

The Dark Side of CAR-T Therapy: CRS

The most common and potentially severe toxicity seen across trials using immunotherapies such as monoclonal antibodies, bispecific antibodies (Bi-specific T-cell engagers or BiTEs) and adoptive T-cell therapies (*e.g.* CAR-modified T-cell) is CRS.

But what does CRS mean?

CRS stands for Cytokine Release Syndrome. Cytokine Release Syndrome is a clinical syndrome resulting from generalized immune activation correlating with marked elevations of serum inflammatory markers and cytokines. The first clinical signs of CRS are fevers, myalgias, and fatigue. But starting from fever with or without constitutional symptoms (CRS grade #1), symptoms can rapidly evolve to hypoxia requiring O₂ (grade #3) and finally death (grade #5).

But is the probability of a CRS event really alarming?

The risk of CRS is influenced by factors related to the type of therapy, underlying disease, and characteristics of the patient. Treatment with most conventional monoclonal antibodies carries a relatively low risk of CRS, whereas CAR-T therapies carry a significantly higher risk of CRS incidence.

With regard to recently approved CAR-T therapies, Yescarta was studied in 107 adults with large B cell lymphoma and ninety-four percent of treated patients developed CRS and 12% developed grade ≥ 3 CRS. Kymriah was tested in 68 paediatric and young adult patients with relapsed/refractory ALL and seventy-nine percent developed CRS with 49% developing grade ≥ 3 CRS!

But what can we do when CRS occurs?

Corticosteroids may be necessary in some cases, but in high doses have proven to have a detrimental effect on CARTs.

Extracorporeal blood purification techniques, such as high-volume hemofiltration, cascade hemofiltration, plasma exchange, and coupled plasma filtration adsorption, have also been reported as a potential alternative to treat CRS syndrome. But they remain time consuming and labour extensive solutions.

Since the initial observation that tocilizumab, an antibody against the IL-6 receptor, rapidly reversed severe CRS, the drug remains at the forefront of CRS treatment.

For the future, many CARTs in development incorporate suicide targets as methods to mitigate toxicity. Another approach is manufacturing CARTs that can be regulated without actually killing them, for example requiring infusion of an additional agent for activation.

But diagnosis is better than treatment.

Early prediction is necessary as the side effects appear rapidly - within 1 to 2 weeks - following CAR-T infusion. The elevation of the signature set of 24 different cytokines is then an interesting and crucial measure to monitor in patients.

The main cytokines implicated in the pathogenesis of CRS include effector cytokines released from activated T cells, but also cytokines mainly secreted by monocytes and macrophages. **IFN- γ** and sgp130 levels, for example, rise early and their elevation is different for severe versus non-severe CRS.

But we can also mention sIL6R, **interleukin-6** (IL-6), **interleukin-10** (IL-10), interferon **INF- α** , chemokines that are chemotactic for monocytes/macrophages (MCP1, MIP1 α , MIP1 β), granulocyte-macrophage colony-stimulating factor (GM-CSF), but also **TNF- α** , **IL-1b**, IL1RA, **IL-2**, sIL2R α , C-reactive protein (CRP) and **IL-8**. Other biomarkers of endothelial cell activation, such as Angiopoietin-2 and von Willebrand factor, have also been recently described to predict CRS severity.

In order to effectively monitor the risk linked to immunotherapy, Diaclone has developed a large panel of standard recombinant cytokines and monoclonal antibodies targeting specific cytokines engaged in Cytokine Release Syndrome, as well as ELISA and DIAplex kits. As a first evaluation test, and for **7 of the targeted set of cytokines**, Diaclone DIAplex is a particularly useful tool for providing a rapid response and with a reduced sample volume requirement starting from only a few μ l.

Diaclone SAS
6 rue Dr Jean-François-Xavier Girod
BP 1985 - 25020 Besançon cedex - France

Tél : +33 (0)3 81 41 38 38
Fax : +33 (0)3 81 41 36 36
Email : Info@diaclone.com

A company of the group

