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A Case of Relapsed Primary Central Nervous System Lymphoma Treated with CD19-directed Chimeric Antigen Receptor T Cell Therapy

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Abstract

Although high-dose methotrexate (HD-MTX) is the standard therapy for primary central nervous system lymphoma (PCNSL), the prognosis remains poor. Because 90% of PCNSL is diffuse large B-cell lymphoma (DLBCL), chimeric antigen receptor (CAR)-T cell therapy is expected to be beneficial. However, there are limited reports on CAR-T cell therapy for PCNSL because of the concern of neurotoxicity. Here, we report a case of relapsed PCNSL treated with anti-CD19 CAR-T cell therapy. A 40-year-old woman presenting with visual disturbance in her left eye was initially diagnosed with bilateral uveitis. Her histological diagnosis was DLBCL, and she was positive for CD19. Although she received chemotherapy including HD-MTX, the tumor relapsed in her right occipital lobe. She underwent remission induction therapy and then anti-CD19 CAR-T cell therapy. Cytokine release syndrome (CRS) grade 2 occurred, but there were no complications of CAR-T cell-related encephalopathy syndrome (CRES). She has achieved complete response for more than 1 year. Anti-CD19 CAR-T cell therapy is a revolutionary immunotherapy for treating relapsed or refractory (R/R) B lineage malignancies. Although there are concerns regarding CRS and CRES in central nervous system lymphoma, the use of anti-CD19 CAR-T cells to treat R/R PCNSL is safe and feasible.

Keywords: primary central nervous system lymphoma, diffuse large B cell lymphoma, chimeric antigen receptor T cell therapy

Introduction

Primary central nervous system lymphoma (PCNSL) is a highly malignant extranodal type of non-Hodgkin lymphoma that is localized to the central nervous system (CNS). The median age at presentation of PCNSL is approximately 60 years old, and the most common histological subtype (90%) is diffuse large B-cell lymphoma (DLBCL), which is part of non-Hodgkin lymphoma.[1)] This lymphoma represents 4% of intracranial neoplasms and 4%-6% of all extranodal lymphomas.[2)] Immunodeficiency is a known risk factor for PCNSL, which occurred with high frequency in patients with acquired immunodeficiency syndrome, and the incidence in immunocompetent patients is progressively increasing.[3)]

High-dose methotrexate (HD-MTX) is the cornerstone of treatment for PCNSL, but the prognosis with this treatment remains poor, and new alternative treatments are imperative. Chimeric antigen receptor (CAR) T cell therapy is a promising immunotherapy, and the United States Food

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and Drug Administration approved anti-CD19 CAR-T cells for the treatment of relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) and DLBCL in 2017. It was also approved in Japan in late 2019. Because 90% of PCNSL is DLBCL, CAR-T cell therapy is expected to be beneficial. However, there are a limited number of reports of cases treated with CAR-T cell therapy in PCNSL. Thus, the efficacy and safety of CAR-T cell therapy in PCNSL remain theoretically effective but unknown.

Here, we report a case of relapsed PCNSL treated with anti-CD19 CAR-T cell therapy that was effective and safe.

Case Report

A 40-year-old woman presented with a visual disturbance, and 2 years later, she was diagnosed with DLBCL, a primary intraocular lymphoma. She had a history of asthma in childhood and no history of familial cancer or previous malignancy. She achieved complete remission (CR) after receiving bilateral intraocular injections of MTX four times. Subsequently, she underwent 4 cycles of chemotherapy that contained HD-MTX (3500 mg/m^2) and cytarabine (2000 mg/m^2) every 12 h.

