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CASE REPORT

Bioactivity and safety of B7-H3-targeted chimeric antigen receptor T cells against anaplastic meningioma

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Abstract

Objective. We conducted a first-in-human study to evaluate the bioactivity and safety of B7-H3-targeted chimeric antigen receptor (CAR) autologous T cells for treating recurrent anaplastic meningioma. **Methods.** Tumor tissues from a patient with recurrent anaplastic meningioma were evaluated for B7-H3 expression. B7-H3-targeted CAR-T cells were delivered into the intracranial tumor resection cavity using an Ommaya device at a maximum dose of 1.5×10^7 cells. Magnetic resonance imaging (MRI) screening and multiple serum indexes were regularly monitored. The patient received surgical intervention after three-cycle infusions, allowing analysis for CAR-T-cell infiltration and target antigen expression in post-CAR-T therapy tumor tissues. **Results.** Immunochemical analysis demonstrated high and homogeneous B7-H3 expression in tumor samples. MRI results indicated that the tumor near the delivery device was relatively stable compared with the rapid progression of tumors distant from the device. We found CAR-T-cell trafficking to regions of B7-H3$^+$ tumor tissues near the device, but not to tumor tissues distant from the device. Decreased B7-H3 expression was observed near the region of CAR-T-cell infiltration after therapy. The intracavitary delivery of B7-H3-targeted CAR-T cells was well-tolerated and not associated with any toxic effects of grade 3 or higher. **Conclusion.** Our results suggested that although intracavitary administration of B7-H3-targeted CAR-T cells was safe and resulted in local bioactivity, addressing antigen loss and CAR-T-cell trafficking may further enhance the applications of B7-H3-targeted CAR-T-cell therapy.

Keywords: anaplastic meningioma, B7-H3, chimeric antigen receptor, immunotherapy

INTRODUCTION

Meningioma is the most common primary tumor of the central nervous system (CNS),[1] and although most subtypes are benign, approximately 5% of meningiomas are malignant [World Health Organization (WHO) grades II and III], characterised by an aggressive profile, high recurrence rate, and resistance to multiple treatments.[2–4] Adoptive chimeric antigen receptor (CAR)-T-cell therapy is a novel immunotherapy used in the treatment of malignant tumors. Notably, CD19-targeted CAR-T cells have been used in the treatment of haematological malignancies, including leukaemia and lymphoma.[5–6] Recent studies have reported the clinical potential of CAR-T therapy targeting epidermal growth factor receptor variant III (EGFRvIII) and interleukin (IL) 13 receptor subunit α2 (IL13Rα2) in treating glioblastoma.[7,8] To date, clinical application of CAR-T-cell therapy against other malignant brain tumors has not yet been reported.

B7-H3, a newly identified checkpoint molecule, has been reported to be highly expressed in multiple types of solid tumors.[9,10] Recently, we and others demonstrated the potent antitumor effects of B7-H3-targeted CAR-T cells in preclinical animal models of several solid tumors, including glioblastoma, medulloblastoma, and neuroblastoma.[11–13] Several B7-H3-directed therapeutic agents have been evaluated in clinical trials. Enoblituzumab, a crystalline fragment optimised monoclonal antibody against B7-H3, is currently being applied in a phase I clinical study of B7-H3$^+$ solid tumors in combination with anti-programmed cell death-1 (PD-1) monoclonal antibodies (NCT02475213). Additionally, radiolabelled 8H9, another B7-H3-targeting antibody, was also evaluated in a phase I study for the treatment of CNS tumors, that is neuroblastoma and sarcoma (NCT00089245).

Accordingly, in this study, we present the results of our first-in-human clinical study of B7-H3-targeted CAR-T cells for the treatment of recurrent anaplastic meningioma.

RESULTS

Case report

A 49-year-old woman presented with multiple recurrent anaplastic meningioma (WHO grade III, Ki67 expression: 30%) accompanied by disorder of the right limb (Supplementary figure 1b). The patient underwent γ-knife treatment twice and neurosurgical resection twice within the last 2 years. The patient also received third neurosurgical resection and implantation of an Ommaya device. As shown in Figure 1a, immunohistochemistry (IHC) indicated high and homogeneous B7-H3 expression in tumor samples, with a histochemistry score of 180. Consistent with the IHC result, immunofluorescence imaging of tumor-isolated primary cells also confirmed the overexpression of B7-H3 (Figure 1b).

