface for viral vector-mediated gene transfer. It shortens the time required to prepare CAR-T-cells and regulates their functions in mice. In comparison to conventional CAR-T-cells, CAR-T-cells generated in vivo, induced by MASTER, have better persistence in a mouse lymphoma model. Altering the route of administration may be a valuable new strategy to enhance the efficacy of CAR-T-cells.

4.3 Antigen escape

After CAR-T-cell therapy, tumoral target antigen escape may contribute to relapse. Maude et al. [101] have reported that 15 patients with recurrent B-cell ALL after Tisa-Cel infusion displayed complete loss of

CD19 expression. Downregulation/loss of CD19 antigen was observed in 30%–70% of patients with ALL who had recurrent disease after CD19 CAR-T-cell treatment [102, 103]. Antigen escape may also be involved in the recurrence of CNSL after CAR-T infusion [104]. However, few large-scale high-quality data are available regarding antigen escape in CNSL. A strategy to decrease the relapse rate caused by antigen escape or loss is concomitant targeting of multiple target tumor antigens. CD19-CD20/CD19-CD22 bispecific CAR-T-cells or dual-targeted (CD19/CD22) CAR-T-cells have demonstrated promising results [105–108]. Further exploration of optimal target antigens is necessary to prevent CNSL relapse, through improving the anti-tumor response and decreasing antigen escape.

4.4 CAR-T-cell associated toxicity

CAR-T-cell therapies are associated with unique acute toxicity of CRS and ICANS. Delayed toxicity, including prolonged cytopenias and a risk of opportunistic infections, is also increasingly being recognized.

CRS is characterized by fever, hypotension and respiratory insufficiency, and is the most common acute toxicity in CAR-T-cell therapy. CRS is triggered by cytokine release after CAR-T-cells recognize and engage with the corresponding target antigen [109, 110]. Patients with high disease burden, a high number of administered CAR-T-cells, a high peak of CAR-T-cell expansion and endothelial activation before CAR-T treatment are at high risk of CRS [111–113]. Because different risk factors and CRS grading systems have been used, the reported incidence of CRS in patients with CNSL ranges from 40% to 100% [44, 45, 48–51].

ICANS is another common acute toxicity with an incidence of 20%–100% for CNSL in CAR-T-cell clinical trials [44, 45, 48–51]. Several risk factors are associated with ICANS, including severe CRS, elevated pre-treatment lactate dehydrogenase, decreased platelets and endothelial growth factor levels, an elevated serum Ang-2/Ang-1 ratio, increased ferritin on day 3 after CAR-T-cell administration and pre-existing neurologic comorbidities [54, 55, 114]. The extent of CAR-T-cell activation and toxicity are partially associated with the affinity of the antigen binding domain toward its target epitope and the costimulatory elements of CAR.

Severe CRS and ICANS are life-threatening, and most acute toxicity is reversible in response to successful high dose glucocorticoid-based treatment. Approximately 27%–50% of patients with NHL treated with Axi-Cel develop high-grade CRS and ICANS, and require hormonal therapy [37, 115, 116]. The duration and cumulative dose of glucocorticoid depend on the severity of CRS/ICANS. Currently, several guidelines for CAR-T-cell related toxicity management recommend that patients with grade 2/3 ICANS receive 10 mg dexamethasone intravenously every 6–8 h, and that patients with grade 4 ICANS be administered 1000 mg methylprednisolone for 3 days [110, 117–119]. However, Neill et al. [120] have reported that patients receiving long-term intensive hormone therapy for severe CRS/ICANS have a higher risk of infection. Another study has found that high dose steroids provide rapid relief of severe CRS in B-ALL, but impair the expansion and persistence of CAR-T-cells [121]. In contrast, other studies have found no association between glucocorticoid administration and poor performance of CAR-T-cells [114, 122]. Liu et al. [123] have reported no differences in the existence of CAR-T-cells in BM and CSF between hormonal and non-hormonal therapeutic groups. In addition, prophylactic application of glucocorticoids has been demonstrated to decrease the incidence of severe CRS/ICANS without exacerbating neurologic toxicity and impairing the function of CAR-T-cells [124–126]. Because the above-mentioned conclusions are based on a small number of patients infused with CAR-T-cells, further studies remain necessary to explore the appropriate initial time, cumulative dose and duration of glucocorticoid administration for toxicity management.

Grade 3 or 4 cytopenias can persist for more than 30 days after CAR-T-cell infusion, and severe hematological toxicity is observed in approximately 30% of patients with B-cell hematologic malignancies receiving Axi-Cel or Tisa-Cel treatment [37, 101, 127, 128]. Prolonged severe neutropenia and lymphopenia are likely to be associated with ongoing CAR-T-cell activity and hematopoiesis disruption [128], thereby increasing the risk of viral, bacterial or fungal infections [129–131]. Thus, a risk-adapted dose or fractionated administration of CAR-T-cells may have the potential to avoid severe hematological toxicity [39, 54, 132].

5. CONCLUSIONS

CAR-T-cell therapy appears to be a novel and promising strategy for CNSL treatment. Limited clinical trials have reported that CAR-T-cell treatment is feasible without excessive toxicity, although its anti-tumor effects are not persistent. Large-scale studies are urgently needed to further confirm the anti-tumor effects and elucidate the underlying mechanisms of CAR-T-cells in CNSL therapy. Moreover, developing strategies to enhance the efficacy of CAR-T-cells will be critical, including modifing CAR design, optimizing the dose and route of CAR-T-cell administration, minimizing CAR-T associated toxicity, circumventing antigen escape and optimizing the combination of CAR-T-cells with other therapeutic approaches.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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