CytoSorb®

Case of the week 18/2020

Extracorporeal cytokine removal in severe CAR-T cell associated cytokine release syndrome

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This case reports on a 64-year old male patient who was admitted to the ICU after he had received a preparation of CD19-specific CAR-T cells six days previously for treatment of relapsed diffuse large B-Cell lymphoma (DLBCL) after three lots of chemotherapy and previous autologous stem cell transplantation.

Case presentation

- The patient developed episodes of fever, mild hypotension and dyspnea on day 4 and was transferred to the ICU for further monitoring
- On admission, he was afebrile, awake and fully orientated but did show mild signs of encephalopathy
- Mean arterial pressure (MAP) was 63 mmHg with a mild tachycardia of 115/min and a normal peripheral O_2 saturation (SpO_2) of 96% while breathing ambient air and passing clear urine at 100 ml/h
- Laboratory evaluations were unremarkable except for increased levels of CRP (215 mg/L)
- At this point, the patient was diagnosed with grade 2 Cytokine Release Syndrome (CRS) following Lee Santomasso consensus criteria so that he received a single dose of Tocilizumab (monoclonal antibody against IL-6 receptor) at the recommended dose of 8 mg/kg (600 mg)
- Over the following 24 hours, the patient received about 5 litres of crystalloid fluid substitution and remained clinically stable
- Sudden onset of severe shock occurred 24 hours later so that, in addition to further aggressive volume expansion, high doses of norepinephrine were necessary to maintain an mean arterial pressure (MAP) above 65 mmHg
- Extended hemodynamic measurements revealed a cardiac index (CI) of 1.54 l/min/m^2 mainly due to a severely reduced preload
- Somewhat surprisingly the systemic vascular resistance was found to be elevated (SVRI 3273 dyn*s*cm^{-5}*m^2) indicating grave underfilling and low preload due to massive capillary leakage as the primary shock mechanism rather than vasoplegia

- The patient rapidly became anuric and developed lactic acidosis and was therefore treated with Slow Low-Efficient Daily Dialysis (SLEDD)
- Inotropic support with dobutamine was additionally started (although the pathophysiological problem behind the low CI was still the underfilling rather than a myocardial contractility problem)
- Tocilizumab was administered 3 more times 8 hourly
- The patient was intubated and mechanically ventilated due to progressive encephalopathy ultimately leading to loss of consciousness
- Given that the patient was unresponsive to treatment with repetitive doses of Tocilizumab, and massive volume substitution resulting in a rapid deterioration in the clinical course requiring vasopressor and inotropic support at exceedingly high doses, extracorporeal cytokine adsorption (CytoSorb) was additionally applied in combination with the dialysis circuit

Treatment

- 5 CytoSorb treatments were performed for a total of approximately 48 hours. The first adsorber was applied for 16 hours while the following adsorbers were changed every 8 hours (to increase adsorption dosage)
- CytoSorb was used in combination with SLEDD using the Genius system (Fresenius Medical Care)

Measurements

- Hemodynamics and catechoalmine requirements
- Circulating cytokines and permeability factors
- Markers of endothelial injury

Results

- Initially, the hemodynamic situation further deteriorated and the clinical course over the next 24 hours was extremely critical. Norepinephrine dose increased up to 0.53 µg/kg/min and epinephrine was additionally required (0.21 µg/kg/min) to maintain organ perfusion. Following intensification of the CytoSorb dose in terms of 8 hourly adsorber changes, shock completely reversed within the next hours, while vasopressor dosage could be reduced to about 1/10 of the peak dose and inotropic support was stopped completely
- After 24 hours of CytoSorb treatment, a wide range of pro-inflammatory cytokines were lowered by more than 50% compared to the concentration before start of CytoSorb treatment and the peak concentrations reached within the CRS course. Importantly, IL-6, IFN-gamma, TNF-α, IL-1α and IL-1β-associated chemokines were decreased substantially during cytokine adsorption
- However, markers of endothelial injury increased steadily (e.g. angiopoietin-2/angiopoietin-1 ratio) leading to profound endothelial activation and leakage in ex-vivo assays

Patient Follow-Up

- The patient recovered further over the following days
- He was extubated and completely off vasopressors on day 8 and then transferred to the hemato-oncological step-down unit two days after
- Unfortunately, the patient had to be re-admitted to the ICU with neutropenia and a triad of vancomycin resistant enterococcus (VRE) sepsis, secondary hemophagocytic lymphohistiocytosis (sHLH) and overt cytomegalovirus (CMV) reactivation
- Despite targeted therapeutic measures the patient died on day 23 after the initial CAR-T-cell therapy

Conclusions

- To the best of the authors knowledge this is the first patient with progressive shock due to CRS that has been treated with an extracorporeal cytokine adsorption strategy
- Results show the impact of CytoSorb on hemodynamic stabilization and its efficacy in absorption of various cytokines but not endothelial growth factors
- The findings suggest the possibility that removal of excessive circulating cytokines rather than pharmacological blockade of a single key cytokine alone might be a more effective treatment strategy for severe CRS