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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has been hailed as a much-awaited treatment for patients with relapsed/ refractory (r/r) haematological malignancies. CARs are synthetic receptors consisting of an extracellular domain that can bind specifically to a target molecule expressed on the surface of tumour cells, a transmembrane domain, and an intracellular signalling and costimulatory domain that provides an activation signal to T cells, when the extracellular domain is engaged with its target.

CAR-T Cell Therapy – What An Intensivist Should Know

CAR-T therapy is a promising treatment for B-cell malignancies but is also associated with toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Frequent monitoring, timely recognition and prompt management in ICU are paramount to ensure good outcomes.

CD19 was selected as an attractive therapeutic target as it is a transmembrane glycoprotein required for normal B-cell development in humans and it is expressed in over 95% of B-cell malignancies. Addition of a costimulatory domain to the CAR T construct (second-generation CAR) promoted T-cell proliferation and persistence, but also increased the risk of cytotoxicity. Several CAR T products are approved in Europe and the United States for acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma and most recently multiple myeloma (Berdeja et al. 2021).

After leukapheresis of autologous T lymphocytes, genetic information for the CAR is transduced into the cells normally by means of viral vectors. The patients then receive lymphocyte-depleting chemotherapy as preparation. Once infused, CAR T cells recognise tumour cells expressing the target antigen. They expand locally and eliminate tumour cells by contact-dependent cytotoxicity (June and Sadelain 2018). Each activated CAR T cell releases cytokines and activates other components of the immune system, preventing tumour recurrence by promoting immune surveillance. Time from CAR T collection to patient infusion is approximately 3 weeks but often closer to 4 weeks. The leukapheresed cells are transferred to a manufacturing facility, sometimes abroad, for T cell engineer-

ing and expansion. The manufactured CAR T cells are transferred back to the centre for infusion, which typically happens as a single infusion, with varying infusion protocols depending on centre, sponsor and product.

Clinical trial data report overall response rate (ORR) between 54-83% and complete response (CR) rate between 40-58% for aggressive B-cell lymphoma, depending on the CAR product used (Tang and Nastoupil 2021). 'Real-world' outcomes of CD19 CAR T cell therapy for aggressive r/r non-Hodgkin lymphoma have response and survival rates that are comparable to the impressive results from pivotal trials. These results become even more pertinent since they demonstrate the efficacy of CAR T therapy in patients who would have been excluded from clinical trials.

Common Toxicities

As CAR T cell therapies become more widely used, recognition of their unique toxicities, distinct from those seen with other immune effector therapies, is of utmost importance. The two most common toxicities after CAR T cell infusion are the cytokine-release syndrome (CRS) and neurotoxicity, recently renamed immune effector cell-associated neurotoxicity syndrome (ICANS) (Lee et al. 2019). Their true incidence, severity and need for support are unclear, as published studies have used different CAR products and

different grading systems. Direct comparison of toxicities has been made easier after the publication of a consensus paper by the American Society for Transplantation and Cellular Therapy (ASTCT) in 2019 (Lee et al. 2019). The ASTCT consensus grading for CRS and ICANS is presented in **Table 1**.

Cytokine Release Syndrome

Activation and proliferation of T cells after engagement with the CAR ligand result in secretion of cytokines and proinflammatory signals from the activated lymphocytes but also other immune cells. In particular, Interleukin (IL) -6 and interferon- γ (IFN- γ) play a decisive role in initiation of this systemic inflammatory response that in extreme cases can result in fluid-refractory hypotension and other organ damage. The range of symptoms varies but the pres-

ence of fever is essential for the diagnosis (**Table 1**). In clinical trials, CRS of any grade was observed between 58-93%, with 13-22% developing grade 3 or higher CRS. Despite differences in the baseline characteristics among patients, similar rates of toxicities were observed in the real-world data (Tang and Nastoupil 2021). Risk of CRS is influenced by pre-treatment factors, such as tumour burden and ALL as the underlying disease, and treatment-related factors such as the costimulatory domain of the CAR, dose of CAR T cells infused and regimen of lymphodepletion.