During CAR-T-cell manufacturing and quality control testing, the tumor recurred in the neurosurgical resection cavity and left parietal–occipital lobe, as detected by magnetic resonance imaging (MRI) scanning. Forty days after the third neurosurgical treatment, the patient received the first cycle of CAR-T-cell therapy. The patient received first-round treatment following a dose-escalating principle, including three doses (cycle 1: 2×10^6 cells, cycle 2: 6×10^6 cells, and cycle 3: 1.5×10^7) of CAR-T cells through the Ommaya device. Because of the rapid invasion of the tumor in the left parietal and occipital lobes, the patient asked for a fourth neurosurgical treatment, and the surgery was performed 6 days after the third cycle CAR-T-cell treatment. After CAR-T-cell therapy, the tumor specimens were subjected to evaluation with IHC. Unfortunately, the patient exhibited expiratory dyspnoea and died of pulmonary embolism the next day after neurosurgical treatment.

Characterisation of B7-H3-targeted CAR-T cells

B7-H3-targeted CAR consisted of the human CD8α leader peptide, anti-B7-H3 single-chain variable fragment (scFv), human CD8α hinge domain, human CD8α transmembrane domain, cytoplasmic domain of 4-1BB/CD3ζ, and a truncated CD19 (CD19t) used for CAR detection (Figure 1c). The anti-B7-H3 scFv sequence used in the CAR vector was derived from a highly specific monoclonal antibody (mAb) against B7-H3 (clone: mAb-J42) generated using a standard hybridoma technique.

The cell phenotype of the manufactured B7-H3-targeted CAR-T cells is shown in Figure 1d. Flow cytometry results indicated that CAR-T-cell clones displayed memory T-cell markers (CD45RO and CD62L), but were negative for or had low levels