Approximately 4 years after the systemic chemotherapy, fluid-attenuated inversion recovery images of head magnetic resonance imaging (MRI) revealed a non-enhancing high-intensity lesion at the medial surface of the right occipital lobe (Fig. 1A, B), which had not been observed 3 months previous. There were no abnormalities on positron emission tomography, including the lesion of the right occipital lobe. Thus, we comprehensively determined that this was a relapsed lesion. She received 3 cycles of MR-CHOP (MTX: 3500 mg/m^2, rituximab: 375 mg/m^2, cyclophosphamide: 750 mg/m^2, doxorubicin: 50 mg/m^2, vincristine: 1.4 mg/m^2, and prednisolone)[4] because the lesion had enlarged 1 month later (Fig. 1C). After chemotherapy, head MRI revealed CR of the right occipital lesion (Fig. 1D). Subsequently, she received an autologous peripheral blood stem cell transplantation with 0.8 mg/kg busulfan 4 times/day for 4 days and 200 mg/m^2/day thiotepa for 2 days as a clinical trial (trial no. DSP-1958).

At the age of 50, approximately 8 years after the initial diagnosis, head MRI revealed another spotty contrast-enhanced lesion (Fig. 1E, F) in the right occipital lobe, distant from the previous occipital lesion. The lesion was responsive to chemotherapy (5 cycles of HD-MTX and R-CHOP at the same doses as previous ones), and she achieved CR after 3 cycles of chemotherapy (Fig. 1G, H). There were no intraocular lesions and no atypical cells in the cerebrospinal fluid. Since immunohistochemistry revealed that the specimen of the left eye at the initial diagnosis was CD19-positive, we decided to utilize anti-CD19 CAR-T cell therapy, tisagenlecleucel.

We prophylactically administered levofloxacin, fluconazole, acyclovir, and sulfamethoxazole-trimethoprim. On days −5 to −3, she received lymphodepleting chemotherapy consisting of fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) with antiemetic drugs. On day −1, we prophylactically started levetiracetam at 1000 mg/day. On day 0, she received a single intravenous injection of 350×10^6 CAR-T cells. On day 1, she had a fever of over 38°C, low systolic blood pressure of approximately 60 mmHg, and facial edema. We diagnosed her with cytokine release syndrome (CRS) grade 2[5] and administered intravenous tocilizumab (8 mg/kg/day). We changed levofloxacin to cefepime to address the continuous fever. Infusion of saline improved the hypotension, and diuretics eliminated the facial edema. On day 3, we discontinued levetiracetam because of elevated liver enzymes. From day 3 to 6, we administered methylprednisolone (2 mg/kg/day) to break her fever; hydrocortisone was not effective. We changed antibiotics from cefepime to piperacillin/tazobactam, and we added vancomycin on days 5-7. On day 25, she received a subcutaneous injection of granulocyte colony stimulating factor (G-CSF; 75 μg) for grade 4 neutropenia. She was discharged home on day 28 and continued receiving G-CSF injections every week for 6 weeks. We confirmed that she was above 500 neutrophils/μL on day 74. We continued fluconazole for half a year and have also continued acyclovir and sulfamethoxazole-trimethoprim based on a previous literature.[6] She remained in CR for 13 months following CAR-T cell therapy and had no neurological deficits. She had no complications of CAR-T cell-related encephalopathy syndrome (CRES).

Discussion

In general, patients diagnosed with PCNSL receive MTX-based chemotherapy and subsequently receive whole brain radiotherapy (WBRT). WBRT after chemotherapy prolongs overall survival and progression-free survival and was thought to be important for improvement of the remission rate and the relapse rate. In contrast, higher brain dysfunction because of neurotoxicity interferes with quality of life (QoL) and leads to reduced life expectancy, especially in older adult patients. Correa et al. reported that patients treated with WBRT + HD-MTX had impairment across most cognitive tests, and that it was severe enough to interfere with QoL compared to patients treated with HD-MTX alone.[7] In addition, Thiel et al. reported that delayed neurotoxicity on head MRI or computed tomography was assessed in 84 patients and was recorded in 35 (71%) of 49 patients receiving WBRT and in 16 (46%) of 35 of those not receiving WBRT (p = 0.04), and that WBRT did not benefit overall survival.[8] In our institute,[4] patients with CR by first chemotherapy for PCNSL have avoided WBRT since 2004, and the median survival for patients over 65 years old was 33 months, which was not significantly different from patients receiving WBRT. Moreover, they had a good outcome of functional prognosis. Thus, we attempted

