Critical care management of CAR-T related Immune Effector Cell related Neurotoxicity Syndrome (ICANS)

Introduction

ICANS (Immune Effector Cell Related Neurotoxicty Syndrome) is a life-threatening complication of immune effector cells (IEC) or immunotherapy.
ICANS is the second most common complication after CRS, with an incidence ranging from 12 - 55%.
The median time of onset of the first neurological symptoms is six days (range 1 - 34 days).
It can be biphasic:

- The first phase usually occurs 1 - 5 days after the immune effector cell (IEC) infusion, alongside CRS (of any grade).
- The second phase occurs later (> 5 days after the IEC infusion) following resolution of CRS (of any grade).

Late ICANS, occurring 3-4 weeks after the IEC infusion, occurs in approximately 10% of patients.

Risk factors include pre-existing neurological co-morbidities and disease specifics (ALL, tumour burden, history of meningeal involvement and prior CNS-directed therapies).

Symptoms usually last between 2 and 9 days though late complications can occur.
Deterioration in hand writing can be an early predictor of neurotoxicity.
Severity correlates with the inflammatory markers - CRP and ferritin.

Management

Early recognition and treatment is essential for patient safety.

All patients should receive seizure prophylaxis (levetiracetam 500mg PO BD for 30 days, starting on the day -1).

All patients should be scored according to the ICE Score (Table 1).

All patients should be graded according to the ASTCT Grading System (Appendix 3).

ICANS is determined by the more severe event for example a patient with an ICE score of 5 who has a generalized seizure is classified as having Grade 3 ICANS.
All patients should have daily writing tests. Assessment and grading should be done 8 hourly and/or whenever a change in the patient's status is observed and recorded on the ICANS Assessment Record (Table 2).

Management of ICANS is detailed in Table 4. Initially all CAR-T patients will be infused within ICU and so decision to transfer to critical care will not need to be made.

Treatment of status epilepticus can be found in Table 5 and raised intracranial pressure in Table 6.

Table 1: ICE score

TEST	POINTS
ORIENTATION: **Orientation to year, month, city and hospital**	4
NAMING: **Ability to name three objects** **- Pen** **- Chair** **- Shoe**	3
FOLLOIWNG COMMANDS: **Ability to follow simple commands eg. put your hand on your head**	1
WRITING: **Ability to write a standard sentence**	1
ATTENTION: **Ability to count backwards from 100 by 10**	1

Table 2: ICANS Assessment Record

Baseline	**Date**	**Time**
Handwriting example		

ICE Score	**Depressed level of consciousness**	**Seizure**	**Motor findings**	**Raised intracranial pressure / cerebral oedema**	**ICANS Grade**

Table 3: ASTCT Grading System

Symptom / Sign	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ICE SCORE *	7-9	3-6	0-2 Grade 3 is awake with global aphasia	0 Unrousable and unable to perform ICE Score
DEPRESSED LEVEL OF CONSCIOUS-NESS*	Awakens spontaneously	Awakens to voice	Awakens to tactile stimuli	Unrousable OR requires vigorous or repetitive tactile stimuli to rouse OR coma
SEIZURE *	-	-	Any clinical seizure (focal or generalised) that resolves rapidly (< 5mins) or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (≥ 5 minutes) or repetitive clinical or electrical seizures without return to baseline in-between
MOTOR FINDINGS *	-	-	-	Deep focal motor weakness such as hemiparesis or paraparesis
RAISED INTRACRANIAL PRESSURE / CEREBRAL OEDEMA *	-	-	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilloedema, or Cushing's triad

Table 4: Management of ICANS according to grade

ICANS Grade	Treatment
GRADE 1	• Liaise with ICU & Neurology and agree plan for ongoing review. • Increase monitoring to 6 hourly and/or whenever a change in patients status. • Supportive care including IV fluids (maintenance rate only if required as these patients are high risk for fluid overload), NBM, convert oral medication to IV (Levetiracetam is bioequivalent when switching oral to IV). • Stop sedating medications. • Rigorous control of BP - aim systolic BP 90-130mmHg. • Correct any uraemia (filter if necessary) / electrolyte / coag abnormalities. • Perform fundoscopy looking for papilloedema – if present refer to Table 6. • If agitated give lorazepam (0.25 – 0.5mg IV every 8 hours) ideally AFTER EEG. • If associated with CRS ≥ grade 1 give tocilizumab (8mg/kg infused over 1 hour) AND refer to CRS policy for ongoing management. • If no improvement within 12 hours give dexamethasone 10mg IV 6 hourly. • EEG within 24 hours, repeat if condition deteriorates. • MRI brain (CT if MRI not possible); diagnostic lumbar puncture for opening pressure; MRI spine for focal deficits if deterioration or no improvement in 24 hours.
GRADE 2	• Transfer to ICU if patient not in critical care area • Supportive care and work up (including imaging and lumbar puncture) as for Grade 1 ICANS (if not already done). • If associated with CRS ≥ grade 1 give tocilizumab (8mg/kg infused over 1 hour) and dexamethasone 10mg IV 6 hourly AND refer to CRS policy for ongoing management. • If NOT associated with CRS give methylprednisolone 1mg/kg 12 hourly for 24 hours (2 doses). • Repeat EEG if no clinical improvement in 24 hours. • In the absence of improvement at **12 hours** (after 2 doses of tocilizumab and 2 doses of dexamethasone) give methylprednisolone 1mg/kg in place of dexamethasone AND refer to CRS policy for ongoing management.
GRADE 3	• Transfer to ICU if patient not in critical care area • Supportive care and work up as for Grade 1 ICANS (if not already done). • Irrespective of whether ICANS is associated with CRS give tocilizumab (8mg/kg infused over 1 hour; if tocilizumab has already been given only administer next dose if ≥ 8 hours have passed since previous dose, **maximum of 4 doses**). • If associated with CRS give dexamethasone 20mg IV 6 hourly AND refer to CRS policy for ongoing management. • If NOT associated with CRS give methylprednisolone 1mg/kg 12 hourly. • In the absence of improvement at **12 hours** (after 2 doses of tocilizumab and 2 doses of dexamethasone) or deteriorating give methylprednisolone 1g/day in divided doses IV (See NHS Lothian IV guideline for administration) for 1 day in place of dexamethasone. • If refractory for >24 hours manage as Grade 4 ICANS. • Repeat imaging every 48-72 hours if no improvement. • For papilloedema / raised ICP by lumbar puncture manage as per Table 6.
GRADE 4	• Transfer to ICU urgently, consider I&V for airway protection. • Supportive care and work up as for Grade 1 ICANS (if not already done). • Administer tocilizumab (8mg/kg infused over 1 hour, **maximum 4 doses;** refer to CRS policy for full details on dosing and administration). • Administer high dose methylprednisolone 1g/day for 3 days then taper. Switch to IV/oral dexamethasone to facilitate taper over 3 days. • If refractory for >24 hours or deteriorating consider anakinra (200mg OD SC for 3-5 days) OR lymphodepleting drugs (See High Dose cyclophosphamide 1.5g/m^2 (with mesna) SACT protocol Regimen number: 947) • For status epilepticus manage as per Table 5 • For papilloedema / raised ICP by lumbar puncture manage as per Table 6
General	• Once sustained improvement at Grade ≤1 is observed steroids can be tapered. • Switch to IV/oral dexamethasone to facilitate taper over 3 days. • IV preparations can be switched to PO • Monitoring intensity can be reduced back to 8 hourly