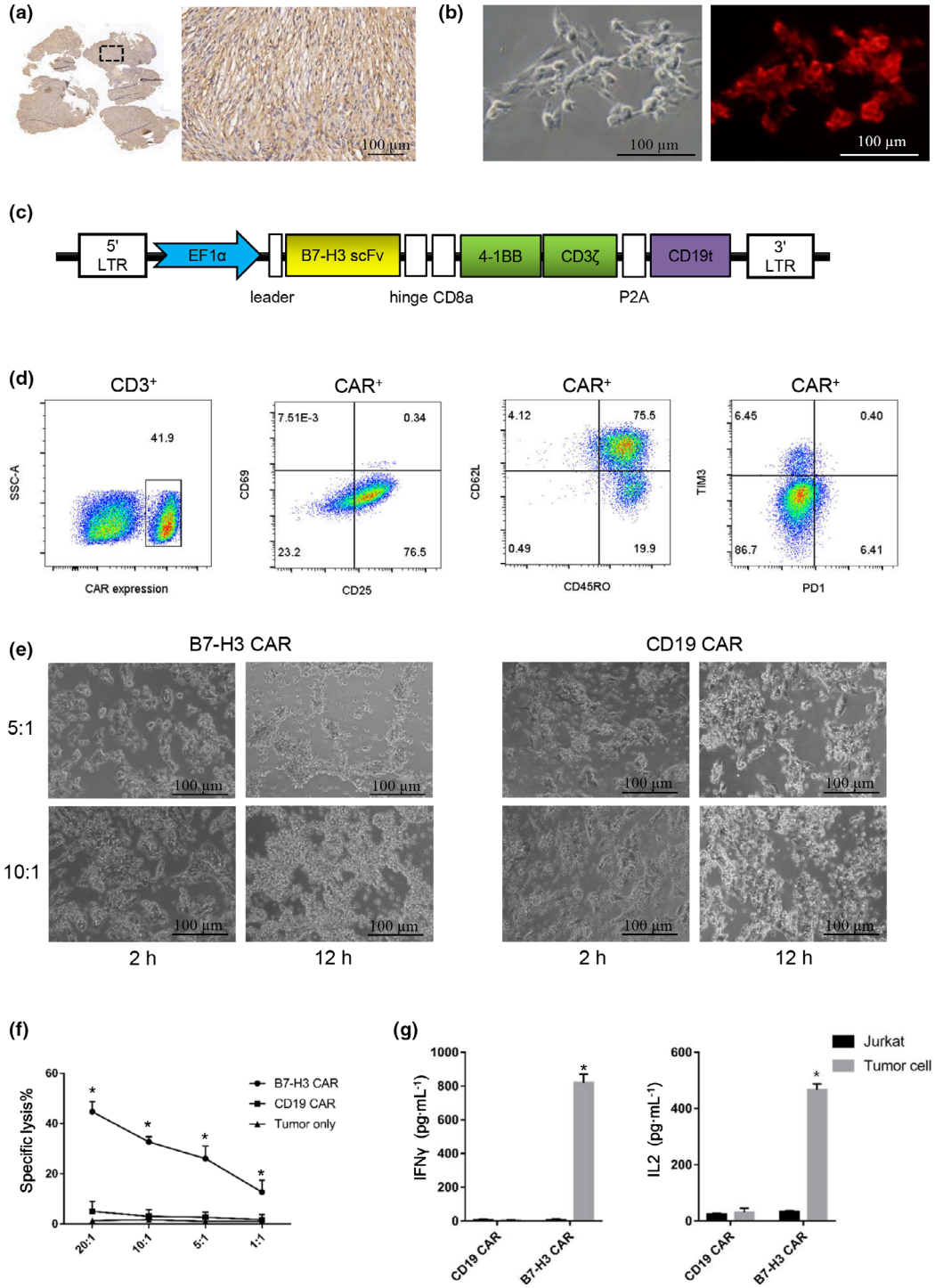

Figure 1. Tumor B7-H3 expression and characteristics of chimeric antigen receptor (CAR)-T cells. **(a)** Immunohistochemical analysis of paraffin-embedded tumor tissues collected before CAR-T therapy. **(b)** Immunofluorescent staining (red) of B7-H3 in anaplastic meningioma primary cells. **(c)** CAR component construction in the lentivirus vector. **(d)** Flow cytometric analysis of surface CAR expression and the T-cell markers CD25, CD69, CD45RO, CD62L, programmed cell death-1, and T-cell immunoglobulin and mucin domain-containing protein 3. CD19 was used for CAR detection. **(e)** Images of CAR-T cells cocultured with autologous tumor (anaplastic meningioma) cells at E/T ratios of 5:1 and 10:1. CD19-targeted CAR-T cells (CD19 CAR) served as controls. **(f)** ^{51}Cr release assays of CAR-T cells against primary tumor cells at different E/T ratios. **(g)** Cytokine (interferon γ and IL2) secretion levels were measured to analyse immunological changes in B7-H3/CD19-targeted CAR-T cells cocultured with primary tumor cells (40,000 T cells to 10,000 tumor cells) for 12 h using enzyme-linked immunosorbent assays. $*P < 0.05$. One representative image from two experiments is shown in **b** and **e**. For **f** and **g**, the results show cumulative data from two independent experiments.

of effector T-cell markers (CD69 and CD25) and exhausted markers (PD-1 and T-cell immunoglobulin and mucin domain-containing protein 3).

We observed a specific killing effect of B7-H3-targeted autologous CAR-T cells against isolated primary cells from the patient tumor tissues after coculturing for 12 h (Figure 1e). ^{51}Cr release cytotoxic assays and enzyme-linked immunosorbent assay results also indicated that CAR-T cells induced specific antitumor effects in B7-H3^{+} primary cells, but not in B7-H3^{-} Jurkat cells (Figure 1f and g).

Clinical response and safety of B7-H3-targeted CAR-T-cell administration

The CAR-T-cell delivery process is shown in Figure 2a. Before treatment, an Ommaya delivery device was subcutaneously implanted, and the pipe orifice of the device was placed into the neurosurgical resection cavity (Figure 2b). Before the first infusion of CAR-T cells, tumor recurrence was clearly detected by MRI scanning of the neurosurgical resection region, near the pipe orifice of the delivery device, and the left parietal/occipital lobe, distant from the pipe orifice of the delivery device (Figure 2c, red and blue arrows).

After three infusion cycles, tumor progression near the pipe orifice (Figure 2c, red arrow) was much slower than the rapid growth rate of tumors distant from the pipe orifice (Figure 2c, blue arrow). MRI scanning revealed a liquefaction area near the treated tumor region (Figure 2c, green arrow). We speculated that this region may be an area of liquefactive necrosis caused by tumor lysis.

Throughout the treatment process, there were no grade 3 or higher adverse events. However, the patient had a moderate headache 3 h after infusion of CAR-T cells in the second and third cycles. This symptom was alleviated by administration of oral analgesic therapy. However, her headaches occurred repeatedly and lasted for about 3 days. To further evaluate the physical condition of the patient, multiple serum biochemical indexes were continuously monitored; no significant changes were observed before and after local administration of B7-H3-targeted CAR-T cells (Supplementary table 1).

After intracavitary administration of cycle 3, CAR-T cells could be detected in the first few days in the cerebrospinal fluid (CSF) sample obtained from the Ommaya device but were absent in peripheral blood, and the number of CAR-T cells decreased with time (Figure 3a). To further evaluate immunological changes, 12 inflammatory cytokines were measured before and after each cycle of CAR-T-cell administration. As a result, the levels of 6 inflammatory cytokines significantly increased in CSF. However, only IL6 (one of the 6 inflammatory cytokines) appeared to increase after cycle3 infusion in serum (Figure 3b). All cytokine changes are shown in Supplementary table 2. Moreover, increased inflammatory cytokines in CSF seemed to correlate with the occurrence of cephalalgia (Supplementary table 3). These results indicated that the immunologic changes were probably restricted to the CSF because no obvious increases in the levels of cytokines and no CAR-T cells were detectable in the peripheral blood.