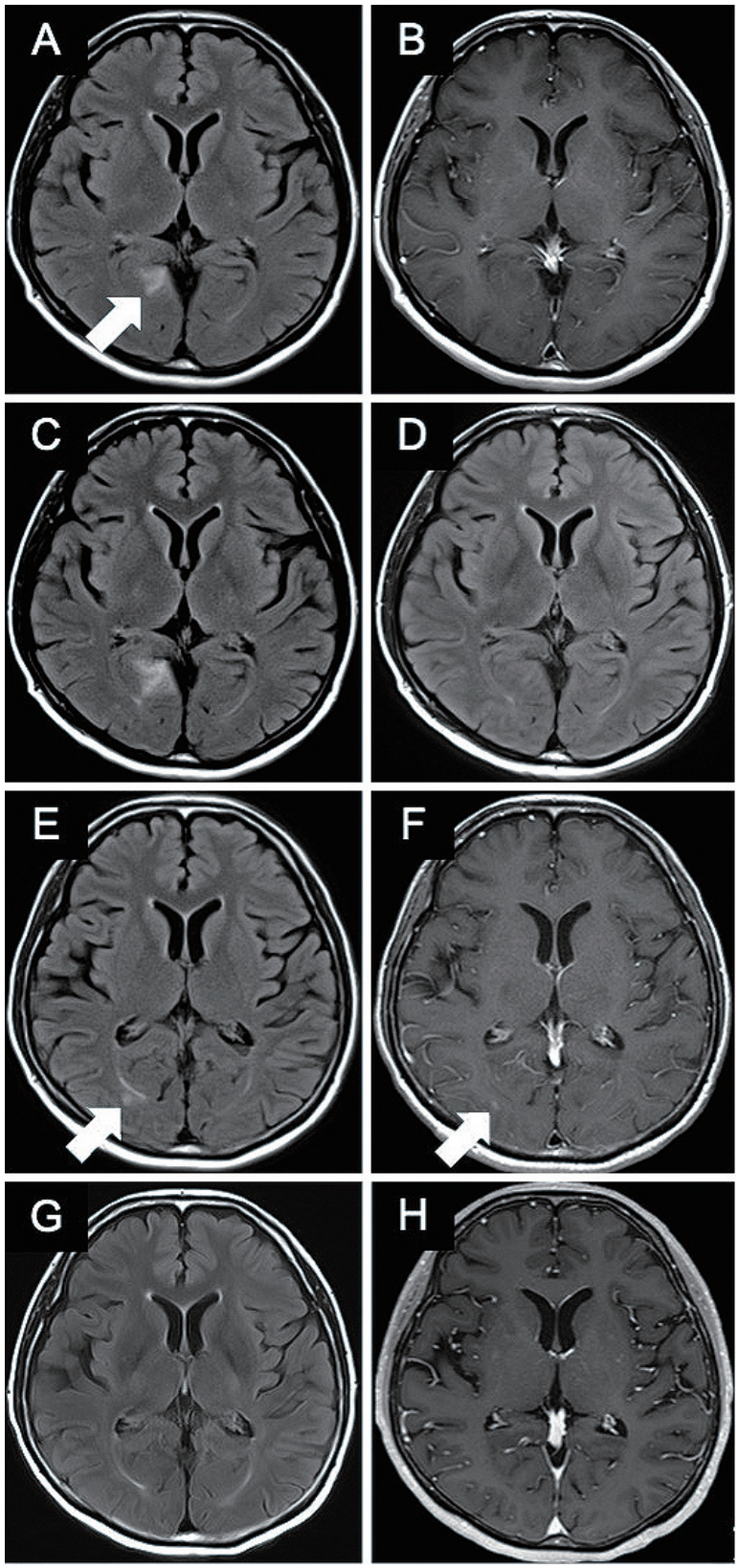

Fig. 1 MRI of intracranial lesions. Fluid attenuated inversion recovery image revealed a high-signal lesion at the medial surface of the right occipital lobe (A), which was not contrast enhanced (B). Although the lesion expanded within 1 month (C), the patient achieved CR after chemotherapy (D). Another contrast-enhanced lesion in the right occipital lobe was detected in MRI (E and F). The patient achieved CR after chemotherapy (G and H). MRI, magnetic resonance imaging; CR, complete response

to defer WBRT as much as possible and considered CAR-T cell therapy for this case.

