CytoSorb®

Case of the week 33/2021

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

Singbartl K[1], Rosenthal A[2], Leis J[2], Patel B[1], Sen A1·
[1] Department of Critical Care Medicine, Mayo Clinic, Phoenix, AZ, USA
[2] Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Phoenix, AZ, USA
Crit Care Explor 2021; 3(7): e0472

This case reports on a 53-year-old male patient with primary refractory high-grade B-cell lymphoma, who was hospitalized to undergo Chimeric Antigen Receptor (CAR) T-cell therapy.

Case presentation

- Previously, he had failed multiple treatments including rituximab, etoposide, prednisone, vincristine, cytoxan, doxorubicin and rituximab, oxaliplatin, cytarabine, and dexamethasone
- Additionally, he had received lymphocyte-depleting chemotherapy with fludarabine and cytoxan 5 days prior to hospital admission
- On the day of hospital admission (day 0), CAR-T infusion (axicabtagene ciloleucel) was commenced without any immediate side effects
- C-reactive protein (CRP) rose on day 3, whereas his ferritin levels remained normal until day 5
- Clinical assessments for cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) were negative at that time
- On day 4, he developed a fever of 39.1°C (grade 1 CRS) while examination was negative for ICANS (Immune Effector Cell-Associated Encephalopathy (ICE) score 10/10), accompanied by continuously increasing CRP levels
- In the evening of day 5, he became mildly disoriented and demonstrated altered handwriting
- Ongoing fever and new hypotension on day 6 prompted the first administration of tocilizumab (grade 2 CRS, ICE 9/10), followed by two additional doses later
- He also required intermittent fluid resuscitation and treatment with dexamethasone
- His CRP levels started to decrease, while 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 (he had been 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 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
- Drastically worsening encephalopathy (ICE 2/10, need to protect airway, on hospital day 9) together with persistently elevated inflammatory markers led to the exploration of novel rescue options
- After careful consideration of risks and benefits, emergency use authorization for extracorporeal blood purification with CytoSorb was obtained from the local Institutional Review Board
- Consequently, as selective blockade of single mediators might not be sufficient to attenuate the overall response, the authors sought a rescue strategy that allowed for broad-spectrum, continuous cytokine elimination and so continuous hemoadsorption with CytoSorb was initiated on hospital day 11

Treatment

- Six CytoSorb cartridges were used for 12–24 hours each over the following 4 days
- CytoSorb was used in conjunction with standard CRRT (Prismaflex M150 with an AN69 membrane hemofilter, Baxter Healthcare Corporation) run in continuous veno-venous hemodiafiltration mode
- Blood flow rate: 250 mL/min
- Fluid removal rate 0–250 mL/hr
- Systemic anticoagulation was omitted due to persistent thrombocytopenia and low fibrinogen levels

Measurements

- Inflammation
- Development of the neurological state
- Renal function
- Safety

Results

- Inflammatory markers, in particular interleukin - IL-6, started to decline rapidly within 48 hours of hemoadsorption and continued to do so throughout the treatment course (greater than 95% reduction)
- Treatment was associated with a complete resolution of the immune effector cell-associated neurotoxicity syndrome over the next three days (ICE score 10/10)
- Hemoadsorption therapy also resulted in complete renal recovery over the next 3 days
- The treatment was well tolerated without any obvious side effects

Patient Follow-up

- 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

CytoSorb®

Case of the week 33/2021

Conclusion

- This case represents the first reported, successful application of extracorporeal blood purification with CytoSorb to treat severe, refractory neurotoxicity following CAR T-cell therapy
- As selective blockade of single mediators might not be sufficient to attenuate the overall response, CytoSorb hemoadsorption therapy was chosen as a rescue strategy that allowed for broad-spectrum, continuous cytokine elimination rather than selectively blocking individual cytokines
- Therefore, this is another case report on the use of CytoSorb therapy in the promising field of chimeric antigen receptor (CAR-)T-cell-therapy complications, and the first publication focusing specifically on neurotoxicity after this cancer immunotherapy
  The authors state that CytoSorb is very unlikely to remove tozilizumab or other antibodies from the circulation, due their large molecular weight >60 kDa
- The authors further point out that the positive effects cannot be explained by standard CRRT alone, as cytokines are not removed in relevant amounts via CRRT