Bioactivity of B7-H3-targeted CAR-T cells

Because of the rapid invasion of tumors distant from pipe orifice, the patient asked for surgical intervention after three cycles of CAR-T therapy. Because MRI imaging findings were complex to interpret, we further performed IHC analysis of CAR-T-cell infiltration and target expression alterations using the resected tumor tissues. Significant decreases in B7-H3 expression and CAR-T-cell infiltration were observed in tumor tissues near the pipe orifice of the Ommaya delivery device (sites 3/4 in Figure 4 and sites 5/6 in Supplementary figure 2). Notably, CAR-T cells could only be detected on the B7-H3-positive tumor site near the pipe orifice of the device (sites 3/4 in Figure 4). In contrast, the tumor tissues far from the pipe orifice of the device still showed high expression of B7-H3 (sites 1/2 in Figure 4 and site 7 in Supplementary figure 2) without infiltration of CAR-T cells. Based on these results, we suggest that B7-H3-targeted CAR-T cells could successfully target B7-H3-positive tumor cells and trigger antitumor responses, although antigen loss may occur after CAR-T therapy.

DISCUSSION

Here, we performed the first-in-human local administration of autologous B7-H3-targeted CAR-T therapy in a patient with anaplastic meningioma. During the treatment process, prior

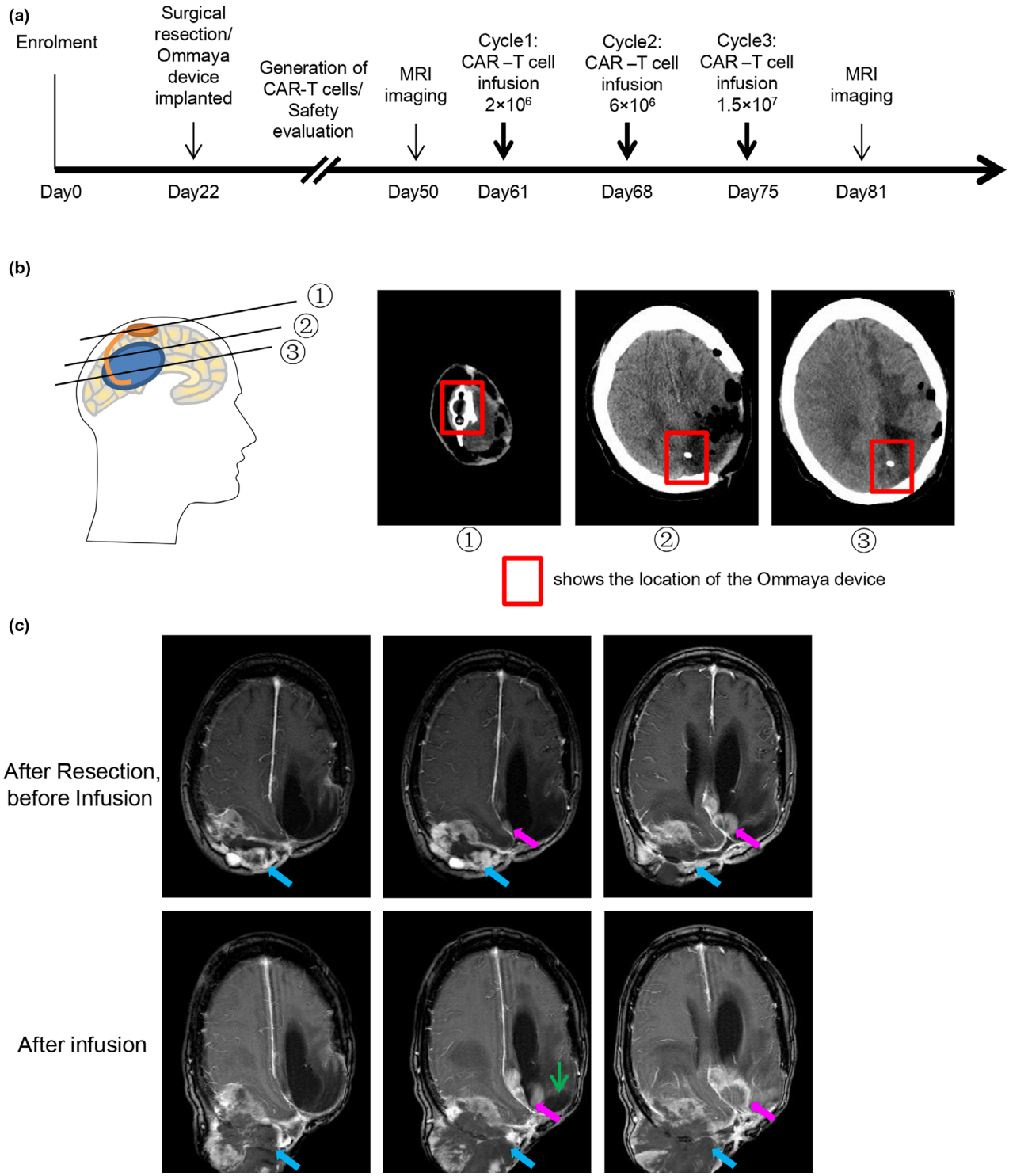

Figure 2. Treatment schematic and imaging results. **(a)** Three cycles of intracavitary administration of chimeric antigen receptor (CAR)-T cells after tumor excision and implantation of the Ommaya device. **(b)** Computed tomography images from the Ommaya device. Images show the locations of the pipe orifice and reservoir of device. **(c)** Magnetic resonance imaging for the patient before and after intracavitary administration of B7-H3-targeted CAR-T cells.

