Editorial

CAR-T Cell therapy; What an intensivist should know?

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CAR- T cell therapy is a recent advancement of immunotherapy, where the gene for a receptor that binds to a certain protein on the patient's cancer cells is added to the T cells with the help of genetic engineering. This receptor is called Chimeric Antigen Receptor (CAR). Thus, these modified CAR -T cells bind and eliminate cancer cells that express the target antigen.[1] These CAR-T cell live and multiply in the body, continuously killing the tumour cells. The therapy was pioneered by Israeli immunologists Zelig Eshhar and Gideon Gross in 1989 by engineering T cells with an immunoglobulin (Ig)-TCR-chimeric molecule.[2] In the last forty years, the evolution of CAR-T therapy has reached its fifth generation.[1] The first generation of CAR relied solely on the CD3ζ chain to simulate T cell receptor, but lack of co-stimulatory elements limited their efficiency in clinical trials.[3] Second generations of CARs were designed to possess both activating and co-stimulatory domain to obtain greater strength of signalling for enhanced proliferation, cytokine secretion, survival and anti- tumour activity. Third generation CARs have multiple co stimulatory domains whereas fourth generation CARs are called T-cells redirected for antigen-unrestricted cytokine-mediated killing (TRUCKs) or armoured CARs. The fifth generation CAR-T cells contain an extra intracellular domain than fourth generation CAR-T cells. These CAR-T cells remain active, generate memory T cells, and also reactivates and stimulates the immune system.[4]

First CAR-T cell therapy was used in renal cell carcinoma but without much success. However major break through with CAR -T cell therapy was seen in haematological malignancies. particularly for acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphomas, such as large B cell lymphoma. Since 2017, six CAR T-cell therapies have been approved by the Food and Drug Administration (FDA). All are approved for the treatment of blood cancers, including lymphomas and, most recently, multiple myeloma. Tisagenlecleucel, Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Lisocabtagene Vicleucel and Ciltacabtagene Autoleucel are the FDA approved CAR-T medicines. Large clinical trials of anti-CD19 CAR T-cell therapy have demonstrated complete remission rates as high as 68% to 93% in patients with ALL [5,6]

However, CART- T cell therapy is not devoid of toxicity and it poses unique challenges to an intensivist. It can affect any organ and causes mild to life threatening organ failure. Apart from severe infection and sepsis, two distinct complications associated with CAR-T cell therapy are cytochrome release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS and ICANS usually carry better prognosis if treated aggressively in critical care unit.[7] Other CAR-T associated complications are cytopenia and disseminated intravascular coagulopathy (DIC).

CRS is the most common serious side effect of CAR-T cell therapy. When CAR-T cells when encounter tumour cells, cytokines are released, this in turn activate other immune cells such as macrophages, endothelial cells, and stromal cells. This trigger further release of proinflammatory cytokines and leading to a cytokine storm.[8,9] IL-6, IL-8, IL-10, IFN-γ, and monocyte chemoattractant protein-1are major cytokines that are released in cytochrome storm and level of IL-6 level corelates with severity.[10] CRS may present as fever, fatigue, rigors, and myalgia. In the most severe cases, patients can develop hypotension, capillary leak syndrome, respiratory insufficiency, and multiorgan failure. Some patients also develop features of macrophage activation syndrome. The risk factors of developing CRS are tumour burden, tumour type, CAR-T-cell dose, peak CAR-T-cell expansion, baseline inflammation etc.[11] CRS is primarily

managed with IL-6 antagonists (tocilizumab) and with corticosteroids. Alternative to tocilizumab are Siltuximab, Clazakizumab and IL-1 receptor antagonist Anakinra.[12]

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is the second most common side effect associated with CAR-T cells therapy. ICANS is thought be due to endothelial activation leading to disruption of the blood-brain barrier. CAR-T cells and other immune cells cross the blood brain barrier and release of cytokines such as IL-1, IL-6, IL-8, monocyte chemoattractant protein-1, and interferon-γ–inducible protein 10 within the CNS. In particular, the production of IL-1 by myeloid cells seems to be a key mechanism in the pathophysiology of ICANS. Clinical manifestation of ICANS are headache, altered sensorium, seizure, myoclonus, comma, confusion and behavioural changes, expressive aphasia or other language disturbance, dysgraphia, dysarthria, fine motor impairment and other weakness, tremor etc. The median time to onset is 4 days after infusion**.** Signs and symptoms ICANS typically subside between 5 and 17 days from onset. The mainstay of treatment of ICANS are supportive care and corticosteroids. Tocilizumab does not resolve ICANS and may worsen it. Several other medication which are still under investigation for treatment of ICANS are Anakinra, Lenzilumab, and Defibrotide.[10,11]

Chimeric antigen may not be tumour cell specific. They can be expressed by another non-malignant cell also. So, CAR-T cell can bind with the target cell but can cause off tumour toxicity. Such on target, off tumour toxicity can cause prolong hypogammaglobulinemia leading to recurrent opportunistic infection.

Off target and off tumour toxicity is due to cross reaction with antigen expressed by non-malignant cells, however, this type of toxicity is rare due to development of highly specific CAR-T therapy.

Underlying disease, chemotherapy cause prolonged immunosuppression in patient with CART-T cells therapy. So, infection and sepsis are quite common in this subgroup of patients. The patient may be infected by bacteria, fungi, virus or multiple pathogens. Due to immunosuppression, sign and symptoms of infection may not be overt. At the same time, other non-infectious toxicity like CRS, ICANS may mimic sepsis posing diagnostic challenge to an intensivist. Diligent sepsis surveillance is of paramount importance in these patients.[12]

The incidence of macrophage activation syndrome (MAS) in patients with CAR-T cell therapy is 3.5%. Many a times clinical features of MAS are similar to that of CRS and sepsis and very difficult to distinguish. Supportive therapy and corticosteroids are the mainstay of treatment. Other therapies are IL-6 antagonist, Etoposide, Anakinra.[12,13]

Anaemia, thrombocytopenia, leukopenia, and neutropenia are not uncommon. Acute cytopenia in three months following CAR-Tcells therapy is more common than prolong cytopenia. Anemia > 10.0-8.0 g/dL; neutropenia >1,000 per mm^3; thrombocytopenia: > 50,000 per mm^3 can be managed with supportive care with or without corticosteroids. More severe cytopenia will require high dose of methylpredisilone and rarely growth factor support.[12,14]

Patient with CAR-T therapy may have DIC and other coagulopathies with or without CRS. DIC in this sub group of patients may need IL-6 antagonist and corticosteroids.[12,15,16]

Intensivist plays a crucial role during CAR-T therapy as 15–47% of the patients in the pivotal clinical trials required ICU admission and if they are managed well in ICU, there is good chance of survival.[14] CAR-T therapy is the most recent development of immunotherapy and they are very expensive and still in nascent stage. As more trials are published, we will be more aware and better prepared to manage critically ill patients with CAR-T therapy.

Conflict of interest: None

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