MANAGEMENT OF CAR T CELL THERAPY (ICANS)	Version: 3.0
DIAGNOSIS AND MANAGEMENT OF IMMUNE EFFECTOR CELL - ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) POST CAR-T CELL THERAPY	
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Contents Page

Document Status

This is an uncontrolled copy and should be used for education purposes only. For clinical decision making, please refer to the controlled document on Q-Pulse, Metavision or Neurology TEAMS folder.

1. Summary

Adapted from Rees, J. H. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome. The EBMT CAR-T Handbook, 2022. [1]

A common and challenging side effect associated with CAR-T cell (Chimeric Antigen Receptor T-cell) therapy is immune cell-associated neurotoxicity syndrome (ICANS), which occurs in 20–60% of patients, of whom 12–30% have severe (≥ grade 3) symptoms. The underlying mechanism driving the syndrome is not fully understood, but there is evidence for the release of inflammatory cytokines secreted by macrophages and monocytes, increasing vascular permeability and endothelial activation and leading to blood–brain barrier breakdown. ICANS is not thought to be directly mediated by CAR-T cells themselves.

Risk factors for ICANS include high disease burden, older age, and the specific CAR-T product.

The onset of ICANS occurs (on average) approximately 5 days following CAR-T cell infusion and sometimes occurs concurrently with or shortly after cytokine release syndrome (CRS). However, in approximately 10% of patients, ICANS presents more than 3 weeks after CAR-T cell infusion. Symptoms of ICANS are variable and can initially be vague.

Patients experience mild tremor and confusion, which can then proceed to agitation, seizures, and cerebral oedema. A prominent and early feature of ICANS is hesitancy of speech and deterioration in handwriting, which can progress to aphasia with both expressive and receptive components, whereby the patient is alert but mute.

The most devastating consequence of ICANS is the occurrence of status epilepticus, fatal cerebral oedema and occasionally intracerebral haemorrhage.

ICANS is a clinical diagnosis—brain MRI and CSF evaluation are rarely helpful but can be used to rule out alternative diagnoses, e.g., CNS infection. The EEG recording can be normal but can also demonstrate a pattern of variable abnormalities, including nonconvulsive status epilepticus.

[1] Kroger et al. The EBMT/EHA CAR-T Cell Handbook. Open access online https://www.ebmt.org/sites/default/files/2022-02/2022_Book_TheEBMTEHACAR-TCellHandbook.pdf

A number of conditions may mimic ICANS, including atypical CNS infection (e.g. HHV-6), metabolic acidosis, sepsis, non-convulsant seizures and drug toxicity.

Most cases spontaneously resolve, often with supportive care and early intervention with corticosteroid therapy.

All patients should be proactively monitored for ICANS twice daily to assess subtle changes in cognition using the 10-point Immune Effector Cell Encephalopathy (ICE) score, which evaluates orientation, attention, writing, and language. This score is then integrated into an overall assessment of neurological function incorporating seizure activity, change in consciousness level, motor findings, and elevation in intracerebral pressure/ cerebral oedema to obtain an ICANS grade. The higher the ICE score is, the lower the ICANS grade.

Any patient with an ICE score less than 2 or with seizures is classified as severe (grade 3 or 4) and should be transferred to intensive care.

Factors associated with a higher risk of ≥ grade 3 ICANS include a higher disease burden, low platelet count, and the development of early and severe CRS.

Management of ICANS is based on the severity of the score and the concurrence of CRS. Management is supportive for grade 1 ICANS, and dexamethasone with rapid taper is given for grade ≥2 ICANS. Suggested doses include 10–20 mg intravenous dexamethasone every 6 h for grades 2–3 and 1 g IV methylprednisolone for at least 3 days for grade 4 until symptoms improve. Seizures are treated with levetiracetam and status epilepticus with benzodiazepines. Whilst practice varies, it is felt prudent to use prophylactic levetiracetam with products associated with a higher risk of ICANS (e.g. Axicel, Tecartus).

