CASE REPORT

OPEN

# Novel Use of Extracorporeal Blood Purification for Treatment of Severe, Refractory Neurotoxicity After Chimeric Antigen Receptor T-Cell Therapy—A Case Report

**Kai Singbartl, MD, MPH**[1]
**Allison Rosenthal, DO**[2]
**Jose Leis, MD, PhD**[2]
**Bhavesh Patel, MD**[1]
**Ayan Sen, MD, MSc**[1]

**BACKGROUND:** Chimeric antigen receptor T-cell therapies (CAR-T) are transforming the treatment of B-cell leukemias and lymphomas. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome represent common, potentially life-threatening toxicities from chimeric antigen receptor T-cell therapy treatment.

**CASE SUMMARY:** We present a 53-year-old patient with primary refractory high-grade B-cell lymphoma who developed severe, refractory neurotoxicity following chimeric antigen receptor T-cell therapy but exhibited complete recovery after extracorporeal blood purification with CytoSorb (CytoSorbents, Monmouth Junction, NJ).

Six days after chimeric antigen receptor T-cell therapy infusion, the patient developed cytokine release syndrome grade 3, prompting administration of dexamethasone and tocilizumab, a monoclonal antibody against the interleukin-6 receptor. His C-reactive protein levels started to decrease with tocilizumab and dexamethasone treatments. However, his ferritin levels continued to rise, and his interleukin-6 levels were above the upper detection threshold. Thirty-six hours later, the patient showed improved cytokine release syndrome but developed severe immune effector cell-associated neurotoxicity syndrome with predominant encephalopathy (grade 3) despite treatment with dexamethasone/methylprednisolone, tocilizumab, and anakinra. We therefore sought a rescue strategy to remove inflammatory mediators. Following emergency use authorization, we initiated extracorporeal blood purification with CytoSorb (CytoSorbents).

Four-day extracorporeal blood purification resulted in complete resolution of immune effector cell-associated neurotoxicity syndrome and greater than 95% reduction in interleukin-6 levels without side effects. The patient was discharged home 10 days later with no signs of neurotoxicity or other secondary end-organ dysfunction.

**CONCLUSIONS:** Our case represents the first reported, successful application of extracorporeal blood purification with CytoSorb (CytoSorbents) to treat severe, refractory neurotoxicity following chimeric antigen receptor T-cell therapy.

**KEY WORDS:** chimeric antigen receptor T-cell therapies; extracorporeal blood purification; neurotoxicity

Anti-CD19 chimeric antigen receptor T-cell therapies (CAR-T) represent a promising approach for treatment of refractory $CD19^+$ B-cell malignancies, for example, acute and chronic B-cell leukemias and B-cell non-Hodgkin lymphomas (1). CAR-T, however, carry unique, potentially life-threatening toxicities that require specialized monitoring and management.



**DOI: 10.1097/CCE.0000000000000472**

CAR-T encompass autologous or allogeneic T cells that are genetically engineered to express chimeric antigen receptors, redirecting the cytotoxic effects toward tumor cells. Recognition of tumor-associated antigens initiates immune proliferation and release of cytokines by effector CAR-T cells. Interleukin (IL)-6, interferon gamma (IFNγ), and granulocyte-macrophage colony-stimulating factor as well as IL-8, IL-10, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1b all are considered crucial mediators in this response (2, 3).

Overwhelming and widespread immune activation after CAR-T can lead to two potentially life-threatening adverse reactions: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (4). CRS typically manifests with general symptoms, such as fever, weakness, and myalgias, but it can involve any organ system and lead to hemodynamic instability, respiratory distress, and acute kidney or liver injury. Cases of fulminant hemophagocytic lymphohistiocytosis (HLH), a severe immune activation with lymphohistiocytic tissue infiltration and immune-mediated multiple organ failure, have also occurred after CAR-T (4). CRS grading includes presence and severity of fever, hypotension, and hypoxemia but not laboratory markers of inflammation (5). ICANS frequently manifests as encephalopathy but also delirium, dizziness, aphasia, motor dysfunction, tremor, ataxia, seizure, dyscalculia, or myoclonus. ICANS grading involves screening for encephalopathy via the Immune Effector Cell-Associated Encephalopathy (ICE) score as well as evaluating for level of consciousness, motor symptoms, seizures, and elevated intracranial pressure/cerebral edema (Tables 1 and 2) (5). ICANS often accompanies CRS, but its clinical course does not always parallel that of CRS (6).

