NIHR | Lancashire Clinical Research Facility

STANDARD OPERATING PROCEDURE

Diagnosis and Management of Cytokine Release Syndrome, Immune Effector Cell Associated Neurotoxicity Syndrome, and Haemophagocytic Lymphohistiocytosis: A Guide for Lancashire Clinical Research Facility

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1. SUMMARY

This guideline covers the clinical presentation of complications associated with immune effector cell (IEC) therapies:

1) Cytokine release syndrome (CRS)

2) Immune effector cell associated neurotoxicity syndrome (ICANS)

3.) Haemophagocytic Lymphohistiocytosis (HLH)

We describe the early investigations and protocol-based management for patients suffering from these conditions. Immune effector cell therapy is extremely exciting and a step change in our treatment technology against malignancy. The number of patients receiving these therapies both in clinical trials and as standard therapy is expected to increase substantially.

BACKGROUND

CRS is a potentially life-threatening systemic inflammatory response caused by widespread immune cell activation releasing inflammatory cytokines. This can be triggered by many factors, the most common being immune-based therapies and in particular T-cell therapies. CRS clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. The symptoms of CRS can range from mild constitutional symptoms to life-threatening multi-organ failure. CRS generally occurs within the first week after therapy although it can occur later. Neurotoxicity (ICANS) is the second most common acute toxicity, again with a range of severity from language disturbance, impaired handwriting, confusion and agitation to cerebral oedema and death. HLH is a rare, but very severe complication related to CRS.

Other toxicities include tumour lysis syndrome, prolonged cytopenia's and B-cell aplasia. These toxicities are not covered in this guidance.

PURPOSE/OBJECTIVE

This standard operating procedure has been written to provide guidance to all clinical personnel providing care for trial patients at the Lancashire Clinical Research Facility (LCRF) on how to recognize, assess, and manage patients suffering from CRS, ICANS, and HLH.

SCOPE

It is important that all clinical staff involved in the care of trial patients understand what CRS is, how to recognize it, what assessments/investigations to carry out, and most importantly how to promptly and effectively manage this emergency condition.

PROCEDURE

1. WHO?

1.1 It is the responsibility of all clinical staff caring for trial patients to screen & highlight at-risk patients that may go on to develop CRS/ICANS/HLH.

At risk are patient groups are those who are actively receiving or who have recently received

- Therapeutic monoclonal antibody infusion
- Alemtuzumab, Rituximab
- Immunotherapies for cancer especially chimeric antigen receptor therapy (CAR) T-cell therapies or other T cell therapies

It is the responsibility of all clinical staff caring for trial patients to familiarize themselves with all documents outlining the assessment and management of suspected CRS. These include this document as well as the trial/treatment specific protocol.

1.2 It is the responsibility of the Principal Investigator (PI) to ensure that staff working on trials that include a risk of CRS/ICANS/HLH have received appropriate training and support in identifying and managing CRS prior to commencement of the trial or staff members involvement.

2. WHEN?

2.1 This SOP must be followed for assessment and management of patients at risk of CRS who have developed:

a) Temperature greater than 38^{o}C
b) Flu-like symptoms including myalgia, arthralgia, malaise
c) Nausea and vomiting
d) Hypotension –Systolic Blood Pressure of less than 90mmHg or less than 80% of patient's baseline
e) Hypoxia – Oxygen Saturation of less than 94%
f) Neurological events

Differential diagnosis includes sepsis and tumour lysis syndrome which should be considered during the initial review of patients presenting as described above.

3. CYTOKINE RELEASE SYNDROME (CRS)

CRS can present with a diverse spectrum of clinical features ranging from a mild flu-like illness to multi-organ failure. It can mimic severe sepsis or tumour lysis syndrome. Other potentially life-threatening complications include cardiac dysfunction, ARDS, neurological toxicity, renal failure, hepatic failure and disseminated intravascular coagulation. Haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) can occur with high fevers, high ferritin and raised triglycerides.

