MASSIVE CRS AFTER CAR-T CELL THERAPY IN HIGH GRADE B CELL LYMPHOMA

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INTRODUCTION

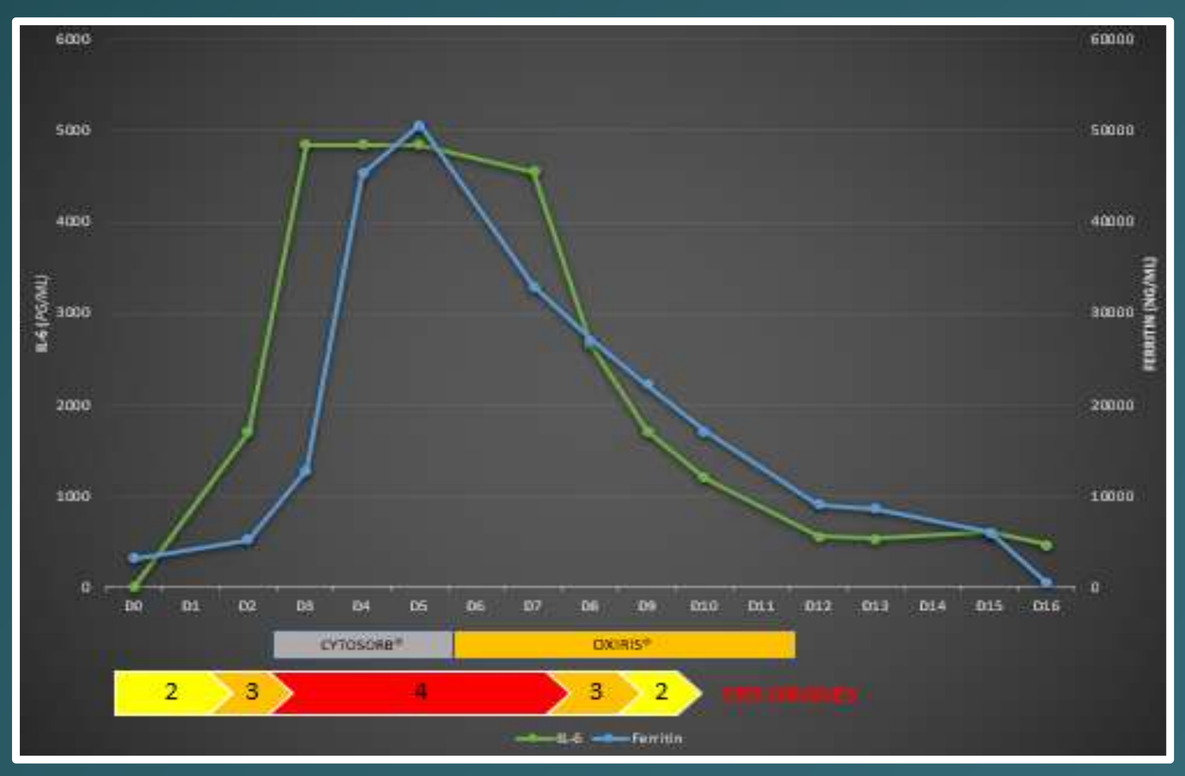
Chimeric antigen receptor (CAR) T-cell therapy is a promising new treatment for chemotherapy-refractory B-cell malignancies that uses genetically engineered T-cells to target a surface antigen (CD19) expressed on B lineage cells. The superactivation of T cells produces a systemic inflammatory response responsible for the toxicities. The most frequent and potentially life-threatening toxicities associated with CAR-T cell therapy are Cytokine Release Syndrome (CRS) and Immune effector Cell Associated Neurotoxicity Syndrome (ICANS). CRS is a clinical syndrome resulting from a widespread immune activation induced by CAR T expansion and correlating with marked elevation of serum inflammatory markers (Ferritin) and cytokines like IL-6, interferon gamma (IFNγ), IL-2 and IL-10. CRS symptoms can range from fever (>38°C) with mild flu-like symptoms to hypotension, hypoxia and/or multiple end-organ dysfunction requiring supportive care in ICU. The observation that IL-6 is elevated in the serum of CRS patients led to consider Tocilizumab the forefront treatment of severe CRS. Targeting IL-6 might reduce CRS toxicity without compromising the efficacy of T cell–therapies. Corticosteroids should be reserved refractory cases to IL-6 blockade or in case of severe neurotoxicity since Tocilizumab does not cross the blood-brain-barrier. Given that a complex cytokine network rather IL-6 alone is involved in CRS it appears reasonable to additionally employ techniques that unselectively remove excessive cytokines from the circulation like extracorporeal cytokine adsorption (CytoSorb® and Oxiris®).