Current management of CAR-T toxicities entails supportive care, corticosteroids, and anti-IL-6 therapy (4). Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor and thereby blocks binding of IL-6 to its receptor. Tocilizumab is U.S. Food and Drug Administration (FDA)-approved for treatment of CRS after CAR-T.

Hemoadsorption is an extracorporeal blood purification technique intended to remove various molecules, for example, cytokines, from the bloodstream. During hemoadsorption, blood flows through adsorbent columns, which are made of porous polymer beads that vary in size, side chains, and chemical properties to target molecules of interest (7). With the exception of emergency use authorization for severe coronavirus disease 2019, hemoadsorbtion devices have not received FDA approval. Some devices, including CytoSorb (CytoSorbents, Monmouth Junction, NJ), have been approved within the European Union for over 10 years and used in over 130,000 treatments with severe inflammatory syndromes (8).

## CASE PRESENTATION

With written informed consent, we present a 53-year-old male patient with primary refractory high-grade B-cell lymphoma and rearrangements of MYC/BCL2 and BCL6, who had failed rituximab, etoposide, prednisone, vincristine, Cytoxan, and doxorubicin and rituximab, oxaliplatin, cytarabine, and dexamethasone

**TABLE 1.**
**Immune Effector Cell-Associated Encephalopathy Score**

| Points | Orientation (Year, Month, City, Hospital) | Naming (Name Three Objects) | Following Simple Commands | Writing a Standard Sentence | Attention (e.g., Count Backward From 100 by 10) |
|---|---|---|---|---|---|
| 4 | 4 (of 4) | | | | |
| 3 | 3 (of 4) | 3 (of 3) | | | |
| 2 | 2 (of 4) | 2 (of 3) | | | |
| 1 | 1 (of 4) | 1 (of 3) | Yes | Yes | Yes |
| 0 | 0 (of 4) | 0 (of 3) | No | No | No |

Maximum score is 10.

Compiled after American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells (5).

**TABLE 2.**
**Immune Effector Cell-Associated Neurotoxicity Syndrome**

| | Neurotoxicity Domain | | | | |
|---|---|---|---|---|---|
| Grade | Immune Effector Cell-Associated Encephalopathy Score | Depressed Level of Consciousness | Seizure | Motor Findings | Elevated ICP/ Cerebral Edema |
| 1 | 7–9 | Awakens spontaneously | | | |
| 2 | 3–6 | Awakens to voice | | | |
| 3 | 0–2 | Awakens only to tactile stimulus | Clinical seizure with rapid resolution or nonconvulsive seizures on electroencephalography with resolution after intervention | | Focal/local edema on neuroimaging |
| 4 | 0 (patient is unable to perform) | Unarousable or requires vigorous or repetitive stimuli to arouse | Prolonged seizure (> 5 min) or repetitive seizures without return to baseline in between | Deep focal motor weakness (e.g., hemiparesis or paraparesis) | Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing triad |

Compiled after American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells (5).

treatments. He received lymphocyte-depleting chemotherapy with fludarabine and Cytoxan 5 days prior to hospital admission. CAR-T infusion (axicabtagene ciloleucel) on the day of hospital admission (day 0) (**Fig. 1**) commenced without immediate side effects.

C-reactive protein (CRP) rose on day 3, whereas his ferritin levels remained normal until day 5 (Fig. 1*A*). Clinical assessments for CRS and ICANS were negative at that time. On day 4, he developed a fever of 39.1°C (grade 1 CRS) (Fig. 1*B*). His examination was negative for ICANS (ICE score 10/10), whereas his CRP continued to rise. In the evening of day 5, he became mildly disoriented and demonstrated altered handwriting.