3.1 Diagnosis & Management

The consultant in charge of the care of the patient must be informed if CRS is suspected. Decisions regarding management of the condition must be made at consultant level. If CRS is suspected, the following approach should be taken to ensure patients receive the correct therapy promptly.

1. **Recognise** – History, examination, investigations
2. **Grade** – CRS severity must be graded to guide management

3. **Supportive Management** – as described below
4. **Targeted management –** tocilizumab +/- corticosteroids
5. **Contact and Escalate Early** – CrCU, oncology and haematology teams

3.2 All patients who exhibit symptoms (see section 2.1) with a likely diagnosis of CRS should be graded in order to direct management.

a) CRS 1

- Temperature greater than or equal to 38^{o}C

b) CRS 2

- Temperature greater than or equal to 38^{o}C
- Hypotension Systolic Blood Pressure of less than 90mmHg or less than 80% of patient's baseline not requiring vasopressors
- Hypoxia – SpO2 less than 94% on air but managed with low flow nasal cannulae to maintain SpO2 greater than 94%

c) CRS 3

-Temperature greater than or equal to 38^{o}C
-Hypotension requiring vasopressors to support MAP greater than 65mmHg
-Hypoxia requiring high flow nasal cannulae or Venturi mask to support SpO2 greater than 94%

d) CRS 4

-Temperature greater than or equal to 38^{o}C
-Hypotension requiring multiple vasopressors
-Hypoxia requiring positive pressure/intubation and ventilation

3.3 ASTCT consensus grading for CRS

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 a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

3.4 CRS Management based on grade

CRS Grade	Management (manage aggressively to avoid deterioration)
CRS Grade 1	Regular vital signs as per NEWS2 protocol Manage as per Neutropenic Sepsis, including: - Paracetamol IV +/- NSAID, Tramadol, Pethidine for rigors - IV fluids - Broad spectrum Antibiotics - Supplementary oxygen if required - Urine output measurements Blood tests: FBC, U&E, LFT, CRP, Blood Cultures, Lactate, Coagulation, Ferritin, Cytokine profile (IL-6) Appropriate further investigations (e.g., CXR, ECG, Sputum Culture) Consider tocilizumab [See section 3.3.3]) if persistent or refractory fever
CRS Grade 2	**Manage as per Grade 1, plus:** Consider escalation to Critical Care Unit (CrCU) Tocilizumab if not already given Consider IV dexamethasone 10mg BD –QDS if CRS persists post tocilizumab treatment (or methylprednisolone 2-4mg/kg/day)
CRS Grade 3	**Manage as per Grade 2, plus:** Escalate to CrCU Vasopressors Dexamethasone if not already given Cardiac monitoring +Echocardiogram
CRS Grade 4	**Manage as per Grade 3, plus:** May require ventilation In refractory grade 4 CRS consider methylprednisolone 4mg/kg IV daily (or 1000mg/day IV) if not responding to dexamethasone May require further agents (e.g. siltuximab, anakinra, anti-TNF)

Adapted from: Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, Böll B. In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy. Hemasphere. 2019 Mar 29;3(2):e191 , Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/articles/diagnosis-and-medical-management-of-acute-car-t-cell-toxicities-in-adults/ (accessed 29/04/24), Newcastle-upon-Tyne Hospital NHS Foundation Trust. Management of CRS, Neurotoxicity and Car-T Cell Related Encephalopathy Syndrome (CRES) Post Chimeric Antigen Recepton (CAR) T-Cell Therapy, Department of Haematological Medicine, King's College Hospital NHS Trust. Diagnosis and management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications in adults 2020.