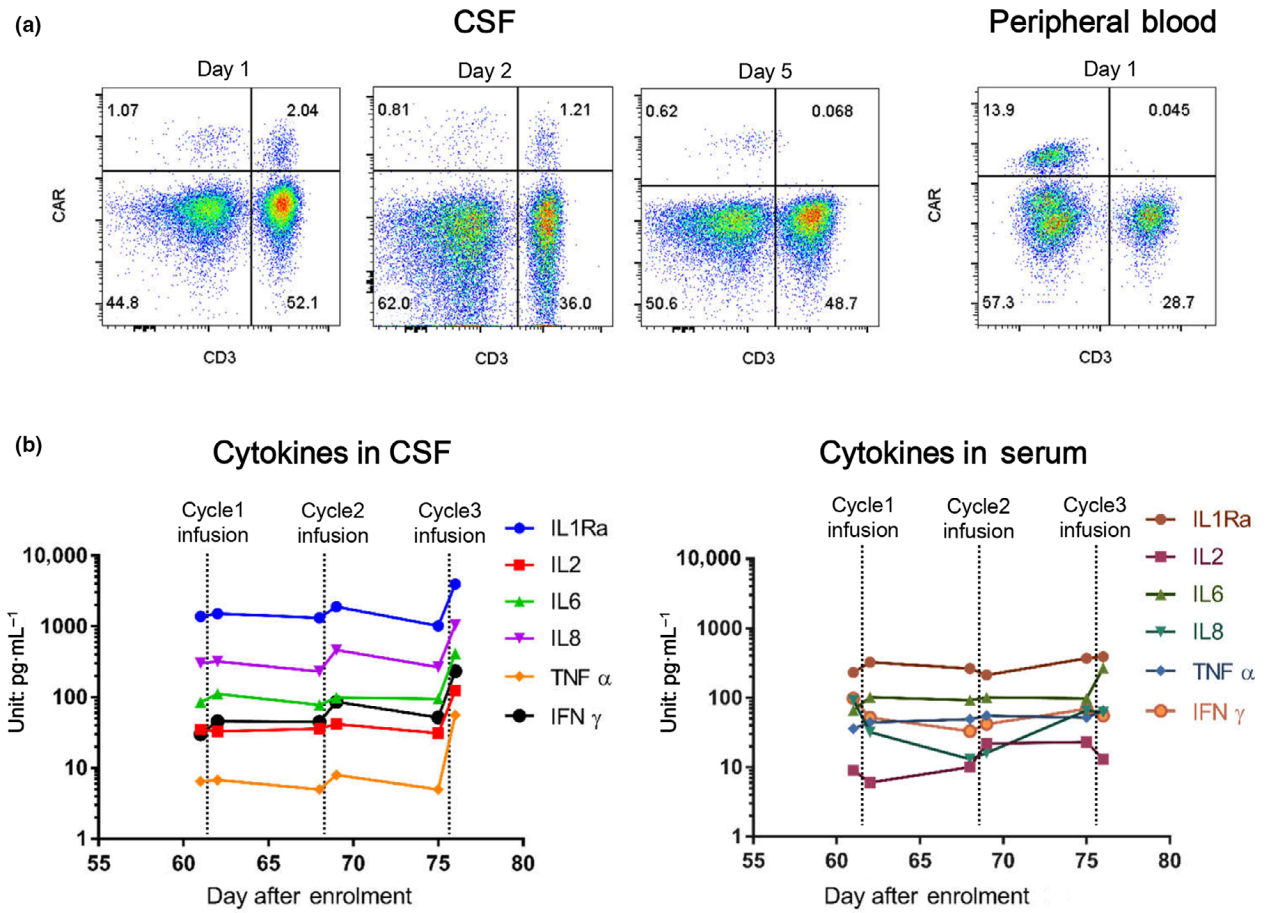

Figure 3. Cerebrospinal fluid (CSF) and serum analysis of immune cell populations and multiple cytokine levels. CSF samples were obtained from the reservoir of the Ommaya device. **(a)** Flow cytometric analysis for detecting chimeric antigen receptor (CAR)-T cells in the CSF and peripheral blood after intracavitary infusion during cycle 3. CD19 was used for CAR detection. **(b)** Changes in cytokine levels following intracavitary treatment during cycles 1–3. Only cytokines that changed by a factor of 3 or more compared with pre-CAR-T-cell infusion levels at one or more time points are shown. The dotted line in the figure indicates the CAR-T-cell infusion data.

chemotherapy designed for the depletion of lymphocytes was not used in this study because the patient suffered from incision infection caused by the large volume of the recurrent tumor, which had broken through the skull and resulted in poor healing of the incision. Another reason was uncertainty as to whether depletion of lymphocytes could augment the CAR-T-cell responses.