Ongoing fevers and new hypotension on day 6 prompted the first administration of tocilizumab (grade 2 CRS, ICE 9/10) (Fig. 1, *A* and *B*), followed by two additional doses later. He also required intermittent fluid resuscitation and treatment with dexamethasone. His CRP levels started to decrease, whereas his ferritin levels increased further.

Worsening renal function, evolving hyperactive delirium, and need for vasopressors mandated a transfer to the ICU on hospital day 8. A bone marrow biopsy at that time showed no evidence of lymphoma but prominent hemophagocytosis, consistent with HLH/macrophage activation syndrome due to CRS.

Despite ongoing supportive care, including continuous renal replacement therapy (CRRT), and treatment with (escalating doses of) dexamethasone, the patient's clinical status did not improve. Workup for underlying infections remained negative, except for positive *Clostridium difficile* surveillance (polymerase chain reaction for toxin) with ongoing diarrhea. The patient had tested positive for *C. difficile* toxin approximately 1 month prior to admission. Neuroimaging and electroencephalography studies were also unremarkable. A lumbar puncture was deferred because of refractory low platelet counts (Fig. 1*B*) and fibrinogen levels (less than 110 mg/dL). He became increasingly encephalopathic (ICE 7/10). His ferritin levels were still rising, and IL-6 levels were above the upper detection limit (greater than 400 pg/mL). Additional doses of tocilizumab and one dose of anakinra (IL-1 receptor antagonist) were given, followed by methylprednisolone.

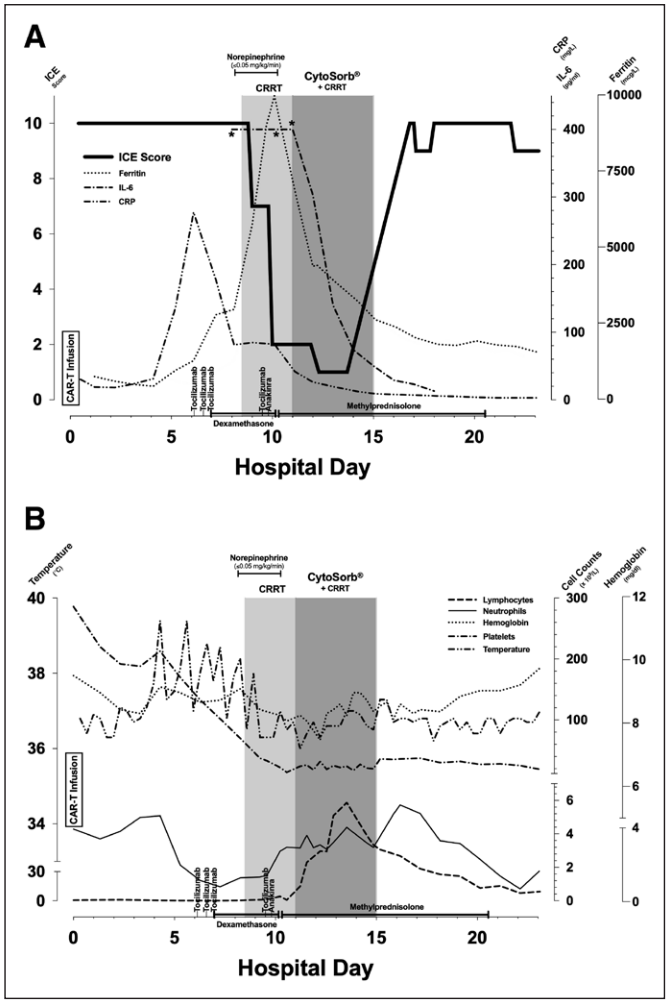


**Figure 1.** Patient's hospital course. **A**, Course of Immune Effector Cell-Associated Encephalopathy (ICE) in relationship to inflammatory markers and treatments throughout hospitalization (days 0–25) for chimeric antigen receptor T-cell therapy (CAR-T) infusion. IL-6 plasma concentrations above the upper detection limit (greater than 400 μg/L) are displayed as equaling 400 μg/L and marked with "*". **B**, Course of hematological parameters and treatments throughout hospitalization (days 0–25) for CAR-T infusion. CRP = C-reactive protein, CRRT = continuous renal replacement therapy.