3.3.1 General supportive management of CRS

- Given how CRS may present (fever, hypotension, hypoxia), all patients should be considered for antibiotics (within 1 hour of triage) as per the trust management of febrile neutropenia guideline [Neutropenic Sepsis: Recognition, Diagnosis and Early Management in Adult Patients]. Antibiotics per-se are not required for the management of CRS.
- If sepsis is suspected patients should have a sepsis 6 bundle completed (blood culture, urine output measurement, serum lactate, IV fluids, antibiotics, supplementary oxygen) as required.
- IV paracetamol can be given for patient comfort. For Adult (body weight up to 50 kg) 15 mg/kg paracetamol every 4–6 hours, dose to be administered over 15 minutes; maximum 60 mg/kg per day. For Adult (body weight 50 kg and above) 1 g paracetamol every 4–6 hours, dose to be administered over 15 minutes; maximum 4 g per day.
- Hourly monitoring of vital signs and an accurate fluid balance chart must be completed. In the context of CRS/ICANS/HLH our recommendation is that patients are discussed with the critical care team and considered for admission to CrCU when the NEWS2 score is greater than or equal to 2.
- The blood glucose should be monitored.
- Check magnesium and phosphate – if less than lower limit of normal then give IV replacement.
- CRS investigations: Specific additional tests to consider:
    - Ferritin, triglycerides, and AST – to facilitate the potential diagnosis of haemophagocytic lymphohistiocytosis and/or macrophage activation syndrome.
    - Troponin. BNP +/- transthoracic echocardiogram – to diagnose associated cardiac toxicity with CRS
    - Uric acid (& U+Es, calcium, phosphate, ABG) if tumour lysis syndrome is suspected.
    - Cytokine profile (predominantly IL-6 performed at local laboratory)

- Steroids (and, in particular, IV hydrocortisone) should not be given to patients who have received CAR-T therapy unless specifically advised by the responsible Oncology/Haematology Consultant. They must only be given when the CRS is refractory to other supportive measures or if allowed per specific protocol.
- Broad spectrum antibiotics can interfere with immunotherapy efficacy. Administer if sepsis is considered, discontinue/omit if CRS is the diagnosis (in the absence of sepsis).

3.3.2 Supportive management of CRS Grade 2 or above

Note any patient who has received immune effector cell therapy and is identified with CRS Grade 2 or above is at increased risk of deterioration. Capillary leak and fluid overload are significant concerns.

Our recommendation is that patients are discussed with the parent clinical team, critical care team and considered for admission to CrCU when the NEWS score is greater than or equal to 2 if CRS is suspected.

Initial management should be focused on stabilising the patient and supporting organ function.

Cardiovascular:

1. Fluid resuscitation should be with bolus of 250mls of crystalloid (such as Plasma-Lyte® or Sodium Chloride 0.9%). This fluid should be infused via an infusion pump over 15mins. The target systolic BP should be greater than 90mmHg or greater than 80% of the patient's baseline SBP. The bolus can be repeated immediately if there is less than 10mmHg response in the patients SBP. If greater than 1L of fluid is given without improvement consideration should be made to admit the patient to CrCU urgently**.**
2. Vasopressors should be started if greater than 30ml/kg (or 2L in total) of fluid is required to support the patients SBP. All patients receiving CAR-T therapy will have dual lumen PICC line and to facilitate safe transfer/admission to critical care, it is reasonable to support the patient's blood pressure with intermittent boluses of metaraminol. The target mean arterial pressure, obtained from invasive blood pressure monitoring, is greater than 65mmHg. Once admitted to CrCU any patient requiring ongoing vasopressor support should have a central venous catheter and arterial line inserted.
3. If patients require more than 2L of crystalloid fluid - troponin, BNP and a screening echocardiogram should be performed to evaluate cardiac toxicity.

Haematology:

1. All Oncology patients should have a special transfusion status form completed and submitted to the transfusion laboratory. This should be checked to confirm that there are no specific indications for irradiated blood products.
2. The transfusion trigger is a target Hb greater than 70g/l.
3. The platelet count should be maintained greater than $20x10^9$/l
4. GCSF is not routinely recommended.
5. Disseminated intravascular coagulation can occur. The INR, APTTr and fibrinogen should be measured daily.