Other experimental approaches to the management of ICANS have been directed at controlling the potency of the CAR itself. Several CAR constructs have been designed with “suicide switches” or as “tunable CARs” by incorporating mechanisms designed to turn off or downgrade the CAR in the event of severe toxicity. In severe unresponsive cases, anakinra (IL-1 receptor antagonist) or chemotherapy to kill the CAR-T cells have been used. However, most cases resolve and do not result in residual neurocognitive damage.

2. Scope and Purpose

To ensure medical / nursing staff managing patients undergoing CAR-T cell therapy understand the clinical features and management of cytokine release syndrome.

This will include staff within Cancer Care (as the primary care team), the General Intensive Care Unit, and Emergency Department.

To ensure that patients with Immune Effector Cell Associated Neurotoxicity receive appropriate care.

Contacts : CAR-T CNS mobile Amy Tooley or Alice Jenkins 07717138754
BMT and Cellular Therapy Consultant on call through switchboard (100)

3. Definitions

ASTCT	American Society of Transplantation and Cellular Therapy
CAR-T	Chimeric antigen receptor T-cell
CNS	Central nervous system
CRP	C-reactive protein
CRS	Cytokine release syndrome
DIC	Disseminated intravascular coagulation
EDC	Emergency drugs fridge
GCSF	Granulocyte colony stimulating factor
GICU	General Intensive Care Unit
HDU	High Dependency Unit
ICANS	Immune effector cell associated neurotoxicity syndrome
ICE	Immune effector cell associated encephalopathy
IEC	Immune effector cell
SPC	Summary of product characteristics

4. Details of Procedure to be followed

All patients should have baseline ICANS assessment prior to CAR-T infusion, and routine assessment should continue from infusion until discharge from hospital, or day 28, whichever is earlier.

Timing of assessment

Assessment and grading should be performed:

- Every 8 hours from CAR-T infusion;
- Every 4 hours if any grade CRS or ICANS
- Whenever a change in the patients' status is observed;

Assessment procedure

Assessment and grading for ICANS involves:

- a 10-point neurological assessment, known as the Immune effector Cell-associated Encephalopathy (ICE) score
- assessment of the level of consciousness
- assessment of the presence of seizures
- assessment of the presence of deep motor weakness
- assessment of the presence of elevated intracranial pressure or cerebral oedema

Immune Effector Cell –Associated Encephalopathy (ICE) score

The ICE score is a 10 point neurological assessment tool in which 1 point is assigned for each of the following tasks performed correctly. See also Appendix D.

- Orientation to year, Month, City, Hospital (4 points)
- Naming three objects e.g. point to clock, pen, button (3 points)
- Following commands e.g. show me 3 fingers or close your eyes and stick your tongue out (1 point)
- Writing a standard sentence (patient can choose at baseline) (1 point)
- Counting backwards from 100 in tens (1 point)

Assessment of conscious level

Conscious state should be documented in the nursing record as:

- Awakens spontaneously
- Awakens to voice
- Awakens only to tactile stimulus (touch)
- Unarousable, or requires vigorous or repetitive tactile stiumulus to awaken. Stupor or coma

Grading of ICANS

ICANS must be graded using the scale below (see table 1) by the nursing and medical staff looking after the patient.

Table 1 – ICANS grading according to ASTCT criteria[2]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7 - 9	3 - 6	0 - 2	0 (patient unrousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awake to voice	Awakes only to tactile stimulus	Patient unrousable or requires vigorous or repetitive tactile stimuli to rouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalised that resolves rapidly; OR non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5mins); OR Repetitive clinical or electrical seizures without return to baseline between seizures
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemi-paresis or paraparesis
Raised ICP/ cerebral oedema	N/A	N/A	Focal or local oedema on neuro-imaging	Diffuse cerebral oedema on neuro-imaging; decerebration or decorticate posturing; OR cranial nerve VI palsy, OR papilloedema; OR Cushing's triad

Laminated copies of this will be available on the wards, and it is the responsibility of the QM to ensure that the most up-to-date version is available.

