Continuous blood purification successfully treated a fatal cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T cell therapy: case report

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Abstract

Cytokine release syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) after Chimeric antigen receptor (CAR) T cell treatment are common, and severe CRS (sCRS) could be life threatening. IL-6 receptor antibody and steroid are recommended for CRS, but no clear strategies exist for steroid-resistant sCRS. Thus, this study reported a case of resistance to tocilizumab and pulse therapy of methylprednisolone while suffering from grade 4 CRS and ICANS. After plasma exchange for two times and continuous renal replacement treatment combined with ruxolitinib, the patient survived with only renal injury, and achieved complete remission with negative minimal residual disease.

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Figures: 2

Abbreviations

CRS	Cytokine release syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome
CAR-T	Chimeric antigen receptor T cell
TPE	therapeutic plasma exchange
CRRT	continuous renal replacement therapy

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Abstract : Cytokine release syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) after Chimeric antigen receptor (CAR) T cell treatment are common, and severe CRS (sCRS) could be life threatening. IL-6 receptor antibody and steroid are recommended for CRS, but no clear strategies exist for steroid-resistant sCRS. Thus, this study reported a case of resistance to tocilizumab and pulse therapy of methylprednisolone while suffering from grade 4 CRS and ICANS. After plasma exchange for two times and continuous renal replacement treatment combined with ruxolitinib, the patient survived with only renal injury, and achieved complete remission with negative minimal residual disease.

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood, with B lineage accounting for 75%–85% of all cases(1). Owing to the development of chemotherapy, B-ALL cure rates exceed 90% in children, but the cure rate for children with relapsed and/or refractory (R/R) B-ALL remains low(2, 3). In 2017, the CD19-targeted CAR T-cell product tisagenlecleucel was approved by the FDA for children and young adults (aged < 25 years) in R/R B-ALL(4). With the development of CAR T-cell immunotherapy, the CR rate has reached almost 90% in R/R B-ALL(5, 6).

As a response to CAR T-cell, cytokine release syndrome (CRS) is an inflammatory syndrome that occurred in 50%–90% of patients after infusion, with fever, hypoxemia, hypotension requiring multiple vasopressors, multiple-organ failure (MOF), or even a life-threatening condition(7). The standardized grading evaluation and first-line therapies for CRS are well established(7, 8). Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) have been described in 30%–64% of patients(9), repetitive seizures or coma have been described in 10%–20% patients, and 1% of patients died from rapid cerebral edema(10). For fatal CRS and ICANS, patient transfer to intensive care unit, mechanical ventilation, multiple vasopressors, anti-IL-6 therapy, high-dose methylprednisolone are recommended(9, 11). However, for patients resistant to methylprednisolone and tocilizumab, no definite treatment is available in published guidelines. Herein, a pediatric case of grade 4 CRS and grade 4 ICANS after CAR T-cell infusion was reported. Through therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT), CRS was controlled, MOF was improved, and ultimately, the patient achieved complete remission (CR). To the authors' knowledge, this study was the first to report the use of TPE combined with CRRT for tocilizumab-resistant CRS and ICANS.

CASE PRESENTATION

Background before CAR T-cell therapy

A 12-year-old girl was diagnosed with B-ALL 14 months ago. Bone marrow (BM) morphology showed that lymphoblastic cells occupied 46%. Immunophenotype via flow cytometry (FCM) demonstrated 51% malignant cells expressing $CD38^+$, $CD10^+$, $CD19^+$, $CD20^+$, $CD34^+$, HLA-DR^+, $CD71^+$, and $cCD79a^+$. Genetic examination showed no specific fusion gene. According to CCLG 2008 protocol(12), she was classified as intermediate risk. She received five courses of intense chemotherapy, and minimal residual disease (MRD) was continuously positive. Three months ago, the BM test showed relapse. Then, she received continuous strengthened chemotherapy, including vincristine, doxorubicin, L-asparaginase, ifosfamide, and three doses of bortezomib. The BM morphology still showed no remission. She was diagnosed as R/R ALL and recruited

to the CAR T-cell clinical trial. This trial was registered at the Chinese Clinical Trial Registry as study ChiCTR-OPN-17013507.

CAR T-cell treatment and related toxic response

She first underwent T-cell collection via apheresis, followed by T-cell engineering and expansion. She received lymphodepleting chemotherapy, including fludarabine 25 mg/m^2 for 3 days and 250 mg/m^2 cyclophosphamide for 3 days before infusion. Then, she was administered a dose of CD19$^+$CAR Ts (a total of 2.97 $\times$ 10^6 cells/kg). The BM morphology before reinfusion showed 11% malignant cells, and FCM showed 6.01% CD19$^+$ malignant cells expressing CD19$^+$, CD34part$^+$, CD10$^+$, CD123$^+$, CD58$^+$, CD38, and$^+$CD20$^+$.