Renal:

1. There is a risk of tumour lysis syndrome.
2. Renal replacement therapy as per the standard indications.

3.3.3 CRS not responding to supportive therapy.

On occasion, despite optimal supportive therapy, the patient's clinical condition will continue to deteriorate. This will manifest as increasing degrees of organ failure with a progressive escalation of organ supportive therapy. Tocilizumab is anti-IL-6R monoclonal antibody approved for the treatment of CAR-T cell induced CRS in adults and paediatric patients 2 years of age and older. It has also been used to successfully manage CRS caused by other immunotherapies. The use of tocilizumab will need to be discussed on a case-by-case basis and the decision to give should be made by the Oncology (+/- ITU) consultant. Trial patients may have tocilizumab funded through the study protocol. Use tocilizumab earlier in the pathway to avoid or delay the need for corticosteroids.

As tocilizumab causes immunosuppression and myelosuppression, patients should be monitored for the development of infection, particularly if neutropenia is present. This is particularly important for patients who have been extensively treated with chemotherapy. Caution should be used in the presence of thrombocytopenia or neutropenia. In addition to FBC, LFTs should be monitored as there is a risk of hepatic dysfunction. Note that patients may have cytopenia and/or LFT abnormalities due to chemotherapy, CRS, or underlying malignancy. If ALT or AST are persistently 1-3 times the upper limit of normal (ULN), tocilizumab should be reduced to 4mg/kg. If ALT or AST levels are more than 3 times the

ULN, consider discontinuing tocilizumab until this improves to less than 3 times the ULN. If ALT or AST are more than ten times the ULN, tocilizumab is not recommended.

Tocilizumab can cause hypersensitivity/allergic reactions, myelosuppression, lipid abnormalities, demyelinating disorders and drug induced liver injury.

Tocilizumab Medication Details
Tocilizumab 8mg/kg for patients greater than 30kg. 12mg/kg for patients less than 30kg (max 800mg per infusion). Given over 60 minutes. Dose can be repeated every 8 hours. Maximum of 4 doses. Stock availability is through pharmacy during usual working hours and then via the on call pharmacy service out of hours. Stock for research patients is funded by the trial sponsor and the pharmacy clinical trials team support the supply and reimbursement (agreed prior to patient enrolment). NHSE commission the use of tocilizumab to treat CRS following CAR-T or bispecific antibody treatment for NICE approved treatments on a drug-by-drug basis (for further information please contact the pharmacy oncology team via OncologyPharmacy@lthtr.nhs.uk).

3.3.4 Logistics and Supply

Clinically appropriate use of tocilizumab for CRS as part of a clinical trial is the decision of the PI and will be reviewed during study set-up. If tocilizumab is required, this will be supplied via pharmacy stock (ordered through LTHTr Pharmacy Procurement), and reimbursement directed to the trial sponsor agreed as part of the study contract negotiation, usually at British National Formulary list price (plus VAT). This arrangement, and the cost of the product, must be captured in the study contract following negotiation with the sponsor.

Sufficient supply of tocilizumab (e.g., 4 available doses) should be available from general pharmacy stock on site prior to IMP dosing. The decision to dose prior to availability of tocilizumab is at the discretion of the PI.

3.3.5 In the event that the interventions listed above are unsuccessful

The following approaches have been suggested if the above approaches are insufficient: TNF-α blocker, T cell-depleting antibody therapies such as, alemtuzumab, IL-1R-based inhibitors (anakinra) or cyclophosphamide. These must be discussed with the treating oncologist/haematologist and CCU. In these circumstances, the use of these medicines may need additional approval/individual funding approval, on a case-by-case basis.

4 IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

ICANS (previously termed CAR T-cell related encephalopathy syndrome or CRES) is a neurological toxicity to IEC therapies and manifests as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral oedema. In rare circumstances it can progress to severe neurological injury and death. These neurological symptoms may occur during CRS but commonly occur afterwards. The pathophysiology is unknown. Classically the earliest signs & symptoms of ICANS are tremor, dysgraphia, mild difficulty with expressive speech, impaired attention, apraxia and lethargy. Expressive dysphasia is a very specific symptom. The progression to severe neurotoxicity may take hours to days.