Drastically worsening encephalopathy (ICE 2/10, protected airway, and hospital day 9) together with persistently elevated inflammatory markers led us to explore novel rescue options. After careful consideration of risks and benefits, we obtained emergency use authorization for extracorporeal blood purification with CytoSorb (CytoSorbents) from our local Institutional Review Board. Continuous hemoadsorption with CytoSorb (CytoSorbents) was initiated on hospital day 11. Six CytoSorb (CytoSorbents) cartridges, for 12–24 hours each, were used over 4 days in conjunction (predialyzer) with standard CRRT (continuous veno-venous hemodiafiltration, Prismaflex M150 with AN69 membrane hemofilter, Baxter Healthcare Corporation, Deerfield, IL, blood flow 250 mL/min, fluid removal rate 0–250 mL/hr, and total effluent flow rate 25–30 mL/kg/hr). Because of persistent thrombocytopenia and low fibrinogen levels, we refrained from systemic anticoagulation. The treatment was well tolerated without any obvious side effects.

Inflammatory markers, in particular IL-6, started to decline rapidly within 48 hours of hemoadsorption and continued to do so throughout the treatment course (Fig. 1*A*). This was followed by complete neurologic and renal recovery over the next 3 days (ICE score 10/10) (Fig. 1*A*). The patient was transferred out of the ICU the next day (hospital day 16) and continued to recover throughout the remainder of his hospital stay. He was discharged home on hospital day 25 without any signs of secondary end-organ dysfunction and is currently undergoing CAR-T follow-up care.

## DISCUSSION

Following CAR-T infusion, our patient developed CRS followed by ICANS 4 days later. Both CRS and ICANS are well-known adverse effects after CAR-T and the result of an overwhelming immune response. Treatment with repetitive doses of tocilizumab and dexamethasone together with supportive care appeared to resolve the clinical symptoms of CRS. On the contrary, ICANS progressed rapidly and was refractory to currently accepted treatment options, including blockade of individual cytokines with tocilizumab and anakinra. Similarly, available data suggest that most patients with neurotoxicity do not respond to tocilizumab treatment (3, 6).

Selective blockade of individual cytokines also poses risks that might have contributed to the observed treatment failure. Administration of tocilizumab can lead to an increase in IL-6 and soluble IL-6 receptor levels, reflecting states of increased production or decreased clearance of IL-6 (9, 10). IL-6 can cross the blood-brain barrier and exert neurotoxic effects. Tocilizumab is not expected to cross over, largely because of its size (11). Published observations that tocilizumab administration is associated with precipitation or worsening of ICANS further support this concept and make a delayed response in our case unlikely (11–13). Here,

our patient did not develop ICANS until after initiation of tocilizumab treatment and drastically deteriorated after the fourth dose.

IL-6 is not the only cytokine involved. Selective blockade of single mediators might not be sufficient to attenuate the overall response. We therefore sought a rescue strategy that allowed for broad-spectrum, continuous cytokine elimination rather than selectively blocking individual cytokines. We selected hemoadsorption with CytoSorb (CytoSorbents), an extracorporeal blood purification technique. Previous case reports and smaller studies of various systemic inflammatory conditions, for example, septic shock, and pancreatitis, have indicated clinical improvement after treatment with CytoSorb (CytoSorbents). Sepsis, like CRS or ICANS, is characterized by the circulation of inflammatory cytokines. Extracorporeal blood purification techniques to remove cytokines during sepsis have been of great interest for a long time (8). Various techniques, including hemofiltration, hemoperfusion, intermittent or continuous high-volume hemofiltration, plasmapheresis, or hemoadsorption, have been studied to remove cytokines. Only plasma exchange or hemoadsorption seem to be effective extracorporeal blood purification techniques during sepsis (8, 14, 15). Standard CRRT protocols and equipment, as in our case, do not remove cytokines in a relevant manner (16–18).

CytoSorb (CytoSorbents) unselectively removes substances from blood by means of hemoadsorption to biocompatible porous polymer beads, packed into cartridges (7). CytoSorb (CytoSorbents) can remove substances, ranging from 5 to 60 kDa in size, including IL-6 and other cytokines (7). Although exact clinical data are not available, it is unlikely that it removes tocilizumab or other antibodies from the circulation. However, CytoSorb (CytoSorbents) will likely remove low-molecular-weight substances like dexamethasone or methylprednisolone.

