MANAGEMENT OF CRS, NEUROTOXICITY AND CAR-T CELL RELATED ENCEPHALOPATHY SYNDROME (CRES) POST CHIMERIC ANTIGEN RECEPTON (CAR) T-CELL THERAPY

PURPOSE

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a potential breakthrough in the treatment of myeloma, leukaemia and lymphoma. CAR-T cell therapies can achieve overall response rates of 50 -90% but are associated with unique acute toxicities that are uncommon with other cancer therapies.

These toxicities can be fatal and require specialized monitoring and prompt treatment. Two specific toxicities unique to treatment with these agents are: cytokine-release syndrome (CRS) and Immune Effector Cell associated neurotoxicity syndrome [ICANS]. These need to be diagnosed as soon as possible, graded and managed specifically

- CRS, the most common adverse event observed after CAR T-cell therapy, is an escalated immune response and on rare occasions can evolve into fulminant hemophagocytic lymphohistiocytosis (HLH). CRS is always associated with fever and may also include hypotension, hypoxia, and/or multiorgan toxicity and typically occurs within the first 14 days after re-infusion of CAR-T cells.
- ICANS is the second most common adverse event and can occur concurrently with or after CRS. ICANS is characterized by a toxic encephalopathic state with early manifestations including tremor, dysgraphia and expressive dysphasia. It can rapidly progress to severe toxicity including seizures and cerebral oedema.

Clinical Approach

Patients receiving CAR-T cell therapy need to be actively monitor for CRS and ICANS but also other toxicities commonly associated with treatment of haematological malignancies such as infection and tumour lysis syndrome. All patients should receive the following routine interventions;

- Double lumen central venous access before administration of CAR-T cells
- Infection prophylaxis including Aciclovir and Septrin
- TLS prevention as per Trust policy [ACLIN.O.012]
- Blood count support including transfusions and GCSF if neutrophils < 0.5
- 4 hourly routine observation monitoring
- Daily clinical assessment and examination
- Twice daily CRS assessment and grading
- 8 hourly neurotoxicity assessment and grading
- Daily bloods including FBC, Coag, U+E, LFT, Bone, CRP and Ferritin

Patients with suspected infection should follow standard neutropenic sepsis guidelines [NP10_004/005/006]. Any infection must be controlled before CAR-T cells can be infused. This may require delay in product infusion.

Grading and management algorithms for CAR-T toxicities can be access through the CARTOX app
https://apps.apple.com/us/app/cartox/id1464005828
https://play.google.com/store/apps/details?id=org.mdanderson.cartox&hl=en

CYTOKINE RELEASE SYNDROME [CRS]

CRS, the most-common toxicity of CAR cell therapy, is triggered by the activation of T cells on engagement of their CARs with cognate antigens expressed by tumour cells. The activated T cells release cytokines and chemokines.

CRS can affect any organ system but will always include fever. Patients at high risk of severe CRS include those with bulky disease, comorbidities, and those who develop early onset CRS within 3 days of cell infusion. The onset of CRS toxicity usually occurs within the first week after CAR-T cells therapy and typically peaks within 1-2 weeks of cell administration.

Grading

CRS is graded in accordance with ASTCT consensus guidelines published in 2018 as outlined below. Patients on CAR-T clinical trials should follow the protocol dictated toxicity grading management.

Table 1. CRS grading

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever[#†]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
	With either:			
Hypotension[#]	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors
	And/ or[‡]			
Hypoxia[#]	None	Requiring low-flow nasal cannula	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

[#]Not attributable to any other cause
[†]In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity
[‡]CRS grade is determined by the more severe event
^Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min
*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