4.1 Differential diagnosis of ICANS

The differential diagnosis of ICANS includes ischaemic or haemorrhagic stroke, central nervous system infection and metastatic spread of the underlying malignancy.

4.2 Investigations:

It is important to grade the severity of ICANS, as below. This includes assessment of the Immune effector cell mediated encephalopathy (ICE) score. A CT scan of the brain is essential, provided the patient's condition is stable enough to facilitate transfer. There is a high probability of thrombocytopenia and deranged coagulation; MRI scan may be helpful in demonstrating cerebral oedema and to exclude other pathologies if lumbar puncture is not safe. Fundoscopy may also aid in assessment (see below).

4.3 Management of ICANS

Management of ICANS is based on the grading system (see below). The consultant responsible for the patient must be informed if ICANS is suspected, and management decisions should be made at consultant level. Similar to the management of CRS, patients with mild ICANS should be closely monitored and receive supportive measures. If a patient develops more severe symptoms (grade $\geq$2), transfer to the critical care unit must be considered. A multidisciplinary approach with intensivist, oncologist, and neurologist input is paramount. An early EEG should be performed to look for subclinical seizures.

Tocilizumab should be given in acute phase ICANS when it is co-existent with CRS. However, it is not that effective in the delayed phase (Day 5 onwards from infusion), where steroids are preferred.

Prophylactic antibiotics or other antimicrobials should be given as clinically appropriate. Rigorous control of blood pressure and electrolytes (particularly calcium and magnesium) should be maintained.

4.4 Papilloedema

Patients with suspected ICANS should have fundoscopy performed by competent staff in order to identify the presence of papilloedema/raised intracranial pressure.

4.5 ICE Score calculation (Immune effector cell mediated encephalopathy)

● **Orientation**: Orientation to year, month, city, hospital: 4 points ● **Naming:** Ability to name 3 objects (e.g., point to clock, pen, button): 3 points ● **Following Commands:** Ability to follow simple commands (e.g., “Show me three fingers” or “Close your eyes and stick out your tongue”): 1 point ● **Writing:** Ability to write a standard sentence: 1 point ● **Attention:** Ability to count backwards from 100 by 10: 1 point
Total Score: **10:** No impairment **7-9:** Grade 1 ICANS **3-6:** Grade 2 ICANS **1-2:** Grade 3 ICANS **0:** (Unrousable): Grade 4 ICANS

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

4.6 ASTCT consensus grading for ICANS

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. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive 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
Elevated ICP/ 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; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

4.7 ICANS management based on grade

ICANS Grade	Management
ICANS Grade 1	Close monitoring/Neurological examination Twice daily ICE scoring IV hydration, consider change medication to IV Neurology & Haematology referral Fundoscopy for papilloedema. Manage raised intracranial pressure (as per Neurology review) Consider Levetiracetam 500mg BD seizure prophylaxis in patients with a history of seizures or central nervous disease Avoid sedating medications unless agitated. Consider lorazepam for agitation Consider MRI Brain or CT if MRI not feasible. +/- Imaging of the spinal cord if focal neurological deficit is present EEG Consider tocilizumab if concurrent CRS (see CRS management guidance) Consider dexamethasone 10mg IV QDS
ICANS Grade 2	**Manage as Grade 1, plus:** Dexamethasone IV 10mg can be given up to QDS if not already given Alternatively consider methylprednisolone 1-**2**mg/kg IV BD Tocilizumab if concurrent CRS (see CRS management guidance) Consider CrCU escalation
ICANS Grade 3	**Manage as Grade 2, plus:** Escalate to CrCU Dexamethasone IV 10mg QDS or methylprednisolone (up to 1000mg/day) Antiepileptic medications if not already given Consider alternate agents if refractory (anakinra, siltuximab, anti-TNF, cyclophosphamide) Consider repeating neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grave 3 or above neurotoxicity
ICANS Grade 4	**Manage as Grade 3, plus:** Alternative agents as above Specific neurointensive treatment

