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LETTER TO THE EDITOR

Chimeric antigen receptor T-cell therapy for a patient Philadelphia chromosome-positive acute lymphoblastic leukemia with leukoencephalopathy who relapsed after bone marrow transplantation

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A short running title: CAR T-cell therapy for ALL with leukoencephalopathy

Key words: chimeric antigen receptor T-cell therapy, leukoencephalopathy, relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia

Abbreviations

ALL	acute lymphoblastic leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
BBB	blood–brain barrier
CAR	chimeric antigen receptor
CNS	central nervous system
CR	complete remission
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
ICANS	immune-related effector cell-associated neurotoxicity syndrome
LP	lumber puncture
mPSL	methylprednisolone
MRD	minimal residual disease

MRI	magnetic resonance imaging
TIT	triple intrathecal therapy

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To the editor:

Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy was developed for refractory and/or multiply relapsed B-cell precursor acute lymphoblastic leukemia (ALL). However, CAR T-cell therapy may cause systemic cytokine release syndrome (CRS) and immune-related effector cell-associated neurotoxicity syndrome (ICANS)[1-3]. The symptoms of ICANS include fatal cerebral edema[2,4]. Patients with active and symptomatic central nervous system (CNS) disease were excluded from the study as multiple deaths due to cerebral edema occurred during an anti-CD19 CAR T-cell treatment trial[5-7].

We report a post-transplant relapsed case of a 14-year-old girl with Philadelphia chromosome-positive ALL who was diagnosed with symptomatic leukoencephalopathy. She was first treated with dasatinib-combined multi-drug chemotherapy regimen when she was 11 years old, but she experienced a relapse during the reinduction phase in January 2019. She achieved a second hematological complete remission (CR) with salvage chemotherapy consisting of a hyper-CVAD regimen, ponatinib, and two cycles of blinatumomab[8]. In November 2019, the patient underwent unrelated bone marrow transplantation, resulting in a second relapse affecting the CNS with minimal residual disease (MRD) in the bone marrow. After achieving a third CR with blinatumomab and triple intrathecal therapy (TIT), CAR T-cell therapy was planned. A decline in cognitive function and language impairment were observed while maintaining CR with bridging chemotherapy consisting of ponatinib, 6-mercaptopurine, weekly vincristine, and bi-weekly TIT. Cranial magnetic resonance imaging (MRI) showed disseminated necrotizing leukoencephalopathy, suggesting active demyelinating lesions (Figs. 1A and 1B). As active leukoencephalopathy may result in severe neurotoxicity, tisagenlecleucel was postponed until leukoencephalopathy improved. As bridging chemotherapy, a mini hyper-CVAD regimen and

ponatinib were administered[9]. On day 21, follow-up MRI showed an improvement of leukoencephalopathy (Figs. 1C and 1D), and her speech and cognitive function gradually improved. The lumbar puncture (LP) before CAR T-cell infusion was normal; a bone marrow aspiration showed bcr-abl negative and flow cytometry-based MRD negative CR.

After lymphodepletion chemotherapy with cyclophosphamide and fludarabine, the patient received a single dose of tisagenlecleucel (total cell dose: 0.9 x 10^8) 7 months after the second relapse (day 1). On day 4, she developed fever ≥38.0℃, grade 3 headache and grade 2 tachycardia, abdominal pain, vomiting, and diarrhea according to the Common Terminology Criteria for Adverse Events version 5[10]; antipyretics and broad spectrum antibiotics were initiated. She shortly developed hypertension, and her C-reactive protein level increased to 35.1 mg/dL on day 5. These symptoms indicated grade 1 CRS, for which tocilizumab (8 mg/kg) is recommended, according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading[2,11]. Despite two additional doses of tocilizumab and the initiation of 2 mg/kg/day methylprednisolone (mPSL), her symptoms worsened on day 6. Dysphasia, anxiety, and a low level of consciousness were also present. On day 7, a grade 3 seizure occurred; midazolam was initiated under mechanical ventilation. Although computed tomography scans of the brain did not show edema, the opening and closing cerebrospinal fluid (CSF) pressures during LP were >30 cmH_2O, which were markedly high. Mononuclear and polynuclear cell counts and protein levels in the CSF were elevated. Fluorescence-activated cell sorting of the CSF showed that 7.8% of the $CD3^+$ cells were CAR T-cells (Supplemental Figure S1). On day 8 and after the fourth administration of tocilizumab, fever resolved, and her blood pressure returned to normal. On day 12, although the follow-up MRI showed exacerbation of leukoencephalopathy (Figs. 1E and 1F), her symptoms continued to improve; thus, mPSL was

tapered off on day 15. On day 26, LP was performed, which showed a normal CSF, and MRI findings on day 30 revealed improvement of leukoencephalopathy (Figs. 1G and 1H). Twelve months after CAR T-cell infusion, she maintained CR and her cognitive function improved.

In this patient, distinguishing neurological changes as symptoms of ICANS from exacerbation of leukoencephalopathy was challenging because most symptoms overlapped. When the CRS began to resolve on day 7, the seizure occurred. According to the ASTCT ICANS Consensus Grading, the elevated intracranial pressure indicated grade 4 neurotoxicity[2]. Increased protein concentration and leukocyte and CAR T-cell infiltration into the CSF in patients with neurotoxicity indicate increased permeability of the blood–brain barrier (BBB), and preexisting neurologic comorbidities are associated with an increased risk of neurotoxicity[12,13]. Higher tumor burden and in vivo CAR T-cell numbers resulted in a higher risk of CRS and neurotoxicity[1,12]. In our case, CRS and ICANS occurred despite negative MRD. The disruption of the BBB due to preexisting leukoencephalopathy might have facilitated the transition of activated CAR T-cells into the CNS[14]. The management and treatment of ICANS remain controversial. Researchers have reported that tocilizumab and/or early corticosteroid administration appears to be more effective in ICANS management that occurs concurrently with CRS[3,4,15], whereas others have reported the limited efficacy of tocilizumab against ICANS[2,16]. As the presence of neurological comorbidities prior to CAR T-cell infusion may increase the risk of ICANS, the time of CAR T-cell infusion should be carefully determined after neurological conditions have been evaluated. When neurological comorbidities are in control, CAR T-cell therapy can be initiated while providing appropriate supportive care and monitoring for neurological adverse events. Further studies are required to clarify the exact timing of CAR T-cell therapy.

Conflict of interest

The authors declare no conflicts of interest.

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142 **Figure legends**

143 Figure 1

144 Left row: Axial high-intensity T2/fluid attenuated inversion recovery magnetic resonance image
145 (MRI) shows wide subcortical edema. Right row: axial T1 MRI with gadolinium shows a
146 necrotic-appearing subcortical enhancement pattern. On admission (A, B), after bridging
147 chemotherapy (C, D), day 12 post CAR T-cell infusion (E, F), and day 30 (G, H).

148

149 Supplemental Figure S1

150 Fluorescence-activated cell sorting of cerebrospinal fluid after seizure on day 7 indicates 7.8% of
151 $CD3^+$ positive cells were detected as CAR T-cells.