The key factor affecting CAR-T therapy is the identification of tumor-specific target antigen. In this study, we stained the resected tumor specimen with antibodies against a panel of tumor antigens, including human EGFR 2, IL13Rα2, programmed cell death ligand (PDL) 1, PDL2, B7-H4, and B7-H3 (data not shown). Of these, B7-H3 was the only antigen found to be highly and homogeneously expressed on tumor cells. In prior studies, B7-H3 was found to be overexpressed in multiple cancers and tumor blood vessels but not in normal tissues,[14] and anti-B7-H3 drug conjugates also cause a noticeable response against B7-H3^{+} tumor.[15] Moreover, B7-H3 expression levels increase with the tumor malignancy grade and are correlated with poor survival.[16] The results of our clinical study indicated that B7-H3-targeted CAR-T cells exhibited local antitumor responses against anaplastic meningioma. There occurred no unmanageable adverse event, and multiple indexes of blood biochemical test revealed no significant changes before and after administration of CAR-T cells, suggesting that B7-H3 may be an ideal target for immunotherapy against anaplastic meningioma.

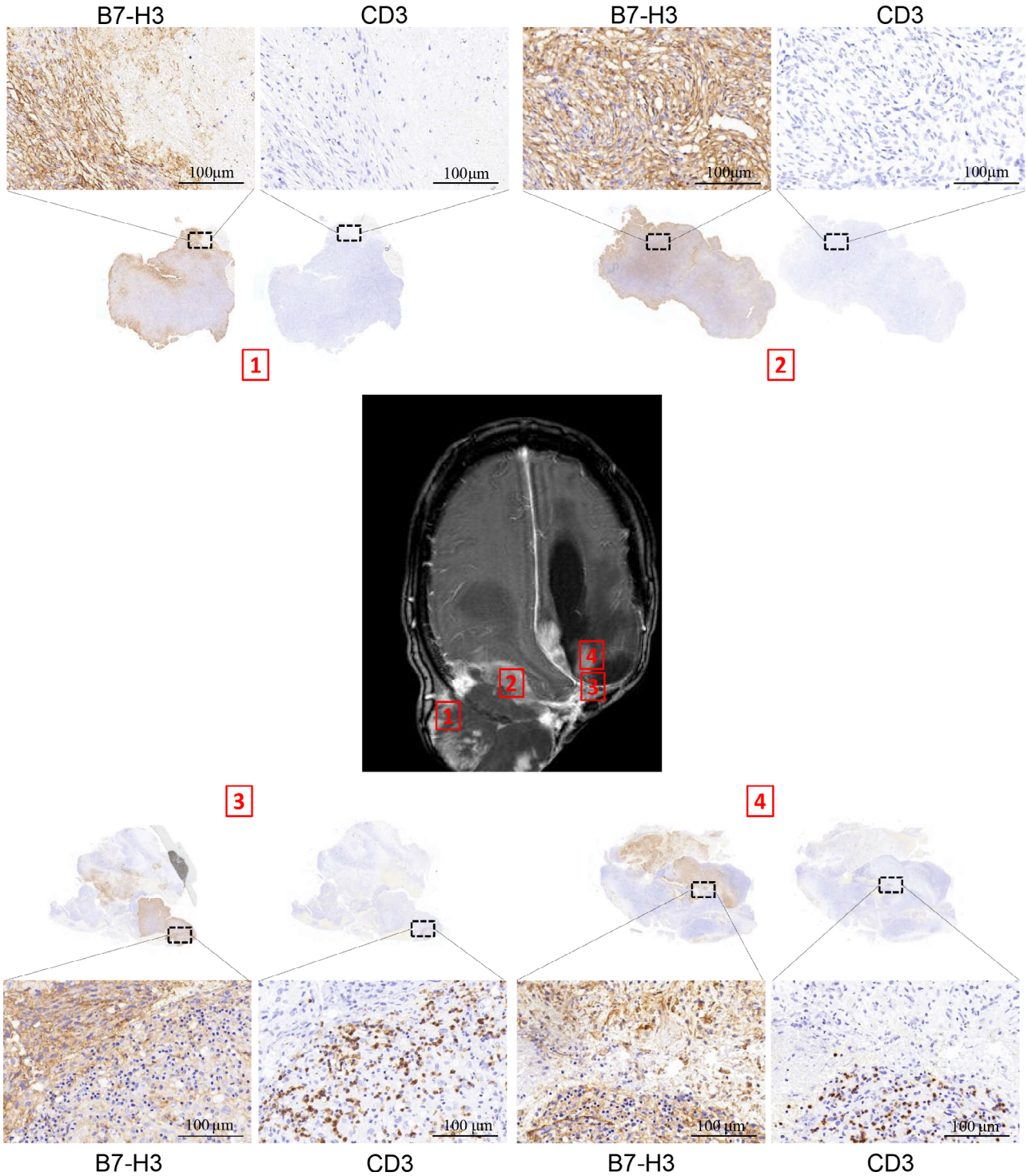

Figure 4. Immunohistochemistry results of the resected tumor after chimeric antigen receptor (CAR)-T therapy. Immunohistochemical analysis of paraffin-embedded tumor tissues from different tumor foci obtained after CAR-T therapy. Tumor sites 1/2 were on the contralateral occipital lobe, and tumor sites 3/4 were near the pipe orifice of the delivery device.

Despite the antitumor efficacy of CAR-T therapy in the treatment of haematological malignancies,[17] the application of CAR-T therapy to solid tumors is still limited by various factors, including target antigen heterogeneity, trafficking and a hostile tumor microenvironment.[18] In our study, specific loss or decreased expression of B7-H3 was observed in the recurrent tumor tissues after administration of CAR-T cells, whereas there were no significant changes in the degree of B7-H3 expression in the tumor region distant from the infusion location. Similar results were also observed for EGFRvIII- and IL13Rα2-targeted CAR-T therapy against glioblastoma,[7,8] indicating that the heterogeneity of target antigen expression and diverse mechanisms of regulation may result in loss or decreased expression of B7-H3. To address the problem of antigen loss, bispecific CAR, such as CD19/CD22 bispecific CAR-T cells used for the treatment of acute lymphoblastic leukaemia (NCT03919526), was proposed to overcome antigen escape relapse. Thus, combination of B7-H3 with another tumor antigen in the CAR design may yield lasting clinical effects.

