How I treat adverse effects of CAR-T cell therapy

Lucrecia Yáñez, Ana Alarcón, Miriam Sánchez-Escamilla, Miguel-Ángel Perales

ABSTRACT
Chimeric antigen receptor (CAR) T cell therapy has demonstrated efficacy in B cell malignancies, particularly for acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphomas. However, this regimen is not harmless and, in some patients, can lead to a multi organ failure. For this reason, the knowledge and the early recognition and management of the side effects related to CAR-T cell therapy is mandatory. In this review, we have summarised the current recommendations for the identification, gradation and management of the cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, as well as infections, and related to CAR-T cell therapy.

CRS management
Currently, tocilizumab (Actemra, Roche, Switzerland), a monoclonal antibody against interleukin (IL)-6 receptor, is the only approved treatment for CRS grade ≥2 or persistent CRS grade 1. Siltuximab, a monoclonal antibody against IL-6, and anakinra, an anti-IL-1 receptor antagonist are under investigation. Steroids are recommended in severe CRS cases and when CRS is associated with neurotoxicity, however recent studies suggest they can be used earlier without deleterious effect on the CAR-T. In addition, fractionated dose of the CAR-T cells may be also an option to diminish the CRS incidence and severity without compromising efficacy.

IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
Immune effector cell-associated neurotoxicity syndrome (ICANS) is the second most common adverse event related to CAR-T cell therapies and can occur concurrently with or without CRS. ICANS incidence seems to be closely related to high disease burden, patient’s age as well as the specific CAR-T cell product.

ICANS gradation scale
Similar to CRS, the ASTCT consensus-based grading scale also includes ICANS for a uniform assessment for clinical trials and daily use. The ASTCT consensus system combines the immune effector cell-associated encephalopathy (ICE) score, based on the patient’s orientation and their ability to name three objects (nomination), follow simple commands, write a standard sentence and count backwards from 100 to 10, with the level of consciousness, presence and severity of seizures, motor impairment and clinical and/or imaging signs of cerebral oedema or elevated intracranial pressure. The ICE score is substituted by the Cornell Assessment of Paediatric Delirium for children aged <12

**Figure 1** shows the current CRS grade scale and its management.
years. Table 1 shows ICANS grading for children and adults.

ICANS management

Today, there are no approved therapies for the prevention/treatment of neurotoxicity; thus, it is primarily managed with supportive care. The use of levetiracetam as antiepileptic prophylaxis is controversial, but it is recommended, for at least 1 month after CAR-T cell infusion, in patients with a history of seizures or central nervous disease.7–9

Manifestations of ICANS can range from mild headache to coma and the continuous observation of patients who develop neurological symptoms after CAR-T cell infusion is mandatory.7–12 The EBMT recommendations also suggest to alert the intensive care unit (ICU) and a neurologist at onset of neurological findings regardless of the ICANS grade. 7

In general, at the first sign of neurological symptoms, the bed’s head should be elevated by ≥30° to minimise aspiration risks and to improve cerebral venous flow. A neurological evaluation should be requested, independently of ICANS grade. Neuroimaging or lumbar puncture should be considered to exclude increased intracranial pressure and cerebral oedema, as well as ruling out other aetiologies. Repeated neuroimaging is recommended to detect early signs of cerebral oedema in patients with ICANS grade ≥3 or with rapid changes in grade. Brain MRI is preferred, but if not feasible, CT is an alternative option.7

Steroids are typically used as first-line therapy of ICANS grade ≥2.7–9 and dexamethasone and high dose of methylprednisolone are the most frequently used.5–4,7,9 Doses and length of therapy are variable and depend on the ICANS grade. 7,9 Whereas dexamethasone is generally used in ICANS with low scores, repeated high pulse dose methylprednisolone is mostly used in grade 4 ICANS.7–9 Steroids are typically tapered over 2–3 weeks but patients should be monitored closely for recurrence of ICANS.8

Tocilizumab combined with corticosteroids is recommended for grade ≥1 ICANS and concurrent CRS,7,9 however it should not be administered for isolated ICANS because it can cause worsening of symptoms.8 Although currently not approved for this indication, siltuximab and anakinra have been used in severe cases of neurotoxicity.7–9,12

ICU monitoring is mandatory for all patients with grade 4 ICANS and recommended for patients with grade 2–3 ICANS.7,9

Non-convulsive/convulsive seizures or status epilepticus can be managed with benzodiazepines and additional antiepileptics (preferably levetiracetam), as needed. Patients with raised intracranial pressure or cerebral oedema should be managed promptly with anti-oedema measures as per standard guidelines.7–9

INFECTIONS, ANTIBIOTIC PROPHYLAXIS AND VACCINATIONS

Infections can be observed for a long period after CAR-T cell infusion,6,13,14 and severe CRS is a major risk factor.13

Bacterial infections, especially bacteraemia, and viral infections are the most common events within the first months after CAR-T cell therapy,13 whereas fungal infections are a rare complication.13 Beyond day 90 post infusion, the most common cause of infections is upper (48%) and lower (23%) respiratory tract infections.14,15 Of them, the majority receive treatment in an outpatient
setting (80%) and only 5% of patients need therapy in the ICU.14