[2]Lee DW, et al. ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 00 (20-18) 1-14

5. Management of ICANS

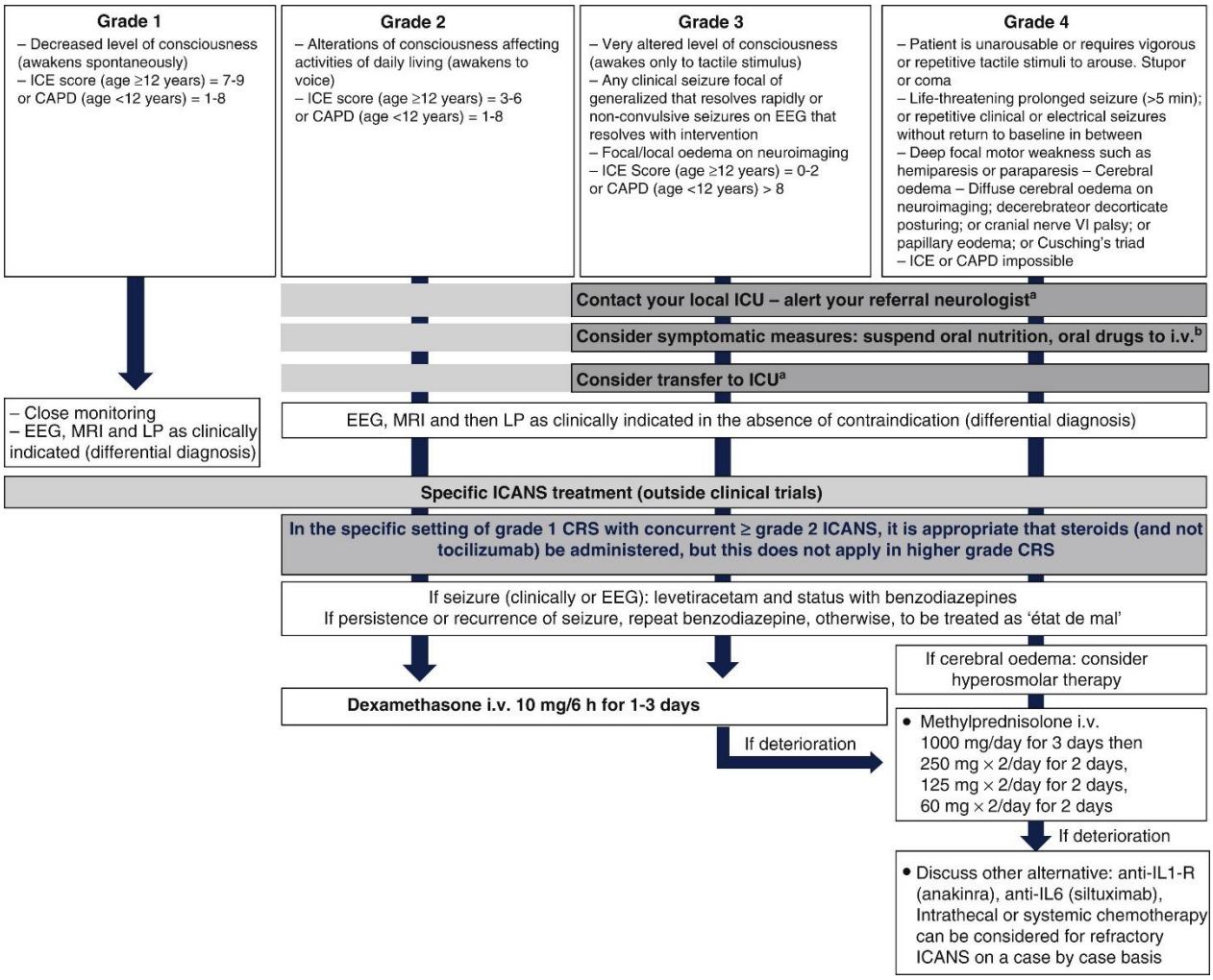
Management of ICANS is largely supportive and depends on severity. Corticosteroids are the mainstay of care for all grades of I ICANS and should be prescribed at high doses with a rapid taper. Patients with concurrent CRS may also receive tocilizumab according to the CRS management recommendations.