CRS Management

Table 2. Management of CRS

CRS Grade	Treatment
Grade 1	• Supportive care including analgesics and antipyretics, • If fever treat for neutropenic infections protocol • Consider tocilizumab for persistent (lasting >3 days) and refractory fever
Grade 2	• IV fluid bolus 500-1000ml to maintain SBP > 90mmHg. • Administer Tocilizumab early if persistent fever of ≥39°C, hypotension after initial fluid bolus or initiation of oxygen supplementation. • If persistent hypotension after two fluid bolus and Tocilizumab transfer to ICU for consideration of low-dose vasopressor therapy. • Add Dexamethasone 10mg IV 6 hourly if hypotension persists after anti-IL-6 therapy, high risk for severe CRS, worsening hypoxia or clinical concern
Grade 3	• Intensive care should be considered • Administer Tocilizumab • Add steroids if unresponsive within 24 hours Dexamethasone 10 mg IV every 6 hours; • If refractory increase to 20 mg IV every 6 hours. • If unresponsive CRS add Anakinra • Consider anti-tumour necrosis factor (TNF) antibodies as clinically appropriate. • Perform echo is persistent hypotension
Grade 4	• Intensive care. • Administer tocilizumab • High dose methylprednisolone 1 g/day IV • If unresponsive CRS add Anakinra [3] • If unresponsive, consider alternative agents such as • anti-TNF, and other agents as appropriate.
Grade 5 Death	

Medications used to treat CRS

A named patient supply of four doses of Tocilizumab will be available on ward 33 for all CAR-T patients. This supply should be transferred with the patient if moved to ICU. A further supply of tocilizumab is stored in Freeman Pharmacy Emergency Drug Fridge in a box labelled: Quarantine - For CAR-T Cell rescue only

Table3. : Pharmacological management of CRS

Drug	Indication	Dose
Tocilizumab	Grade 2 CRS or persistent fever	8 mg/kg infused over 1 hour, Total single dose not to exceed 800 mg. Repeat dose if no response within 6 to 12 hours and consider steroids as below.
Anakinra	Grade 3 OR 4 CRS refractory to tocilizumab and steroids	2mg/kg daily for 3-5 days.

IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME [ICANS]

The pathophysiological mechanism underlying ICANS remains to be determined. Two potential explanations can be postulated. Firstly, passive diffusion of cytokines into the brain or trafficking of T cells into the CNS.

ICANS typically manifests as a toxic encephalopathy, with the earliest signs being diminished attention, language disturbance and impaired handwriting; other symptoms and signs include confusion, disorientation, agitation, aphasia, somnolence, and tremors. In severe cases of ICANS (grade >2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilloedema, and cerebral oedema can also occur. The manifestation of ICANS can be biphasic; the first phase occurs concurrently with high fever and other CRS symptoms, typically within the first 5 days after cellular immunotherapy, and the second phase occurs after the fever and other CRS symptoms subside, often beyond 5 days after cell infusion. Notably, delayed neurotoxicity with seizures or episodes of confusion occurred during the third or fourth week after CAR-T-cell therapy in approximately 10% of patients. Anti-IL-6 therapy can reverse ICANS during the first phase, but is generally not effective in the second phase, when corticosteroids are the preferred treatment.

Grading

ICANS will be graded using the 10-point neurological assessment score called Immune effector Cell-associated encephalopathy score (ICE Score, previously CARTOX-10)

- Orientation to year, month, city, hospital (total of 4 points)
- Follows commands (1 point)
- Naming three nearby objects (maximum of 3 points)
- Writing a standard sentence (1 point)
- Counting backwards from 100 in tens (1 point).

A patient with normal cognitive function would be able to achieve an overall score of 10. In addition to the CARTOX-10, parameters including conscious level, seizures, motor findings or evidence of raised intracranial pressure contribute to the grading of ICANS.

Table 4. Grading of ICANS

Neurotoxicity Domain‡	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly ; or Non-convulsive seizures on EEG, resolves with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

‡ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, and raised ICP/cerebral oedema) not attributable to any other cause.

Management

Table 5: Management and Follow-up of Neurological AEs

Management and Follow-up of Neurological AEs	
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Consider conversion of oral medication or nutrition to IV • Avoid sedating medications • Lorazepam (0.25 to 0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) can be used for agitated patients • Organise neurology consultation • Fundoscopic exam to assess for papilloedema • Consider MRI of the brain; diagnostic lumbar puncture including opening pressure; MRI spine if focal neurological deficits; CT brain can be performed if MRI of the brain is not feasible • Early EEG ideally within 24 hours, repeated if condition deteriorates • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Table 6. • Consider tocilizumab 8 mg/kg IV, if neurotoxicity associated with CRS.