On day 1 after reinfusion, the patient started having fever, with a continuous high temperature of up to 39.7 °C, accompanied with dizziness and hypotension refractory to fluid boluses. Her condition was graded as grade 2 CRS, and she was administered with tocilizumab (8 mg/kg) and dopamine (5 ug/kg/min). Her blood pressure (BP) was maintained at 90/40 mmHg. Meanwhile, here IL-6 level rapidly rose to 874 pg/mL, but her heart function remained normal. From day 2 to day 4, the patient was continuously febrile, and her temperature was up to 39.7 °C, with hypotension, dizziness, lassitude, and edema of the limbs. Her BP ranged 85–101/33–64 mmHg. Multiple vasopressors, including dopamine and dobutamine, were used, and the condition was evaluated as grade 3 CRS. Routine blood tests showed that the white blood cells, hemoglobin, and platelet decreased at a very low level (Table 1), and the IL-6 level was over 5000 pg/mL (Figure 1A). The patient was administered with a total of seven doses of tocilizumab (8 mg/kg/dose) and 5 mg dexamethasone every 12 h to control sCRS. Albumin, platelets, and red blood cells were administered as supportive treatments. Meropenem, vancomycin, and voriconazole were used against infection. On day 5, the patient presented with disseminated intravascular coagulation (DIC). Blood products, including fibrinogen, plasma, and platelets, were provided to treat DIC and capillary leakage. On day 6, the patient suddenly felt depressed, she was unarousable, and her physical examination showed chemosis. Then, she developed seizure three times, lasting approximately 2–3 minutes every time. Computerized tomography (CT) showed diffuse cerebral edema (Figure 2). She was classified as grade 4 ICANS with elevated intracranial pressure. Diazepam was given to control the seizure, and sufficient mannitol and methylprednisolone (25 mg/kg) pulse therapy was administered. However, the patient's condition still deteriorated. On day 8, she was in a comatose state, with a Glasgow coma scale of 6. She also developed acute kidney injury (AKI) with oliguria, dyspnea, heart failure, cerebral edema, and DIC. Laboratory examination showed that the IL-6 level was more than 5000 pg/mL, and the creatinine clearance rate (Ccr) decreased to 38 ml/min/1.73m^2, classified as grade 3 AKI, while the CAR-T cell reached 6990 copies/μg DNA.

She was immediately administered with invasive mechanical ventilation due to her deep coma state and dyspnea. The B-type natriuretic peptide increased to more than 35000 pg/mL. Echocardiography showed 51% left ventricle ejection fraction. Chest CT showed pulmonary edema. Abdominal CT showed intestinal wall thickening. Dexamethasone and methylprednisolone were continuously provided to control sCRS. Levetiracetam was used to prevent symptomatic epilepsy. TPE was also used continuously for 2 days at 2000 ml (50 mL/kg) plasma once a day to remove cytokines. The blood pump flow rate was 100 ml/min, and the flow rate of replacement fluid was 1000 mL/h, lasting for 2 h every day. On day 9, the patient still had fever, and her maximum body temperature was 38.6 °C (Figure 1B). Thus, ruxolitinib (RUX, 0.25 mg/kg, every 12hour) was used to inhibit the immune response. The patient's condition still deteriorated, and she had continuous oliguria (less than 1 mL/kg/h). The Ccr decreased to 25.9 mL/min/1.73m^2 . Creatine kinase increased to 1208 U/L, considering rhabdomyolysis. CRRT was administered as the patient presented with acute kidney injury, oliguria, edema, and heavy volume load. However, she had low coagulation function and could not tolerate systemic anticoagulant therapy. Thus, regional citrate anticoagulation (RCA) was administered for the increased bleeding risk. The dialysate was formulated without calcium. The initial RCA flow rate was 120 ml/h [calculated using the formula (1.5–2.0) $\times$ blood pump flow rate every minute]. The initial blood pump flow rate was 80 ml/min (2 mL/kg/min). Initial 10% calcium gluconate flow rate was 10 mL/h [calculated using the formula (0.1–0.2) $\times$ blood pump flow rate every minute]. The Ca^{2+} concentration of external circulation was maintained at 0.25–0.35 mmol/L, while that of internal circulation was 0.8–1

mmol/L, as shown by the dynamic determination of arterial blood gas. Interleukin and renal function were tested before and after plasma exchange and CRRT. On day 10, the IL-6 and creatine levels obviously decreased (Figure 1A). Due to economic reasons, the patient's guardian refused continuing CRRT. Afterwards, by continuing to administer RUX and Dex, the patient's consciousness gradually recovered, with only with a continuously high level of creatine (Figure 1C). On day 28, the BM smear achieved CR, and FCM was negative. As of now, she is still in complete CR 3 months after CAR-T treatment, and CAR-T cell could be still found in PB (Figure1D).