In this study, although no direct imaging evidence demonstrated tumor regression, our IHC results, along with the observed immunological changes, supported the specific antitumor effects of CAR-T cells. Our initial clinical study used a relatively low infusion dose (maximum dose: 1.5×10^7 cells) compared with the doses used in other clinical reports of CAR-T therapy.[7,19] Thus, we could not exclude the possibility that the dose of CAR-T cells was insufficient for triggering indirect tumor-killing effects induced by multiple immune cells after CAR-T-cell activation, resulting in elimination of the remaining tumor cells.[18] Further studies are needed to evaluate treatment with B7-H3-targeted CAR-T therapy and to assess the appropriate infusion dose for inducing tumor regression.

Trafficking is another obstacle that limits the efficacy and function of CAR-T cells. In this case, an Ommaya device was implanted to facilitate the infusion of CAR-T cells. Although immunoreaction was obvious near the pipe orifice of the device, the recurrent tumor distant from the device progressed rapidly without CAR-T-cell infiltration after repetitive local delivery. Considering the location of the recurrent tumor (on the contralateral occipital lobe), we supposed that trafficking of CAR-T cells was restricted by the cerebral falx, suggesting that local delivery of B7-H3-targeted CAR-T cells may not enter and target the distant tumor focus effectively. In a phase I clinical trial, intravenous infusion of retrovirally transduced autologous peripheral blood lymphocytes mediated complete and durable regression of melanoma brain metastases.[20] Recent studies have also demonstrated the availability of intravenously delivered CAR-T cells in treating glioblastoma.[8] Based on these reports, we planned to administer higher doses by intravenous infusion after tumor resection. Unfortunately, the patient died of pulmonary embolism after surgery.

In summary, our clinical results provided evidence that local delivery of B7-H3-targeted CAR-T cells could suppress tumor progression without off-tumor toxicity or serious side effects, indicating the tolerability, safety and potential efficacy of this therapy. Few clinical benefits could be interpreted from this case study; however, we observed that B7-H3-targeted CAR-T cells infused intravenously migrated to the local tumor tissues and exerted antigen-directed activity. Future exploration of B7-H3-targeted CAR-T cells focusing on efficient delivery and tumor targeting may prove beneficial.

METHODS

Study design

This phase 1 study (ChiCTR1900023435) to evaluate the feasibility and safety of B7-H3-targeted CAR-T-cell therapy against B7-H3-positive malignant tumors in the CNS was initiated in 2018. The clinical protocol was approved by the West China Hospital of Sichuan University Biomedical Ethics Committee (ethical approval document: 2018-061), and the participating patient provided written informed consent.