In contrast to allogeneic stem cell transplantation, reactivation of herpes viruses such as cytomegalovirus, Epstein-Barr virus or human herpesvirus 6 is infrequent.13 Scarce information about the risk of CAR-T cell therapy in patients with hepatitis B or C is available because of the exclusion of these patients from CAR-T cell trials.12

Infection prophylaxis may follow institutional guidelines, covering bacteria, fungi and herpes simplex virus and varicella zoster virus. Prophylaxis for bacteria and candida species may be stopped when neutropenia

Table 1 ICANS gradation scale for children and adults

| CAPD score (children <12 years) | Eye contact with the caregiver | Actions deliberated | Aware of their surroundings | Communicate their needs and wants | Is the child restless? | Is the child inconsolable? | Is the child underactive? | Does it take the child a long time to respond to interactions? |
|-------------------------------|-------------------------------|--------------------|-----------------------------|----------------------------------|--------------------|-----------------------------|--------------------------|-------------------------------------------------------------|
| Never (4 points) | Rarely (3 points) | Sometimes (2 points) | Often (1 point) | Always (0 point) | Never (0 points) | Rarely (1 point) | Sometimes (2 points) | Often (3 points) | Always (4 points) | NEVER (0 points) | RARELY (1 point) | SOMETIMES (2 points) | OFTEN (3 points) | ALWAYS (4 points) |
| ICE score (adults and children ≥12 years) | Orientation to year, month, city, hospital: 4 points | Naming three objects: 3 points | Following simple commands: 1 point | Writing a standard sentence: 1 point | Counting backwards from 100 to 10: 1 point |
| ASTCT ICANS consensus grading* |

ASTCT, American Society for Transplantation and Cellular Therapy; CAPD, Cornell Assessment of Pediatric Delirium; ICANS, immune effector cell-associated encephalopathy score; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable.

*Original version in Lee et al.6

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resolves; in contrast Pneumocystis jirovecii prophylaxis and acyclovir prophylaxis may last at least 6 and 12 months after CAR-T cell infusion, respectively.12 Finally, mould fungi prevention may be individualised depending on patient risk of infection and antibacterial prophylaxis will be according to local bacterial resistance patterns.7 12

Because long-lived plasma cells are not a direct target of CD19+ CAR-T cells, the humoral immunity may be preserved.16 In the absence of data, we recommend complete vaccinations according to the patient’s age and seroprotection status.

MANAGEMENT OF CYTOPOENIAS POST-CAR-T CELL THERAPY

Cytopoenia after CAR-T cell are usually observed up to day +28 (early cytopoenia) but some patients can experience them beyond day +90 (late cytopoenia).

Early cytopoenia

Within the first month after CAR-T cell infusion, grade ≥3 neutropenia, anaemia and thrombocytopenia have been reported.2−4,17 In this period, cytopoenias are related to the lymphodepletion, and to a prior stem cell transplant, the severity of CRS and macrophage syndrome activation.17 For patients with neutropenia, granulocyte cell stem factor may be considered after CRS period risk, in general after the second week.12 Some patients can experience prolonged cytopoenia.

Delayed cytopoenia

Cytopoenia beyond the third month have been described in 16% of patients with ongoing complete remission14 and they are more frequent in patients with grade ≥3 CRS. The mechanism related to late cytopoenia is not well known but inflammation may have a role. In addition, it is important to keep in mind that the majority of patients have received many prior lines of therapy and MDS diagnosis needs to be ruled out.

HYPOGAMMAGLOBULINAEMIA AND IMMUNOGLOBULIN REPLACEMENT

Secondary moderate (IgG >400 mg/dL) to severe (IgG ≤400 mg/dL) hypogammaglobulinaemia due to B-cell aplasia is commonly ‘the price to pay’ for the success of the CD19 antigen targeting malignant B cells in acute lymphoblastic leukaemia,3 however at least three of four patients with ongoing responses treated with axi-cell in the ZUMA-1 trial showed evidence of B-cell recovery by 2 years.15

Recently, Hill et al.38 proposed a practical algorithm for hypogammaglobulinaemia management:

1. Screening for serum IgG prior to and in the first 3 months post-CAR-T cell therapy.
2. Consider prophylactic IgG replacement in patients with IgG ≤400 mg/dL.
3. Beyond the third month post-CAR, the only recommend IgG replacement if IgG is ≤400 mg/dL and the patient is experiencing infections.

In conclusion, CAR-T cell therapy is emerging as a curative option for some haematological malignancies. The recent ASTCT grading consensus provides a common approach for the grading of CRS and ICANS and may help guide common treatment guidelines. Furthermore, an improved understanding of the pathophysiology of cytopoenias may uncover new strategies to improve supportive care.

Twitter Lucrecia Yáñez @DrLucreciaYSS

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ORCID iD

Lucrecia Yáñez http://orcid.org/0000-0001-9925-3048

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