Two case reports have shown hemodynamic and respiratory improvement during CytoSorb (CytoSorbents) treatment in patients with CRS after CAR-T infusions (17, 18). A current randomized controlled trial focuses on changes in plasma IL-6 in patients with severe CRS or ICANS after CAR-T (clinicaltrials.gov; NCT0404843).

## Conclusion

To this end, we present the first successful treatment of severe, refractory CAR-T-induced neurotoxicity employing extracorporeal blood purification with CytoSorb (CytoSorbents). Considering the inherent limitations of a case report, we cannot truly assess the impact of this treatment on our patient's recovery. Nonetheless, the results of our novel approach to treat an otherwise potentially fatal complication from CAR-T deserve future research efforts.

1 *Department of Critical Care Medicine, Mayo Clinic, Phoenix, AZ.*

2 *Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Phoenix, AZ.*

*The authors have disclosed that they do not have any potential conflicts of interest.*

*For information regarding this article, E-mail: ks.ms@posteo.de*

## REFERENCES

1. June CH, Sadelain M: Chimeric antigen receptor therapy. *N Engl J Med* 2018; 379:64–73
2. Schmidts A, Wehrli M, Maus MV: Toward better understanding and management of CAR-T cell-associated toxicity. *Annu Rev Med* 2021; 72:365–382
3. Freyer CW, Porter DL: Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies. *J Allergy Clin Immunol* 2020; 146:940–948
4. Neelapu SS, Tummala S, Kebriaei P, et al: Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nat Rev Clin Oncol* 2018; 15:47–62
5. Lee DW, Santomasso BD, Locke FL, et al: ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019; 25:625–638
6. Santomasso BD, Park JH, Salloum D, et al: Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov* 2018; 8:958–971
7. Bonavia A, Groff A, Karamchandani K, et al: Clinical utility of extracorporeal cytokine hemoadsorption therapy: A literature review. *Blood Purif* 2018; 46:337–349
8. Honore PM, Hoste E, Molnár Z, et al: Cytokine removal in human septic shock: Where are we and where are we going? *Ann Intensive Care* 2019; 9:56
9. Uchiyama Y, Yoshida H, Koike N, et al: Anti-IL-6 receptor antibody increases blood IL-6 level via the blockade of IL-6 clearance, but not via the induction of IL-6 production. *Int Immunopharmacol* 2008; 8:1595–1601

10. Nishimoto N, Terao K, Mima T, et al: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008; 112:3959–3964
11. Gust J, Hay KA, Hanafi LA, et al: Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov* 2017; 7:1404–1419
12. Nellan A, McCully CML, Cruz Garcia R, et al: Improved CNS exposure to tocilizumab after cerebrospinal fluid compared to intravenous administration in rhesus macaques. *Blood* 2018; 132:662–666
13. Lee DW, Gardner R, Porter DL, et al: Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014; 124:188–195
14. Rimmer E, Houston BL, Kumar A, et al: The efficacy and safety of plasma exchange in patients with sepsis and septic shock: A systematic review and meta-analysis. *Crit Care* 2014; 18:699
15. Chang T, Tu YK, Lee CT, et al: Effects of polymyxin B hemoperfusion on mortality in patients with severe sepsis and septic shock: A systemic review, meta-analysis update, and disease severity subgroup meta-analysis. *Crit Care Med* 2017; 45:e858–e864
16. Hattori N, Oda S: Cytokine-adsorbing hemofilter: Old but new modality for septic acute kidney injury. *Ren Replacement Ther* 2016; 2:41
17. Stahl K, Schmidt BMW, Hoeper MM, et al: Extracorporeal cytokine removal in severe CAR-T cell associated cytokine release syndrome. *J Crit Care* 2020; 57:124–129
18. Bottari G, Merli P, Guzzo I, et al: Multimodal therapeutic approach of cytokine release syndrome developing in a child given chimeric antigen receptor-modified T cell infusion. *Crit Care Explor* 2020; 2:e0071