Treatment of CRS varies between institutions and is mainly supportive. Enhanced monitoring, regular antipyretics, fluids and broad-spectrum antibiotics are suggested for grade 1 CRS. When grade 1 symptoms persist or progress to grade 2, treatment with

tocilizumab, an IL-6 receptor antagonist, is recommended (8mg/kg; maximum of 3 doses and 800mg/dose). Corticosteroids are considered if symptoms do not subside after tocilizumab administration or if there is progression to grade 3. We advocate the use of intravenous dexamethasone (up to 10mg QDS), as the corticosteroid of choice. In our institution, all patients with grade 2 CRS and/or ICANS are followed up with our critical care outreach team (CCOT). Severe cases of CRS (\geq grade 3) are admitted to the intensive care unit (ICU) and may require additional supportive measures, such as vasopressor agents for hypotension and supplemental oxygen or intubation for hypoxaemia. Refractory CRS can be treated empirically with further immunosuppression (methylprednisolone 1g/day, anakinra, siltuximab).

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with/without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Table 1: Consensus grading for Cytokine Release Syndrome

* Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L}/\text{minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L}/\text{minute}$. Source: Lee et al 2019.

Immune Effector Cell-Associated Neurotoxicity Syndrome

The exact pathophysiology behind the neurotoxicity observed after CAR T cell therapy is not fully understood. Systemic inflammation appears to also be important

in ICANS but less so than in CRS, with IL-1 playing a more significant role than IL-6. The presence of pro-inflammatory cytokines has been demonstrated in the cerebrospinal fluid (CSF) and is linked with increased endothelial activation. It is

unclear whether elevated levels of cytokines in CSF are a consequence of the blood-brain barrier disruption or a result of CAR T cell engagement with CD19-expressing cerebral endothelial cells. ICANS symptoms often occur a few days follow-

ing CRS but can manifest independently. They range from mild word-finding difficulties, aphasia, toxic encephalopathy, impaired

cognitive skills, altered consciousness, or hallucinations to more devastating symptoms including seizures, motor weakness,

and cerebral oedema (**Table 2**) (Tang and Nastoupil 2021).

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7 to 9	3 to 6	0 to 2	0 (patient is unrousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unrousable or requires vigorous or repetitive tactile stimulus to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalised that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life threatening prolonged seizure (> 5 mins); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging§	Diffuse cerebral oedema on neuroimaging; decorticate or decerebrate posturing; or cranial nerve VI palsy; or papilloedema; or Cushing's triad

Table 2: Consensus grading for Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unrousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. Source: Lee et al 2019.

Management of low grade ICANS is based on increased frequency of neurological observations using the Immune Effector Cell-Associated Encephalopathy (ICE) score (**Table 3**) and administration of antiepileptics in case of seizures. Tocilizumab is ineffective, unless there is concurrent CRS, whereas corticosteroids

are the immunomodulator of choice. In our institution, we use intravenous dexamethasone (up to 10mg QDS), followed by methylprednisolone 1g/day for refractory symptoms. Close monitoring by the CCOT, admission to ICU when ICANS \geq grade 3 and close collaboration with neurology and neurosurgery in severe cases are standard

practice. When managing neurotoxicity, it is important to exclude alternative causes, such as infection, stroke or haemorrhage. The choice of diagnostic modalities (e.g., magnetic resonance vs. computer tomography imaging, electroencephalogram, cerebrospinal fluid analysis) is tailored to the severity and nature of symptoms.

Domain	Assessment	Point(s)
Orientation*	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects e.g. point to clock, pen, button	3
Following commands	Ability to follow simple commands e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue"	1
Writing	Ability to write a standard sentence e.g. "Our national bird is the bald eagle"	1
Attention	Ability to count backwards from 100 by 10	1

Table 3: Immune Effector Cell-Associated Encephalopathy score

Scoring: 10, no impairment; 7-9, grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unrousable and unable to perform ICE assessment, grade 4 ICANS.

Source: Lee et al. 2019.

Tips for the Intensivist

Consensus grading system

The new classification aimed to simplify and streamline the grading system, and has enabled comparison of outcomes and adverse events between CAR T products. Its use is not without caveats, which become very important when assessing the severity of CRS/ ICANS and hence the appropriate response.