The prognosis is good, and most patients fully recover without any long-term sequelae.

Any prescription, or change to a prescription, of corticosteroid or anti-cytokine therapy (e.g. tocilizumab, anakinra) should be first approved by the attending CAR-T consultant.

We do not recommend the use of prophylactic anti-epileptic drugs unless grade 1 or greater ICANS is documented

EBMT/EHA consensus recommendations for management of ICANS



UHS specific management of ICANS according to Grade

	Grade 1 **ICE 7-9** **Decreased level of consciousness, awakens spontaneously**	**Grade 2** **ICE 3-6** **Alterations of consciousness affecting activities of daily living (awakens to voice)**	**Grade 3** **ICE 0-2** **Very altered level of consciousness (awakens only to tactile stimulus)** **Rapidly resolving seizures or non-convulsant seizures on EEG that resolves rapidly with intervention**	**Grade 4** **ICE impossible** **Patient unrousable (or rousable to very vigorous tactile stiumulus); coma** **Life-threatening prolonged seizures (>5mins);** **Repetive clinical or electrical seizures without return to baseline in between.** **Deep focal motor weakness** **Cerebral oedema**
ICANS grading frequency	4-hourly	4-hourly	4-hourly	4-hourly (where feasible)
Senior r/v	SpR or consultant review at first documented grade 1 ICANS, and at least twice daily thereafter	SpR or consultant review at first documented grade 2 ICANS, and at least twice daily thereafter	SpR or consultant review at first documented grade 3 ICANS, and at least twice daily thereafter	SpR or consultant review at first documented grade 4 ICANS, and at least twice daily thereafter
Supportive	Assess swallow, convert all oral medications and/or nutrition to IV if impaired.	Assess swallow, convert all oral medications and/or nutrition to IV if impaired.	Assess swallow, convert all oral medications and/or nutrition to IV if impaired.	Assess swallow, convert all oral medications and/or nutrition to IV if impaired.
Medication				
Steroid	IV dexamethasone 10mg stat (Single dose).	IV dexamethasone 10mg bd. If no improvement after 48hrs increase to qds for 1-3 days	IV dexamethasone 10mg qds for 1-3 days If no improvement after 48hrs switch to methylprednisolone as per grade 4 ICANS	IV Methylprednisolone 1000mg/day for 3 days, then 250mg bd for 2 days, then 125mg bd for 2 days, then 40mg bd for 2 days
Anti-convulsant	Levetiracetam 500mg bd po/iv	Levetiracetam 500mg bd po/iv	Levetiracetam 500mg bd po/iv Follow neurology guidance if non-status seizures present	Levetiracetam 500mg bd po/iv Follow neurology guidance if non-status seizures or status epilepticus present
Anakinra			Anakinra 200mg s/c od for steroid refractory grade 3/4 ICANS	Anakinra 200mg s/c od for steroid refractory grade 3/4 ICANS
Other	Give tocilizumab only if indicated by concurrent CRS grade Avoid medications causing CNS depression unless required for agitation	Give tocilizumab only if indicated by concurrent CRS grade Avoid medications causing CNS depression unless required for agitation Posaconzaole 300mg od as fungal prophylaxis	Give tocilizumab only if indicated by concurrent CRS grade Consider siltuximab if anakinra-refractory (not routinely funded) Avoid medications causing CNS depression unless required for agitation Posaconzaole 300mg od as fungal prophylaxis	Give tocilizumab **only** if indicated by concurrent CRS grade Consider siltuximab if anakinra-refractory (not routinely funded) Avoid medications causing CNS depression unless required for agitation Posaconzaole 300mg od as fungal prophylaxis

Continues overleaf….