Grade 2	• Supportive care and neurological work-up as indicated for Grade 1. • Tocilizumab 8 mg/kg IV if associated with concurrent CRS. • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for neurotoxicity without concurrent CRS.
Grade 3	• Supportive care and neurological work-up as indicated for Grade 1 if not done already. • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 neurotoxicity and if not administered previously. • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for neurotoxicity without concurrent CRS; continue corticosteroids until improvement to Grade 1 neurotoxicity and then taper. • Stage 1 or 2 papilloedema with CSF opening pressure <20 mmHg should be treated as per algorithm presented in Table 5. • Consider repeat neuroimaging (CT or MRI) every 2 to 3 days if patient has persistent Grade ≥3 neurotoxicity.
Grade 4	• Supportive care and neurological work-up as outlined for Grade 1 neurotoxicity. • ICU monitoring; consider mechanical ventilation for airway protection. • Anti-IL-6 therapy if concurrent CRS • High-dose corticosteroids continued until improvement to Grade 1 neurotoxicity and then. • Consider repeat neuroimaging every 2-3 days for persistent ICANS • For convulsive status epilepticus, treat as per algorithm in Table 6. • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in Table 7. • Worsening: May consider use of lymphodepleting drugs such as cyclophosphamide or other drugs if unresponsive to standard immunosuppressive therapies such as Anakinra
General	• Once sustained clinical improvement is observed steroids can be taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier • Prophylactic antibiotics or other antimicrobials as clinically appropriate. • Rigorous control of blood pressure and electrolytes (particularly calcium and magnesium).

Table 6: Recommendation for the Management of Status Epilepticus after CAR-T Cell Therapy

Event	Management
Non-convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose. • Lorazepam 0.5 mg IV, with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures. • Levetiracetam 500 mg IV bolus, as well as maintenance doses. • If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg IV. • Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hours for three doses; levetiracetam 1000 mg IV every 12 hours; phenobarbital 30 mg IV every 12 hours.
Convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose. • Transfer to ICU. • Lorazepam* 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures. • Levetiracetam 500 mg IV bolus, as well as maintenance doses. • If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV. • Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 hours for three doses; levetiracetam 1000 mg IV every 12 hours; phenobarbital 1–3 mg/kg IV every 12 hours. • Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment.

Table 7: Recommendation for Management of raised intracranial pressure (ICP) after CAR-T cell therapy

Condition	Management
Stage 1 or 2 papilloedema with CSF opening pressure of <20 mmHg without cerebral oedema	• Acetazolamide 1000 mg IV, followed by 250 to 1000 mg IV every 12 hours (adjust dose based on renal function and acid–base balance, monitored 1 to 2 times daily).
Stage 3, 4, or 5 papilloedema, with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg	• Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for Grade 4 CAR-T-cell-related encephalopathy syndrome. • Elevate head end of the patient's bed to an angle of 30 degrees. • Hyperventilation to achieve target partial pressure of arterial carbon dioxide (PaCO2) of 28 to 30 mmHg, but maintained for no longer than 24 hours. • Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below) • Mannitol: initial dose 0.5 to 1 g/kg; maintenance at 0.25 to 1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40. • Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50 to 75 mL/h while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/l. • For patients with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed. • If patient has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg. • Consider neurosurgery consultation and IV anaesthetics for burst suppression pattern on electroencephalography. • Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

CAR-RELATED HLH

HLH/MAS encompasses a group of severe immunological disorders characterized by hyperactivation of macrophages and lymphocytes, proinflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure. These disorders have similar clinical manifestations, irrespective of the underlying cause. Patients with CRS after CAR-T-cell therapy have clinical features and laboratory findings that resemble those of HLH/MAS, including high fever; multiorgan dysfunction; CNS disturbances; high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as IFNγ and IL-6); and low serum levels of fibrinogen (see table 6). Thus, CRS and HLH/MAS might belong to a similar spectrum of systemic hyperinflammatory disorders.