For patients to be graded as level 3 of CRS, vasopressor use, with or without vasopressin is required. However, there is significant difference between patients that receive vasopressin and those that don't, as in many institutions use of vasopressin signifies catecholamine-resistant/ refractory shock. These patients will be at risk of significant mortality and expedited ICU admission and initiation of rescue therapies should be escalated rapidly. Furthermore, the lack of differentiation in the consensus grading system between patients on low-dose single vasopressor vs high dose noradrenaline plus high dose vasopressin should be noted. Currently, both patients are classified as grade 3 and their treatment includes varying doses of steroids. Early identification of deteriorating patients (irrespective of the grade) should lead to timely escalation of treatment and hopefully prevent further deterioration.

The same caveats need to be considered regarding oxygen requirements for patients with grade 3 and 4 CRS. Those requiring high-flow nasal cannula, which is defined as oxygen delivered at > 6 L/min, are classified as grade 3, whereas patients in need of positive pressure ventilation (whether invasive or not) are grade 4. However, no mention is made of high flow nasal cannula oxygen (HFNCO) therapy, the relatively novel strategy of respiratory support that can supply high flow (up to 60 L/min) of heated and humidified gas with an adjustable inspiratory fraction of

oxygen up to 100%, through a dedicated nasal cannula. Under the consensus classification, a patient requiring 100% via HFNCO is considered less critical than one on 40% CPAP, with the potential delays in escalating interventions mentioned above.

Differential diagnosis

Patients treated with anti CD19 CAR T for B-cell haematologic malignancies are at high risk of infection due to prior cytotoxic treatments, development of CRS, the risk for prolonged cytopenia and B-cell aplasia with associated hypogammaglobulinemia. Approximately 20–40% of patients develop infections within the first month after CAR T therapy despite antimicrobial prophylaxis, with bacterial and viral microorganisms being the most common culprit, followed by fungal infections (Hill et al. 2018). Since microbiologically documented infection at admission to ICU has been associated with increased mortality (Azoulay et al. 2021), diagnosing infection is critical and extensive diagnostic workup should be carried out during ICU admission. Despite that, differentiating CRS from sepsis can be very challenging and empirical antibiotics should always be started, especially since laboratory tests like CRP become uninterpretable after administration of tocilizumab.

Limitation of life-sustaining treatment

CAR T therapy has significantly improved the prognosis of patients with r/r lymphomas, without which their median survival would not exceed 6 months. The ICU and hospital mortality of patients treated with CAR T were reported as 5.8% and 14.9% respectively (Azoulay et al. 2021), lower than those quoted for patients with haematological malignancies admitted in ICU without having received CAR T cells. Nonetheless, and with the expected extension of the therapy in other types of haematological but also solid tumours, the

number of patients being treated and hence developing toxicities and requiring ICU will increase. A number of these patients will be critically ill, with a proportion not responding to CAR T therapy, and continuing to have limited life expectancy despite aggressive treatment. Deciding who will benefit from continuation of ICU treatment is difficult, as response cannot be assessed until 3–4 weeks post infusion whereas the toxicities appear hours or days post therapy. Close collaboration between intensivists and haematologists, as well as open communication with and expectation management of patients and their families are paramount to ensure that treatment is administered appropriately and in accordance with patient wishes.

Take-Away Messages

- CAR T therapy prolongs survival in patients with end-stage B-cell malignancies.
- Common toxicities include Cytokine Release Syndrome (CRS) and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS).
- Treatment for CRS includes the IL-6 receptor antagonist, tocilizumab and corticosteroids.
- Tocilizumab is not the treatment for ICANS; corticosteroids are first-line treatment
- Higher grade toxicities should be managed in ICU.
- Close collaboration between intensivists and haematologists is necessary to ensure that treatments are administered according to patient wishes.

Conflict of Interest

Victoria Metaxa and Tasneem Pirani have received speaker fees from Kite/Gilead. Neeraj Singh and Rohit Saha have no conflict of interest. ■

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For full references, please email editorial@icu-management.org or visit <https://iii.hm/1d7u>