	Grade 1	Grade 2	Grade 3	Grade 4
Imaging	Urgent CT brain	Urgent MRI brain	Urgent MRI brain if not previously done Consider repeat brain imaging if no improvement >48hrs	Urgent MRI brain if not previously done Consider repeat brain imaging if no improvement >48hrs
Lumbar puncture	Only if clinically or radiologically indicated to rule out alternative cause	Lumbar puncture - send for cell count, MC&S, protein, paired glucose, haematology cytospin, virology (PCR for HSV, CMV, VZV, JC, adeno and HHV-6)	If not previously done: Lumbar puncture - send for cell count, MC&S, protein, paired glucose, haematology cytospin, virology (PCR for HSV, CMV, VZV, JC, adeno and HHV-6)	If not previously done: Lumbar puncture - send for protein, glucose, haematology cytospin, virology (PCR for HSV, CMV, VZV, JC, adeno and HHV-6)
EEG	Only after discussion with neurology, for suspected non-convulsant status	Only after discussion with neurology, for suspected non-convulsant status	Only after discussion with neurology, for suspected non-convulsant status	Only after discussion with neurology, for suspected non-convulsant status
GICU	Alert GICU outreach team	GICU outreach review	Transfer to GICU	Transfer to GICU
Neurology	Alert neurology	Discussion with neurology	Regular Neurology review	Regular Neurology review

Cerebral oedema

Consider hyperosmolar therapy for cerebral oedema, and discussion with neurosurgery/neuro-ICU. See Appendix B for ASTCT recommendations.

6. Roles and Responsibilities

This policy applies to all medical and nursing staff working in University Hospitals Southampton NHS Foundation Trust.

Contacts : CAR-T CNS mobile Amy Tooley or Alice Jenkins 07717138754
BMT and Cellular Therapy Consultant on call through switchboard (100)

7. Related Trust Policies

Infection prevention therapy protocols (adults) version 4th July 2014.

Management of patients receiving CAR T cell therapy No 1 : Diagnosis and Management of Cytokine Release Syndrome
CAR-T SOPs and Policies available on :-

Transplant Q Pulse 7

Metavision

Neurology TEAMs folder

8. Communication Plan

Training sessions will be held throughout Cancer Care, Neurology and Intensive care based on the policies.

9. Process for Monitoring Compliance/Effectiveness

Key aspects of the procedural document that will be monitored:

What aspects of compliance with the document will be monitored	What will be reviewed to evidence this	How and how often will this be done	Detail sample size (if applicable)	Who will co-ordinate and report findings (1)	Which group or report will receive findings
Reading and acknowledgment of document by staff within the Southampton Wessex Blood and Marrow Transplant Service	Q Pulse document acklowdeg-ment	Each time document updated and when new staff start. QM meetings held every 2 months	All WBMTU staff	JACIE QM	Wessex Blood and Marrow Transplant Quality Meeting Group

Where monitoring identifies deficiencies actions plans will be developed to address them.