Table 5: Management of status epilepticus in patients receiving CAR-T

Event	Management
Non-convulsive status epilepticus / Focal or Generalised Seizures	• Assess airway, breathing, and circulation. • Check blood glucose. • Give diazepam* 2mg IV initially up to 10mg over 5mins OR 4mg IV lorazepam (see appendix 7 for preparation and administration). • Repeat diazepam once 15mins later up to a total of 20mg if required OR repeat lorazepam once 15mins later up to a total of 8mg • Give Magnesium to maintain Mg > 1.0mmol/l. • Give Thiamine 100mg IV 8 hourly for 5 days, switch to oral when route available. • If seizures persist, transfer to ICU and treat as per Critical Care guideline for the treatment of Status Epilepticus.
Convulsive status epilepticus	• Assess airway, breathing, and circulation. • Check blood glucose. • Give diazepam* 2mg IV initially up to 10mg over 5mins OR 4mg IV lorazepam. • Transfer to ICU. • If seizures persist, transfer to ICU and treat as per Critical Care guideline for the treatment of Status Epilepticus. • Continuous EEG monitoring should be performed if seizures are refractory to treatment.

Table 6: Management of raised intracranial pressure in patients receiving CAR-T therapy

Event	Management
Papilloedema without diffuse cerebral oedema or other signs of raised intracranial pressure	• Acetazolamide 1g IV followed by 250-1g IV every 12 hours (monitor renal function and bicarbonate BD and adjust dose accordingly. • Dexamethasone 20mg IV every 6 hours, taper after resolution of papilloedema. Switch to IV/oral dexamethasone to facilitate taper over 3 days.
Diffuse cerebral oedema on neuro imaging or signs of raised intracranial pressure (decerebrate or decorticate posturing, cranial nerve VI palsy, or Cushing's triad)	• Methylprednisolone 1g/day in divided doses IV for 3 days followed by taper as clinically indicated. Switch to IV/oral dexamethasone to facilitate taper over 3 days. • Elevate head end of patient's bed to an angle of 30 degrees. • Titrate sedation and analgesia to optimize synchrony with mechanical ventilation in order to achieve blood gas targets • Set minute ventilation to achieve target $PaCO_2$ of 5-6kPa • Control BP to achieve target mean arterial pressure of 90mmHg. • Hyperosmolar therapy with either mannitol (20g/dL solution) **or** hypertonic saline (5% or 23.4% as detailed below). • Mannitol: initial dose 0.5-1g/kg IV with Plasmalyte 148 250mls; maintenance dose 0.25-1g/kg IV every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours; withhold mannitol if serum osmolality is ≥ 320mOsm/kg or osmolality gap is ≥ 40. • Hypertonic 5% saline: initial dose 125 mL IV over 15 minutes, maintenance dose of 50-75mL/hour IV while monitoring electrolytes every 4 hours; withhold infusion if serum sodium levels reach ≥ 155 mEq/L). • For patients with imminent herniation (NPIs 0 ie fixed pupils) : initial dose of hypertonic 5% saline 125 mL IV over 15 minutes; repeat after 15 minutes, if needed. • If patient has ventricular access device (VAD) drain in situ, drain CSF to target OP < 20 mmHg. • For spontaneous burst-suppression pattern on EEG perform CT scan and sedation hold to assess neurology • Other measures: correct any uremia (dialysis if needed) and/or coagulopathy (transfuse to keep platelets > 20-50x10^9/l, fibrinogen > 200 mg/dL and INR < 1.5). • Metabolic profile every 6 hours and repeat CT scans of head without contrast if clinical deterioration, with adjustments in usage of aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolaemia and hypotension.

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