There are several regimens of chemotherapies for PCNSL, including MR-CHOP and R-MPV (rituximab, MTX, procarbazine, and vincristine). The 5-year overall survival was 46%, in the case of incorporating rituximab in MTX-based chemotherapy for PCNSL.[1] In addition, the 2-year overall survival was 67% with treatment of R-MPV, and 78% of patients who received 7 cycles of R-MPV achieved CR.[9] Although advances in chemotherapy have improved the survival of patients, the prognosis of PCNSL remains poor.

Eshhar et al. designed and constructed the first-generation CAR-T cells of chimeric genes composed of single-chain variable regions (Fv) of an antibody linked with γ or ζ chains in 1993.[10] A CAR consists of antigen-binding Fv domains, transmembrane domains, signaling domains, and additional costimulatory domains. The first-generation CAR-T cells showed limited expansion and antitumor efficacy because the CAR-T expansion was solely dependent on interleukin-2 production. Recently, second-generation CAR-T cells that contain a costimulatory domain, such as CD28, 4-1BB, or OX-40, have been used in clinical trials of CAR-T cell therapy to improve CAR-T cell expansion capacity and antitumor activity. In addition, researchers have developed third-generation CAR-T cells that contain multiple costimulatory domains, and fourth-generation CAR-T cells, so-called T cell redirected for universal cytokine-mediated killing T cells, which are additionally modified with a constitutive or inducible expression cassette for a transgenic protein to the targeted tumor site.[11] Anti-CD19 CAR-T cell therapy was approved for B-ALL and DLBCL,[12] and currently, three second-generation CAR-T cell products (i.e., tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel) are in clinical use in Japan. Anti-CD19 CAR-T cell therapy is a revolutionary immunotherapy for treating R/R B lineage malignancies and has been reported to induce a 64%-86% response rate in patients with DLBCL.[13] Importantly, 90% of PCNSL is DLBCL, and normal tissue of the CNS lacks CD 19 expression. Thus, CAR-T cell therapy is theoretically beneficial for R/R PCNSL, and tisagenlecleucel is eligible for use in CNS lesions among the three clinically approved CAR-T cells in Japan. However, it has not yet been widely extended to non-Hodgkin lymphoma with CNS lesion, primarily due to concerns for potential toxicity.[14] There are a few reports of anti-CD19 CAR-T cell therapy for PCNSL (listed in Table 1). The major side effect of CAR-T cell therapy is CRS and CRES. CRS is defined as a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines from the cells.[5] The term CRES has been proposed to describe neurotoxicity associated with CAR-T cell therapy, and the term immune effector cell-associated neurotoxicity syndrome (ICANS) is suggested for any immune effector cell-engaging therapy, not just for CAR-T cell therapy. Schuster et al. reported that CRES occurred in 64% of patients with DLBCL who received CAR-T cell therapy (28% with grade ≧3).[15] Fortunately, our case did not suffer from CRES. If CRS or neurotoxicity occurs, the management should be based on the toxicity grade. For example, we define grade 2 CRS as fever over 38°C with hypotension not requiring vasopressors and/or hypoxia requiring the use of a low-flow oxygen delivery system. We tend to use anti-cytokine therapy such as tocilizumab and high-dose corticosteroids before CRS develops severity.[5] ICANS is managed with corticosteroids and prophylactic antiepileptic drugs, but tocilizumab is ineffective at alleviating it. It appears that tocilizumab has no action in the CNS because it cannot penetrate the blood-brain barrier (BBB).[16] As for the efficacy in previous cases, despite the lack of a large cohort study, Siddiqi et al. reported the safety and feasibility of CAR-T cell therapy in PCNSL.[14] Furthermore, a previous study confirmed the presence of anti-CD19 CAR-T cells in the cerebrospinal fluid, which suggests the ability of these cells to cross the BBB.[17]