10. Arrangements for Review of the Policy

Will be reviewed every two years or sooner if evidence or guidance changes

Appendices

Appendix A Recommendations for the management of status epilepticus after CAR T Cell therapy

Non convulsive status epilepticus	• Assess airway, breathing and circulation; check blood glucose • Lorazepam titrated 0.5mg intravenously (IV) with additional 0.5mg IV every minute, against response, up to a maximum of 0.1mg/kg in the first 10 minutes. • Levetiracetam 30mg/kg loading dose IV infusion (maximum dose 3000mg) , then continue as maintenance with 1000mg BD • If seizures persist, transfer to intensive care unit and treat with Phenobarbital loading dose of 10mg/kg IV • Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hrs for three doses, Levetiracetam 1000mg IV every 12 hours; Phenobarbital 30mg IV every 12 hours
Convulsive status epilepticus	• Assess airway, breathing and circulation, check blood glucose • Transfer to ICU, consider mechanical ventilation to protect airway • Lorazepam titrated 0.5mg intravenously (IV) with additional 0.5mg IV every minute, against response, up to a maximum of 0.1mg/kg in the first 10 minutes. • Levetiracetam 60mg/kg loading dose IV infusion (maximum dose 4500mg), then continue as maintenance with 1000mg BD • If seizure persists, add pheytoin as per neurology guidance. • Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 hrs for three doses, Levetiracetam 1000mg IV every 12 hours; phenytoin as per neurology guidance. • Continuous electroencephalogram monitoring should be performed if seizures are refractory to treatment.

Appendix B ASTCT Recommendations for the management of raised intracranial pressure (ICP) after CAR T-cell therapy

Stage 1 or 2 papilloedema* with CSF opening pressure of <20mmHg without	• Acetazolomide 1000mg intravenously, followed by 250-1000mg IV every 12 hour (adjust dose based on renal function and acid-base balance, monitored 1-2 times a day.
Stage 3,4 or 5 Papilloedema* with any sign of cerebral oedema on imaging studies or a CSF opening pressure of ≥20mmHg	• Use high dose corticosteroids with methylprednisolone IV 1 g/day as recommended for grade 4 ICANs (table 2) • Nurse 30 degrees head up Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 4.5-5kPa, for at least 24 hours, weaning back to normal over 24-48 hours period if swelling settled. - "Hyperosmolar therapy with mannitol or hypertonic saline to provided sodium levels of <150mmol/l and serum osmolality <320. - Mannitol: initial dose 0.5-1g/kg, maintenance at 0.25-1g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320mOsm/kg or the osmolality gap is ≥40 • If patient has ommaya reservoir, drain CSF to target opening pressure of <20mmHg • Consider neurosurgery consultation and IV anaesthetics for burst-suppression pattern on electroencephalography • Metabolic profiling every 6 hr and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolaemia, and hypotension *papilloedema grading should be performed according to the modified Frisen scale

Appendix C Drugs used in the treatment of CRS and ICANS

Tocilizumab

Tocilizumab, an IL-6 receptor antagonist, can effectively diminish CRS-related toxicity with a rapid response. As a guide Tocilizumab should be dosed at 8mg/kg, and administered over 1hour. The dose may be repeated 8 hourly up to 4 times, at the discretion of the supervising consultant. Tocilizumab should be diluted in 100mls 0.9% sodium chloride. Tocilizumab comes in different size dose vials,

- 80mg in 4mls
- 200mg in 10mls
- 400mg in 20mls

Once Tocilizumab is added to the infusion bag, gently invert the infusion bag to avoid foaming. Dose should not exceed 800mg

Do not infuse with any other medicines

Tocilizumab does not cross the blood brain barrier and should not be used to treat ICANS in the absence of CRS. However, it may be given if CRS is also present.

Four doses of tocilizumab will be kept in the fridge on C6. This pack will contain information on dosing of tocilizumab, safe preparation of tocilizumab and equipment/devices to ensure safe preparation of tocilizumab. This will guide team collecting tocilizumab on how best to prepare dose for a patient of a given weight

Several strengths of tocilizumab will also be kept in the emergency drugs fridge (EDC). This is located behind pharmacy next to the security desk. A tocilizumab pack will be kept in the EDC. This will contain information on dosing of tocilizumab, safe preparation of tocilizumab and equipment/devices to ensure safe preparation of tocilizumab. This will guide team collecting tocilizumab on how best to prepare dose for a patient of a given weight

Storage of tocilizumab in the EDC ensures tocilizumab is available for patients at point of need and can be prepared and administered in safe way for patient and staff involved. Training on safe preparation of tocilizumab and use of safety needle free devices will be provided to staff

The staff member administering a dose of tocilizumab is responsible for informing pharmacy so that stocks can be replenished as soon as possible

Corticosteroids

Corticosteroids are a second-line therapy for CRS because the clinical response to corticosteroids is delayed compared to Tocilizumab. Furthermore, corticosteroids may lead to greater anti-tumour activity than Tocilizumab.

