Management of patients following CART

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Introduction

Chimeric antigen receptor T-cells (CART) are genetically engineered T cells that target antigens on tumour cells resulting in tumour cell killing. It is classed as a 'living drug' being generated from autologous T cells or unrelated allogeneic donors.

The indications for use are currently narrow, restricted to a subset of haematological malignancies that have failed advanced therapies. However, this need is likely to grow, expanding to other haematological and solid tumours.

There is a robust governance structure around case selection including an MDT approach between haematology and critical care.

This document is a focused look at the management in critical care. Further information can be found in the documents produced by haematology.

CART is a very effective cure for even refectory malignancy and the outcomes from even severe toxicities are good. Therefore, in the absence of other reasons, aggressive critical care management including full escalation is the default for these patients including mechanical ventilation and multiorgan support.

Complications

A range of toxicities are associated with treatment with CART:

- **Cytokine release syndrome (CRS) is the most common**
  It can occur in up to 95% of recipients ranging from mild to life-threatening multi-organ failure. CRS generally occurs within the first week after CART therapy and peaks between 1-2 weeks.

- **Neurotoxicity (NT) is the second most common toxicity**
  It affects up to 80% of patients with a range of severity from language disturbance, impaired handwriting, confusion and agitation to cerebral oedema and death. It can occur early within the first 5 days and again at 3-4 weeks following treatment.

- **Less common toxicities include:**
  Macrophage activation syndrome, anaphylaxis, tumour lysis syndrome and infection.

Cytokine release syndrome

CRS is triggered by the activation of T cells when their receptor engages with antigen on their target cells. Activated T cells release cytokines and chemokines as do bystander immune cells such as monocytes and/or macrophages and dendritic cells.

Patients with bulky disease, comorbidities and early onset CRS (within 3 days of infusion) are at highest risk of developing severe CRS.

Symptoms of CRS can occur within 24 hours but peak at 3 days and generally occur within the 2 weeks following infusion. Treatment with the Il-6 antagonist Tocilizumab is effective in 95% of cases and does not decrease the effectiveness of CART. Addition of steroids may be needed but may decrease the effectiveness of CART.

Patients may experience:

- Symptoms including fever, rigors, headaches, myalgia and arthralgia
- Tachycardia, troponin increases and prolonged QTc with other arrhythmias
- Deteriorating LV function and hypotension in around 25% of patients
- Hypoxia in 10% of patients with pulmonary oedema and pneumonitis which can require mechanical ventilation.
- Acute kidney injury with electrolyte disturbances which may be multifactorial, due to tumour lysis syndrome or drug toxicity.
- Elevation in serum transaminases, bilirubin, diarrhoea, colitis, nausea and abdominal pain can also occur.

Who will be referred?

- Referrals to critical care will be made in patients with hypotension not responsive to fluid challenges and first line treatment with the IL-6 antagonist tocilizumab. These patients will have the CRS grading 2 or above (see Appendix).

What should we do first?

- Use paracetamol and the IL-6 antagonist Tocilizumab
  8mg/kg IV capped at 800mg
  Repeat after 8hrs
  Maximum of 3 doses in 24hrs and 4 doses throughout whole episode in total

- Supportive care with noradrenaline as first line agent aiming for MAP 65mmHg
  Use cardiac output monitoring if > 0.5 mcg/kg/min
  Consider adding a second agent including vasopressin or an inotrope if low cardiac index

- Provide further organ support as necessary. Isolation is not mandatory.

- Investigate other causes
  Exclude sepsis and If neutropenic treat as neutropenic sepsis

Organise echocardiography, CTPA or other imaging as appropriate

What if this isn't working?

- Be aware blocking IL-6 can impair an increase in CRP.

- Consider MAS and test ferritin levels (often >10,000ng/ml)
  If present discuss with haematology for alternative treatments.

- Discuss with haematology and then consider adding:
  Dexamethasone 10mg – 20mg IV 6hrly

- If further deterioration discuss with haematology and consider:
  Methylprednisolone 1g/day for 3 days IV instead of dexamethasone
  Then taper by ½ dose every 2 days to 60mg
  Further taper when no hypotension

Neurotoxicity

Neurotoxicity can be seen in up to 80% of patients receiving CART. In severe cases seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilloedema and cerebral oedema can occur.

A two-phase onset can occur with the first phase occurring alongside CRS symptoms within the first 5 days. A second phase can occur up to 3-4 weeks following CART infusion. This delayed neurotoxicity presents in up to 10% of patients typically with seizures and confusion.

Neurotoxicity typically lasts 2-4 days but this can vary from a few hours to weeks. Typically, neurotoxicity occurring with CRS is of shorter duration and lower grade whereas later onset neurotoxicity tends to be more severe and protracted. Whilst disturbing for the patient, their family and medical staff, neurotoxicity is generally reversible although rare fatal cases have occurred.

Whilst tocilizumab is generally effective at reversing the early neurotoxicity associated with CRS, it is often ineffective in the 2nd phase, when corticosteroids play a more important role.

Who will be referred?

Those with grade 3 or above (responsive to painful stimulus only, with any seizures or cerebral oedema, see Appendix).

What should we do?

- Intubate and ventilate as needed. Isolation is not mandatory.
  Standard sedation and BIS monitoring
  Avoid prolonged paralysis if possible to monitor clinical seizures

- CT or MRI brain to assess severity and exclude other causes
  Interpretation is difficult even by experienced neuroradiologists.

- Be aware blocking IL-6 can impair an increase in CRP.

- EEG
  Often shows diffuse generalised slowing
  It can demonstrate epileptiform discharges or non-convulsive electrographic seizures in 10% of patients.

- Consider LP
  After CT/MRI but consider risk of cerebral oedema and coagulopathies.

- Use drugs
  Use levetiracetam 750mg NG/IV 12hrly
  Use tocilizumab only if associated with CRS
  If no CRS or no improvement after 24 hours of tocilizumab
  Add Dexamethasone 10mg – 20mg IV 6hrly OR
  Methylprednisolone 1g/day for 3 days IV instead of dexamethasone
  Then taper by ½ dose every 2 days to 60mg
  Further taper when no hypotension

Further reading:

Internal guidelines:

- Guideline for the Assessment and Management of Specific Complications of Chimeric Antigen Receptor T-cell (CART) Therapy

- Guidelines for the Monitoring and Management of Patients Receiving CART Cell Therapy

Review articles:

- Critical Care Management of Chimeric Antigen Receptor T Cell-related Toxicity. Be Aware and Prepared. 2019 Jul 1;200(1):20–3.

Appendix

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[#] **O_2 sat <90%**	None	Low-flow O_2 via nasal cannula (or FiO_2 <40%)	Requiring high-flow O_2 (or oxygen requirement ≥40% FiO_2)	Requiring non-invasive ventilation or 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

Neurotoxicity Grading

Table 4. (Adapted from ASBMT consensus grading)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Neurotoxicity Assessment Tool Score	7-9	3-6	0-2	0 (patient unable to complete assessment)
Depressed level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens only to painful stimulus	Patient not rousable or requires vigorous stimuli to arouse or 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 in between
Motor findings	n/a	n/a	n/a	Focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/ cerebral oedema	n/a	n/a	Focal/ local oedema on neuroimaging	Diffuse cerebral oedema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilloedema, Cushing's triad.