Adapted from: Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, Böll B. In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy. Hemasphere. 2019 Mar 29;3(2):e191 , Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf#:~:text=diagnosis%20and%20medical%20management (accessed 18/03/22), Newcastle-upon-Tyne Hospital NHS Foundation Trust. Management of CRS, Neurotoxicity and Car-T Cell Related Encephalopathy Syndrome (CRES) Post Chimeric Antigen Recepton (CAR) T-Cell Therapy, Department of Haematological Medicine, King's College Hospital NHS Trust. Diagnosis and management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications in adults 2020.

4.8 Steroid Tapering

Once sustained clinical improvement is observed steroids can be tapered as toxicities allow. For example, methylprednisolone IV 1g/day for 3 days, followed by rapid taper at 250mg every 12 hours for 2 days, 125mg every 12 hours for 2 days, and 60mg every 12 hours for 2 days. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg prednisolone) when methylprednisolone dose is less than 80mg per day. Usual prednisolone dose is 60mg per day, reducing by 10mg every 5 days. After 10mg, patients should reduce to 5mg per day for 5 days and then stop. Steroid tapering is to be conducted as toxicities or flares/relapses allow.

5. CAR-RELATED HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

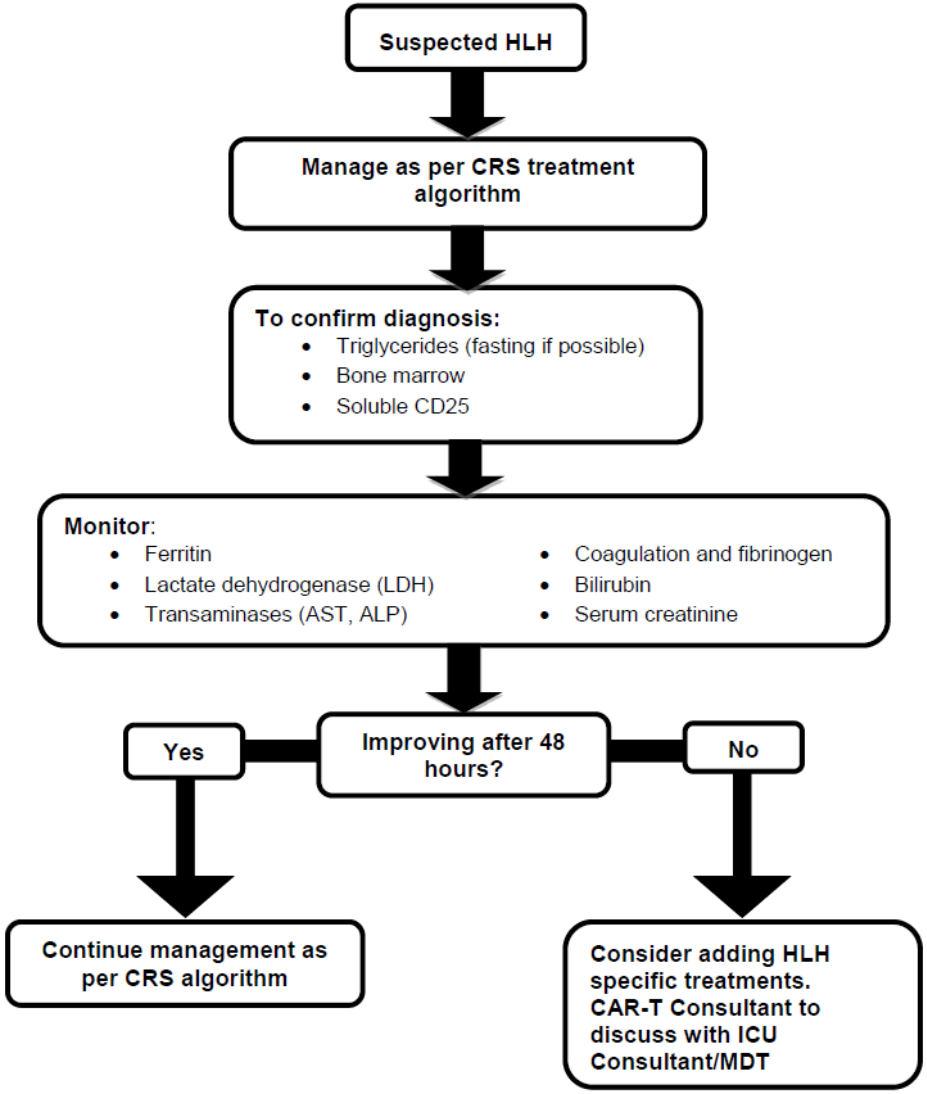
5.1 Initial management

Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by activated macrophages and cytotoxic T cells. Secondary (acquired) HLH is triggered by infections or malignancies but may also be induced by autoinflammatory/autoimmune disorders. In rare cases severe CRS can evolve into HLH. Diagnosis may be difficult as traditional markers are non-specific. Proposed diagnostic criteria are:

- Peak serum ferritin level of greater than 10,000 ng/ml during the CRS phase

AND, subsequently, any two of the following;
- Grade 3 or above increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels
- Grade 3 or above oliguria or increase in serum creatinine levels
- Grade 3 or above pulmonary oedema
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

The diagnosis and treatment of CAR-related HLH is not established, and therefore specialist consultant and MDT input is needed to decide on patient management.



From: Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf#:~:text=diagnosis%20and%20medical%20management (accessed 18/03/22).

5.2 Refractory HLH