CLINICAL CASE

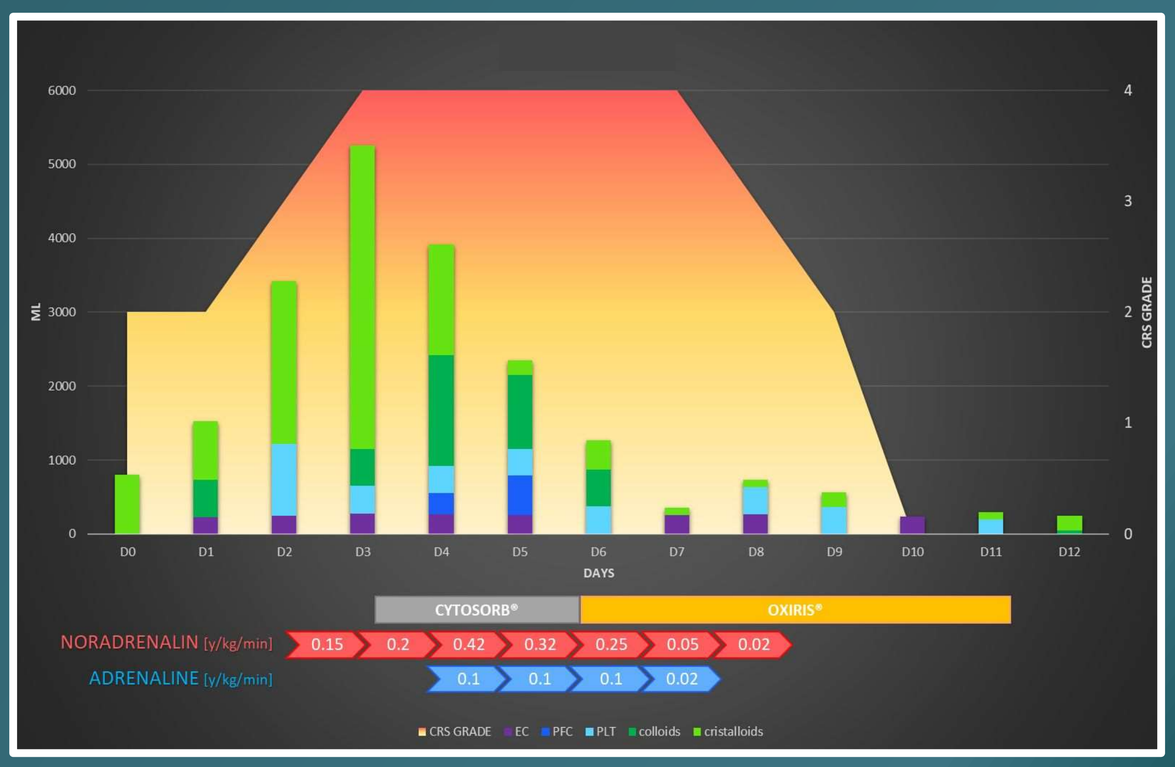
We present the case of a 44-years-old woman with high-grade B-cell lymphoma who developed a massive CRS following CAR-T-cell therapy. She was admitted in ICU on D0 (CAR-T infusion day). Soon after infusion she developed a grade 2 CRS (ASTCT Consensus Grading) with fever (>38°C) and hypoxia, rapidly worsening up to grade 4 CRS with hypotension and respiratory failure requiring massive fluid resuscitation (20.2 L in 6 days), vasopressor therapy and mechanical ventilation. Contextually the patient showed signs of neurological toxicity, ICANS grading was 1 at the onset of CRS but was not evaluable in the following days due to severe worsening of clinical conditions.

We performed daily blood tests and observed that the severity of CRS was strongly related with the trend of serum Ferritin and IL-6 during days (Graph 1) both reaching the highest values on D3-D4-D5, when CRS grade was maximum and she required the highest rate of Adrenaline and Noradrenaline infusion and fluid resuscitation (Graph 2). She was treated with Anakinra and Corticosteroids starting on D3, Tocilizumab (D4) and Ruxolitinib (D5). On D3, as renal function worsened (Creatinin 2.4 mg/dL) and clinical conditions deteriorated, we applied CRRT with Cytosorb® filter followed by Oxyris® filter. On graph 2 is shown the link between filters application and the reduction of serum inflammatory markers. We believe that extracorporeal cytokine adsorption played an important role in gaining control over the massive immune activation.

In the following days hemodynamics improved and vasopressor support was no longer required, renal and respiratory failure regressed and her clinical conditions stabilized. After 27 days of ICU hospitalization the patient was transferred to the hematology department.



[GRAPH 1]



[GRAPH 2]