Dexamethasone 10mg IV is the standard steroid used, with frequency of administration dictated by the grade of CRS/ICANS. Methylprednisolone IV at high doses may be used for high grades of CRS/ICANS.

Steroids should be rapidly weaned on clinical improvement, and attention should be paid to anti-fungal prophylaxis in any patient receiving high dose steroids.

Anakinra

Anakinra targets the IL-1 cytokine receptor and is able to cross the blood-brain barrier, potentially limiting the toxic side effects of CRS[6,7]. Anakinra is not licensed for treatment of IEC-related CRS, but may be considered in patients with CRS refractory to tocilizumab and steroid. It is given as a fixed dose of 200mg subcutaneous once daily. This is dispensed in a pre-filled syringe.

Patients and their carers should be counselled to seek immediate attention should the signs or symptoms of ICANS occur post discharge.

If patients are admitted within 8 weeks of CAR T cell therapy with neurological symptoms then 4 hourly monitoring should be recommenced, using the integrated CRS/ICANS assessment sheet.

Appendix D

EXAMPLE Integrated CRS/ICANS Assessment Chart – front sheet and continuation

Assessment Sheet to be printed off Q Pulse and placed in each patient's ward notes on admission. Controlled Copies available in C6 CAR-T folder.

Cytokine Release Syndrome (CRS) Grading and Action

Cytokine Release Syndrome (CRS) is graded on the basis of: pyrexia, hypotension and hypoxia.

The grade is determined by the more severe event.

In patients who have CRS who are receiving tocilizumab or steroids, fever is no longer required for grading.

See the table below for guidance.

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or 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, 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

Lee et al. *Biol Blood Marrow Transplant*, 2019 Apr;25 (4):625-638

ANY abnormalities or any CRS/ICANS grade above 0 must be escalated immediately to physicians as require timely treatment.

IF IN DOUBT – ESCALATE TO PHYSICIAN

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) Grading and Action

ICANS grading is completed by assessing multiple neurological functions of the patient. It uses a combination of the ICE Score, and presence of other neurological symptoms.

ICE Scoring Tool

	Immune Effector Cell Associated Encephalopathy Tool	
Monitors	**How**	**Points**
Orientation	Ask the patient the year, month, city and hospital	1 point for each correct answer. **Total of 4 points.**
Naming	Point to 3 objects in the room and ask the patient to name them (e.g. pen, book, clock)	1 point for each correct answer. **Total of 3 points.**
Following commands	Ask the patient to do a command (e.g. show me three fingers or close your eyes and stick your tongue out)	1 point for the correct action
Writing	Ability to write a standard sentence (e.g. I took the dog for a walk in the woods)	Compare to the handwriting prior to cell infusion. 1 point for correct action.
Attention	Ask the patient to count backwards from 100 in tens	1 point for the correct answer.

Once all parts of the assessment are completed, add all points up to the maximum total of 10.
Relate this to the grading tool below.

Neurotoxicity Domain‡	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and 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 or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly ; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); 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
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, raised ICP/cerebral edema) not attributable to any other cause

Lee et al. *Biol Blood Marrow Transplant*, 2019 Apr;25 (4):625-638

If the patient's ICE score is 9 or below, or there is a new a neurological symptom, or you are unsure, escalate to physician.