DISCUSSION

The common and severe toxicities related to CAR T-cell therapy for patients with B-ALL are CRS and neurotoxicity. After CAR-T cells are reinfused to the body, they could bind to target antigen and then mediate the destruction of tumor cells. After the tumor cell is destroyed, cytokines could be released, including INF-γ, TNF-α, IL-2, IL-6, and IL-10(13), which all mediate CRS. IL-6 contributes to the key symptoms of CRS, leading to vascular leakage, DIC, myocardial dysfunction. These AEs are reversible and treatable with appropriate strategies, but they could become severe or life threatening(14).

The guidelines show IL-6 receptor antibody and corticosteroids are effective strategies for sCRS. Corticosteroids could be administered, especially in situations in which tocilizumab is not fully effective. Rebecca reported that the preemptive use of tocilizumab and steroids could reduce the sCRS rate, with no effect on MRD-negative rate or severe neurotoxicity(15). Thus, in the present case, several doses of IL-6 receptor antibody and dexamethasone were used preemptively, but the patient's condiction still deteriorated rapidly, followed by neurotoxic manifestations and resistance to high-dose methylprednisolone.

NCCN demonstrated that plasma exchange may be useful for CRS combined with HLH(16). However, for conventionally therapeutic-resistant fetal CRS and ICANS, no clear guidelines about blood purification could be found. Prior case reports showed that plasma exchange or hemofiltration may be the alternative therapies for sCRS(17, 18). For sCRS, Heng recommended that TPE may be useful to eliminate cytokines, such as IL-6, IL-10, and TNF-γ(19). However, in CRS caused by sepsis and septic shock, CRRT seems more common. Aygun preferred hemofiltration, not only for AKI but also for reducing cytokine storms in a model of continuous venovenous hemofiltration(20). Ning showed that in sepsis, IL-6, IL-10, and TNF-α could be eliminated rapidly in high-volume hemofiltration compared with CRRT. The rates of replacement fluid at 60 mL/kg/h were more beneficial than at 30 mL/kg/h(21). In the present study, CRRT not only kept the fluid balance but also decreased the level of interleukins. For severe cytokine storm, TPE and high-dose CVVH are recommended in COVID-19. TPE could clear factors, including all cytokines, antibodies, complement components, immune complexes, and endotoxin. However, it could not fully remove cytokines in the immune system. High-dose CVVH ($>$ 35 mL/kg/min) are recommended at the interval time. CVVH may have extra-renal benefits in increasing the clearance of middle-sized molecular inflammatory factors, and it may be suitable for hemodynamically unstable patients with cytokine storm. These findings showed that combination therapy could remove most toxic substances; however, disadvantages could not be warranted in single treatment for CRS(22). In addition, CRRT did not influence the expansion of CAR T-cell, indicating the effectiveness and safety of continuous blood purification in sCRS.

For patients refractory to steroids and developing life-threatening consequences, RUX may be useful for numerous pro-inflammatory cytokines to promote signaling via intracellular pathways involving Janus kinases. However, whether RUX could control CRS without toxicity against therapeutic T cells remains unclear. Jing reported that JAK-state inhibitor RUX could rapidly resolve CRS in a small-scale cohort(23). Similar with prior studies, the present study showed that RUX is useful in reducing CRS, with no influence in CAR T-cell amplification.

The mechanism underlying the development of ICANS remains unclear, and massive release of inflammatory cytokines and alterations in blood–brain barrier exacerbate the development of ICANS. Serum cytokine levels, including those of IL-6, IL-10, IFN-γ, TNF-α, and Ang-2, continuously increased in ICANS(24). For severe ICANS with grades 2, 3, or 4, corticosteroids are recommended to decrease systemic and CNS

inflammation. However, no consensus guidelines are available with regard to the exact dose, timing, and duration of steroids(9). For the patient in the present study, high doses of methylprednisolone seemed to show no reaction. As tocilizumab could not cross the blood-brain barrier, levetiracetam was administered to control epileptic seizure. Plasma exchange was administered to reduce the IL-6 level, and continuously administering it two times seemed useful, followed by RUX and a low dose of methylprednisolone. The brain function of the patient rapidly recovered without neurologic symptoms and/or signs.

The incidence of AKI in adults accounts for 30%, mostly in patients with previous autologous or allogeneic stem cell transplantation. Though the incidence of grade 3 AKI was 8.7%, most patients could recover kidney function within 30 days(25). The patient in the present study had severe AKI due to sCRS but no recovery to baseline was observed, mainly because of insufficient administration of CRRT.