Table 6. Diagnostic criteria for CAR-T-cell-related HLH/MAS
A patient might have HLH/MAS if he/she had a peak serum ferritin level of >10,000 ng/ ml during the cytokine-release syndrome phase of CAR-T-cell therapy (typically the first 5 days after cell infusion) and subsequently developed any two of the following: • Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels* • Grade ≥3 oliguria or increase in serum creatinine levels* • Grade ≥3 pulmonary oedema* • Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry
CAR, chimeric antigen receptor; HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage-activation syndrome. *Grading as per Common Terminology Criteria for Adverse Events, version 4.0

Fulminant and refractory HLH/MAS to steroids and toculizumab is observed in ~1% of all patients treated with CAR-T-cell therapy. If the patient has no improvement within 48 h after commencement of steroids and toculizumab, additional therapy with etoposide 75–100 mg/m^2 should be considered. This agent can be used in patients with liver and kidney dysfunction. Indeed, rapid initiation of etoposide therapy, in spite of organ dysfunction, is imperative for patients with high probability of a HLH diagnosis, owing to the high risk of death. Etoposide can be repeated after 4–7 days, as indicated clinically or serologically, to achieve adequate disease control. Intrathecal cytarabine, with or without hydrocortisone, should also be considered for patients with HLH-associated neurotoxicity. Although etoposide and cytarabine are often used in the treatment of familial and malignancy-associated HLH, at present, direct evidence to support their use in patients with CAR-T-cell-associated HLH is lacking (see figure 1).

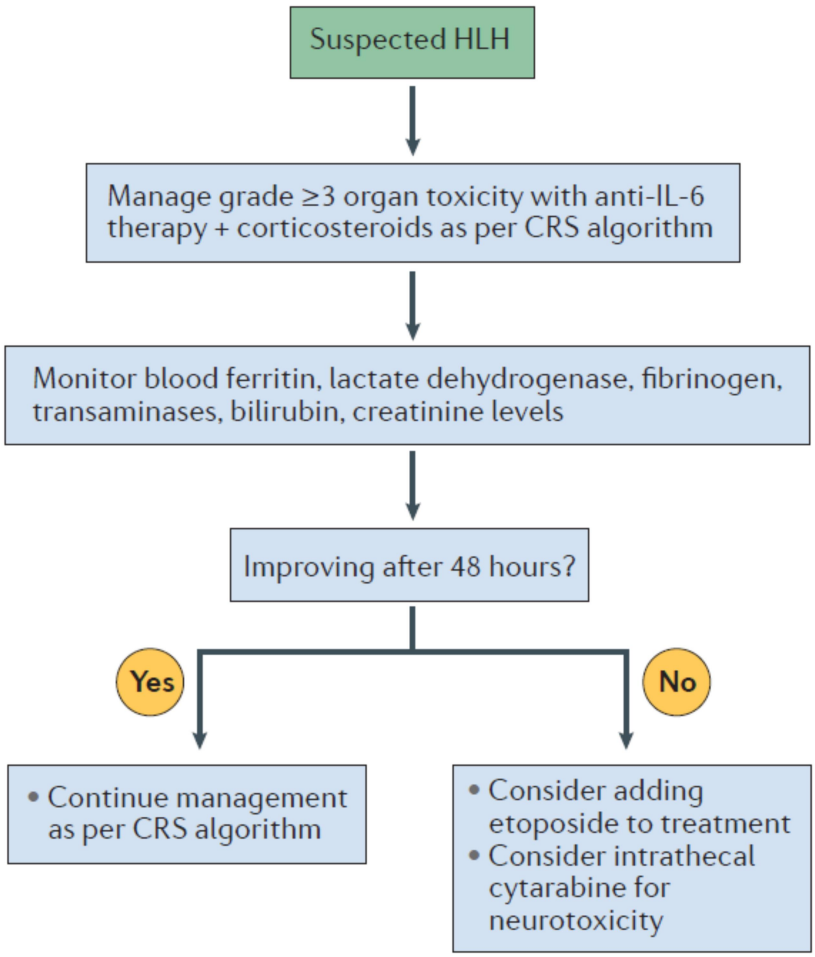

Figure 1.
Recommendations for the management of Chimeric antigen receptor (CAR)-T-cell-related haemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS) [8]
HLH/MAS should initially be managed according to the guidelines for cytokine-release syndrome, with appropriate subsequent laboratory testing to monitor response to treatment. If the results of these tests reveal no improvement within 48 h, escalation of treatment should be considered.

References

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RESPONSIBILITIES

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