BMT and Cellular Therapy Consultant on call through switchboard (100)

Assessment and grading should be done:

- **Every 8 hours from CAR-T infusion;**
- **Every 4 hours if any grade CRS or ICANS**
- **Whenever a change in the patients' status is observed;**

Affix patient label here:

BASELINE ASSESSMENT – TO BE PERFORMED IMMEDIATELY PRIOR TO CAR-T INFUSION

Date	**CRS**	**Fever ≥38°C**		**Hypotension**				**Hypoxia O_2 required to maintain SpO_2 ≥92%**				**CRS Grade**
	circle	N	Y	None	No pressor required	Requiring 1 pressor	Requiring >1 pressor	None	Low-flow < 6L/min	High flow ≥6L/min	NIV or I&V	
Time	*min grade*	*0*	*1*	*0*	*2*	*3*	*4*	*0*	*2*	*3*	*4*	
	ICANS	Year	Month	City	Hospital	Object 1	Object 2	Object 3	Follow command	Hand-writing	Attention	**Total**
	ICE score											/10
Staff initials	Handwriting											**ICANS Grade**

Date	**CRS**							**Hypotension**				**Hypoxia O_2 required to maintain SpO_2 ≥**				**CRS Grade**
	circle							None	No press required	Requiring 1 pressor	Requiring >1 pressor	None	Low-flow < 6L/min	High flow ≥6L/min	NIV I&V	
Time	*min grade*								*2*	*3*	*4*	*0*	*2*	*3*	*4*	
Staff initials	**ICANS**	Year	Month	City	Hospital	Object	Objec				Follow command	Hand-writing	Attention	**Total**		
	ICE score											/10				
	Handwriting															**ICANS Grade**

Date	**CRS**	**Fever ≥38°C**		**Hypotension**				**Hypoxia O_2 required to maintain SpO_2 ≥92%**				**CRS Grade**
	circle	N	Y	None	No pressor required	Requiri 1 presso	ng or	None	Low-flow < 6L/min	High flow ≥6L/min	NIV or I&V	
Time	*min grade*	*0*	*1*	*0*	*2*	*3*		*0*	*2*	*3*	*4*	
	ICANS	Year	Month	City	Hospital	Object 1		Object 3	Follow command	Hand-writing	Attention	**Total**
	ICE score											/10
Staff initials	Handwriting											**ICANS Grade**

Date	**CRS**	**Fever ≥38°C**		**Hypotension**				**Hypoxia O_2 required to maintain SpO_2 ≥92%**				**CRS Grade**
	circle	N	Y	None	No pressor required	Requiring 1 pressor	Requiring >1 pressor	None	Low-flow < 6L/min	High flow ≥6L/min	NIV or I&V	
Time	*min grade*	*0*	*1*	*0*	*2*	*3*	*4*	*0*	*2*	*3*	*4*	
	ICANS	Year	Month	City	Hospital	Object 1	Object 2	Object 3	Follow command	Hand-writing	Attention	**Total**
	ICE score											/10
Staff initials	Handwriting											**ICANS Grade**

MANAGEMENT OF CAR T CELL THERAPY ICANS DIAGNOSIS AND MANAGMENT OF IMMUNE EFFECTOR CELL - ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) POST CAR-T CELL THERAPY	Version: 3.0

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Summary of most recent changes if applicable:	**Appendix A** Recommendations for the management of status epilepticus after CAR T Cell therapy 1. Prophylactic levetiracetam in the absence of seizures 2. Change 'levetiracetam PO' to 'levetiracetam PO/IV' 3. Lumbar puncture should be sent for: cell count, protein, paired glucose, MC&S, virology 4. EEG guidance 5. generally to use phenytoin as 2nd line, and valproate as 3rd line for status epilepticus rather than phenobarb 6. For status preference is levetiracetam 60mg/kg, up to maximum dose 4.5g 7. Integrated CRS/ICANS assessment sheet
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