Previous studies suggested an acceptable profile of CAR-T in R/R PCNSL; however, some CNS-specific aspects may hamper the success of this therapy in R/R PCNSL. The first problem is antigen loss. In patients with B-cell leukemia, 7%-25% of relapsed patients lost CD19 expression,[18] which resulted in the loss of target antigen. Thus, some PCNSL was treated with dual targeting CAR-T, such as CD 19, CD22, or CD70 (Table 1). Tu et al. reported the efficacy of CD70, which is expressed on various malignancies, including 71% of DLBCL as the cellular ligand of the tumor necrosis factor receptor family. The combination of CD19- and CD70-specific CAR-T cells may effectively target PCNSL and maintain disease-free survival without inducing CRS or CRES.[13] The second problem is CD19-positive mural cells. Recent single-cell RNA-sequencing found that in the human brain, there is a small population that co-expresses the B-cell marker CD19 and the mural cell marker CD248, indicating that the brain perivascular tissue is also targeted by CAR-T cells. However, the patients treated by other B-cell antigens, including CD20 and CD22, also exhibited the neurotoxicity, highlighting the complicated mechanism of ICANS. The last problem is the immunosuppressive tumor microenvironment (TME) in the CNS.[19] The immunosuppressive TME is known to contribute to tumor progression or treatment resistance in CNS malignancies.[20,21] Similar to other CNS malignancies, M2 macrophages are associated with less favorable outcome in PCNSL. The immunosuppressive TME may attenuate the efficacy of CAR-T.

In conclusion, we report a case of R/R PCNSL treated with CD19-directed CAR-T cell therapy that has maintained CR for over 1 year. There are few reports regarding CAR-T cell therapy for R/R PCNSL, but it is expected to be a new treatment for R/R PCNSL if the effectiveness and

Table 1 Previous reports regarding CAR-T cell therapy for PCNSL

Author, year	Age (years)	Sex	Disease location	KPS at study entry	Before CAR-T treatment	Infused cells	Cell dose ($\times 10^6$)	CRS max grade	Symptoms of neurotoxicity	Intervention for CRS/ neurotoxicity	Best response	Duration of response (days)
Siddiqi et al., 2021[14]	53	F	Left temporal lobe	90	NA	CD19	200	2	Headache, agitation, restlessness	Tocilizumab, dexamethasone	CR	273
	53	F	Corpus callosum	80	NA	CD19	115	1	Headache, dizziness, memory impairment	None	SD	13
	47	F	Bilateral temporal lobe, right basal ganglia	70	NA	CD19	200	1	Tremor, dysarthria, hallucinations	None	SD	32
	49	F	Right temporal lobe	90	NA	CD19	600	2	Concentration impairment, dysphasia	Tocilizumab, dexamethasone	CR	520
	42	F	Left basal ganglia	90	NA	CD19	600	1	Seizure, dizziness	None	CR	43
Li et al., 2020[19]	49	F	Left occipital parietal lobe	20	HD-MTX, rituximab, temozolomide, lenalidomide, ibrutinib	CD19/ CD22	6.0/kg	1	None	None	PR	30
Tu et al., 2019[13]	67	M	Right frontal lobe, right temporal parietal lobe	NA	HD-MTX, rituximab, temozolomide, ibrutinib, glucocorticoids	CD19/ CD70	182	None	Mild fatigue	None	CR	510
Siddiqi et al., 2019[22]	NA	NA	NA	NA	NA	CD19	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	CD19	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	CD19	NA	NA	NA	NA	NA	NA
This case, 2022	40	F	Right occipital lobe	100	Intraocular injection of MTX, HD-MTX, Ara-C, rituximab, CHOP, auto-PBSCT	CD19	350	2	None	Tocilizumab, methylprednisolone	CR	390

KPS, Karnofsky Performance Status; F, female; M, male; NA, not available; CR, complete remission; SD, stable disease; PR, partial remission

safety are demonstrated.

Ethics Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IRB#1911-023) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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