For sCRS, MOF, and ICANS in patients refractory under steroids, continuous blood purification seemed useful. This case demonstrated that at least two times of plasma exchange combined with CRRT could be administered at intermission. RUX also may be useful in reducing the toxic effects. As ICANS and AKI are reversible, active interventional strategies should be conducted.

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Conflict of Interest statement The author declare that they have no conflict of interest.

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`Table1 Blood routine test and coagulation function after CAR.docx` available at https://authorea.com/users/622168/articles/711693-continuous-blood-purification-successfully-treated-a-fatal-cytokine-release-syndrome-and-immune-effector-cell-associated-neurotoxicity-syndrome-after-chimeric-antigen-receptor-t-cell-therapy-case-report

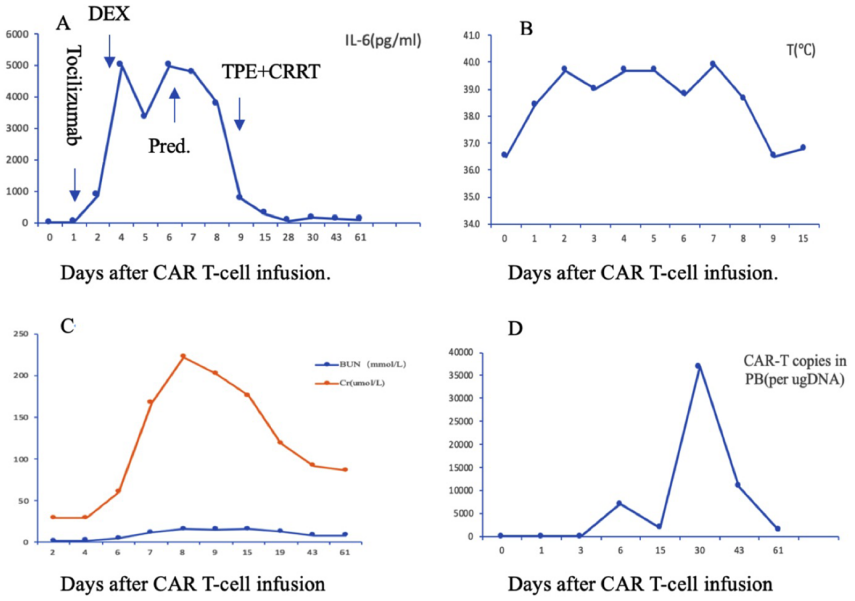

Figure1A-D: Figure1A: The IL-6 level after CAR-T treatment, on day 7 it achieved peak level then rapidly declined on day9 after TPE and CRRT. Figure 1B :The temperature after CAR-T cell infusion, it returned to normal level on day 9.Figure1C:The renal function after CAR-T cell infusion.Figure1D:The CAR-T cell copies after CAR-T treatment, it achieved peak level on day30,and now it still can be tested at a low level.

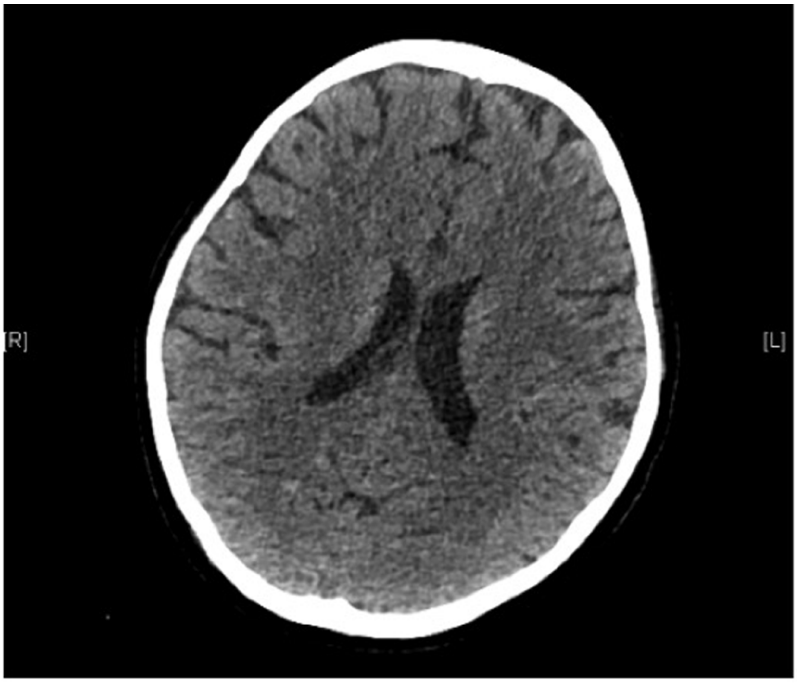

Figure2: head CT showed the sulci swelling and unclear structure.