Enrolled patients underwent venous blood collection in order to obtain peripheral blood mononuclear cells (PBMCs). These PBMCs were subsequently sorted and used to engineer B7-H3-targeted CAR-T cells. After confirming the cell phenotypes and antitumor effects *in vitro*, CAR-T cells were cryopreserved for later use. Before administration of CAR-T cells, enrolled patients were implanted with an Ommaya device in the location of tumor resection and underwent baseline MRI. The designed treatment schedule included 12 CAR-T-cell doses administered by intracavitary infusion within 4 months (Supplementary figure 1a). The first and second rounds of clinical therapy consisted of three weekly, dose-escalating CAR-T-cell infusions up to a maximum dose of $1–2 \times 10^8$ cells per infusion depending on the tumor volume. The maximum dose was used for the next six doses of CAR-T cells. Clinical responses were assessed by MRI scanning every two rounds after initiation

infusion. Adverse events during CAR-T-cell treatment were graded according to the NIH Common Terminology Criteria for Adverse Events, version 5.0 (http://ctep.cancer.gov). The process of CAR-T-cell manufacturing and other experimental schemes are presented in the Supplementary methods.

Manufacturing of B7-H3-targeted CAR-T cells

For CAR-T-cell manufacturing, PBMCs were isolated by density gradient centrifugation using Lymphoprep (Greiner Bio-One, Kremsmünster, Austria) on the day of leukapheresis. After centrifugation, PBMCs were cultured in TexMACS GMP Medium (Miltenyi Biotec, Cologne, Germany) and stimulated with OKT3 and anti-CD28 antibodies [anti-CD3 mAbs; 600 ng mL^{-1} (Novoprotein, Shanghai, China); CD28 mAbs; 300 ng mL^{-1} (Novoprotein)] with addition of recombinant human (rh) IL2 (100 U mL^{-1}; PeproTech, Rocky Hill, IL, USA) and rh-IL15 (5 ng mL^{-1}; Miltenyi Biotec) in a 37°C incubator with an atmosphere containing 5% CO_2. Two days after PBMC isolation, anti-CD3 (OKT3)-/anti-CD28-activated T cells were transduced with lentivirus (multiplicity of infection = 1–5) harbouring the recombinant fibronectin fragment (CH-296; Novoprotein) in the presence of IL2. After 12 h, T cells were cultured for 8–10 days and harvested for cryopreservation before use. Following lentivirus transduction, T-cell culture was required to maintain the density between 1.0×10^6 and 2.5×10^6 cells mL^{-1} in the presence of 100 U mL^{-1} rh-IL2 and 5 ng mL^{-1} rh-IL15. For cryopreservation, CAR-T cells were harvested, washed in phosphate-buffered saline containing 2% human serum albumin, and resuspended in Serum-Free Cell Freezing Medium (BioLife Solutions, Bothell, WA, USA). The entire CAR-T-cell manufacturing process was completed within approximately 2 weeks. Quality test results for lentivirus and CAR-T-cell production are presented in Supplementary tables 4 and 5.

Infusion of CAR-T cells

The patient was premedicated 30 min before CAR-T-cell infusion with acetaminophen per os (P.O.) and diphenhydramine (intravenous injection or P.O.) according to standard protocols for glioblastoma CAR-T-cell therapy.[7] CAR-T-cell infusions were administered manually via the Ommaya device in a 1.0-mL volume over approximately 10 min using a 21-gauge butterfly needle, followed by a 1.0-mL normal saline flush over 5 min. After CAR-T-cell infusion, the patient was monitored for 3 h.

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AUTHOR CONTRIBUTIONS

Xin Tang: Writing – Original Draft Preparation; Data Curation; Project Administration. **Fujun Liu**: Project Administration; Formal Analysis. **Zhiyong Liu**: Investigation; Data Curation. **Yi Cao**: Investigation; Visualization. **Zongliang Zhang**: Project Administration. **Yuelong Wang**: Resources; Methodology. **Jianhan Huang**: Resources; Software. **Shuangming Fan**: Validation; Visualization. **Shasha Zhao**: Resources. **Yaxin Chen**: Software. **Gaowei Li**: Resources. **Shan Wang**: Project Administration. **Meijun Zheng**: Validation. **Yating Hu**: Visualization. **Hongjian Li**: Visualization. **Caiying Jiang**: Methodology. **Meijia Yang**: Validation. **Hui Yang**: Funding Acquisition. **JianGuo Xu**: Funding Acquisition. **Gang Guo**: Conceptualization. **Aiping Tong**: Conceptualization; Writing – Review & Editing; Supervision. **Liangxue Zhou**: Conceptualization; Funding Acquisition; Supervision.

CONFLICT OF INTEREST

Aiping Tong, Gang Guo and Liangxue Zhou filed a patent for the mAb, scFv and CAR targeting B7-H3. Other authors declare no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Supplementary figures and tables
Supplementary methods