Fulminant and refractory HLH to steroids and tocilizumab is observed in ~1% of all patients treated with CAR-T cell therapy. If the patient has no improvement within 48 hours after commencement of steroids and tocilizumab, 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.

6. RELATED INFORMATION

Clinical Response Team (CRT) and Intensive Care

Patients should be discussed with CrCU promptly as there is a potential for rapid deterioration necessitating organ support, even if the patient only exhibits grade 1 symptoms. Patients with grade 2 symptoms and above should be transferred to CrCU for monitoring and organ support. Critical care outreach are available on bleep 3388 or extension 1556.

Oncology/Haematology teams

For all patients with suspected CRS, even if not known to have cancer, there should be a discussion with the oncology/haematology Specialist Registrar (SpR). The oncology and haematology SpR can be contacted via switchboard and if necessary, this discussion can be escalated to the oncology/haemato-oncology consultants on-call (also available via switchboard), e.g. in cases where the SpR cannot be reached.

Tocilizumab should be administered with approval from the oncology/haemato-oncology consultant (preferably with input from ITU consultant); therefore, early discussion is required to avoid delayed treatment.

Supertertiary Care

Patients with HLH, ICANS or severe CRS may require input from a supertertiary centre or, if stable, be transferred to those centres.

Pharmacy Team

For any suspected cases, please contact the clinical trials pharmacy team/ ward pharmacist to ensure timely supply of medication. It is the responsibility of the ward pharmacist to liaise with the treating team, contact the oncology pharmacy team and escalate to the lead oncology pharmacist if required. The oncology pharmacy team will liaise with the relevant medical teams if clinically appropriate.

For any suspected cases out of working hours, the clinical team will need to contact the on-call pharmacist (via switchboard) who will liaise with the senior pharmacy team where necessary.

Clinical Trials Team

For patients involved in a clinical trial the PI should be contacted. The NIHR LCRF team should also be contacted via telephone: 01772 522031 or email: LancashireCRF@LTHTR.nhs.uk.

Contracts

In the context of clinical trials, trial sponsors will be asked to fund a minimum of 4-8 doses of tociluzimab plus anakinra 2mg/kg daily for 5 days per trial in the upfront stage of trial setup. Trial contracts will need to take into account the possibility of critical care costs.

7 FURTHER READING/REFERENCES

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