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Cytokine Release Syndrome, a Controversial and Interesting, how Far we have Come?

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Introduction

Cytokine Release Syndrome (CRS) represents potentially life-threatening and systematic inflammatory response which has been observed to occur after antibody administration and adoptive T cell therapy. The term CRS in clinical practice appeared during 1990's when anti-T-cell antibody muromonab CD3 (OKT3) was presented as an immunosuppressive treatment for solid organ transplantation. CRS may go under the picture of mild symptoms such as fatigue, fever, myalgia to severe clinical picture of hypotension, renal and/or liver toxicity, Acute Respiratory Distress Syndrome (ARDS) and Disseminated Intravascular Coagulation (DIC) [1,2]. At the beginning, it is important to explain whether is there a difference between the term CRS and cytokine storm. The term cytokine storm is often used alternately with CRS but, despite the fact that they have similar clinical phenotype, their characteristics are different.When occurring as a result of a therapy, CRS symptoms may be deferred until days or weeks after treatment. Immediate-onset CRS is a cytokine storm although severe cases of CRS have also been called cytokine storms [3].

Pathophysiology of CRS: Five phases of CRS development have been described in the literature. Phase one include the trafficking of Chimeric Antigen Receptor (CAR) T cells to the tumour site following their infusion into a patient and CAR-mediated recognition of antigen-expressing target cells. In phase two there is proliferation of CAR T cells at the tumour site, in situ cytokine production by both activated CAR T cells and cellular components of the tumour microenvironment, activation of 'bystander' endogenous immune cells, direct and indirect tumour cell killing, and onset of CRS. In phase three, there is an increase in cytokine levels and expansion of CAR T cell populations in the peripheral blood, which is associated with a systemic inflammatory response. This leads to endothelial injury and vascular leakage in multiple tissues and organs, and their associated effects including hypoxia, hypotension and/or organ damage. The diffusion of cytokines and transmigration of CAR T cells, endogenous T cells and peripherally activated monocytes into the Cerebrospinal Fluid (CSF) and Central Nervous System (CNS) in phase 4, including breakdown of the Blood Brain Barrier (BBB), coincides with the onset of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). In phase 5, activation-induced cell death of T cells following eradication of the tumour results in decreased serum cytokine levels and a reduced systemic inflammatory response, the end of CRS and/or ICANS symptoms and, potentially, the persistence of long-term memory CAR T cells. The complete mechanism is shown schematically in Figure 1 [4].

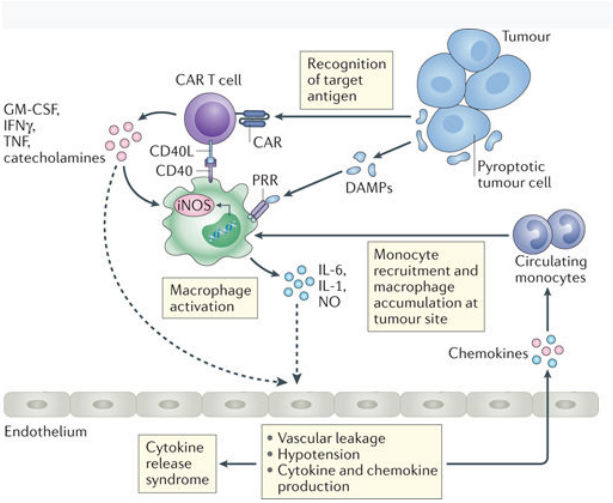

Figure 1. Pathophysiological mechanisms of CRS.

CRS in COVID 19: Critically ill COVID 19 patients with pneumonia are at the highest risk of developing of CRS [5]. In COVID 19 infection, in addition to monitoring inflammatory markers such as C Reactive Protein (CRP), ferritin, Lactat Dehydrogenase (LDH), Interleukine 6 (IL-6) values are also monitored. Can IL-6 levels indicate whether CRS or another disease has developed? According to the data from one meta-analytical study in which data of IL-6 values were collected in more than 9000 patients, the following results were obtained: in COVID 19 infection, IL-6 values were from 21,6-62,3 pg/ml; in CRS (632,3-15302,9 pg/ml), sepsis (550,1-1758,4 pg/ml) and in ARDS unrelated to COVID 19 (216,3-978,7 pg/ml) [6]. This study showed an important values of IL-6 in making a difference between CRS and others conditions.

Treatment of CRS: According to some researchers the treatment of CRS include: a) tocilizumab with or without corticosteroids, b) high doses of corticosteroids if not already used and c) agents agents such as siltuximab or multiple tocilizumab doses. This is in

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contrast to isolated, severe neurotoxicity, which should be initially managed with corticosteroids rather than tocilizumab [7].

Conclusion

CRS is a complex syndrome that significantly complicates the clinical picture and treatment outcome, especially of hospitalized COVID 19 patients. In the near future, it is necessary to work on educating doctors about this syndrome, but also on the development of drugs whose goal would be to reduce the inflammatory response in already developed diseases.

Abbreviations: ARDS-Acute Respiratory Distress Syndrome; BBB-Blood Brain Barrier; CAR-Chimeric Antigen Receptor; CNS-Central Nervous System; CRP-C Reactive Protein; CRS-Cytokine Release Syndrome; CSF-Cerebrospinal Fluid; DIC-Disseminated Intravascular Coagulation; ICANS-Immune Effector Cell-Associated Neurotoxicity Syndrome; LDH-Lactat Dehydrogenase

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