Guidelines for Management of Cytokine Release Syndrome

Lead Organisation: iMATCH

Author: The Christie NHS Foundation Trust

Version Number: 9.0

Finalisation Date: 07/2023

Funded by

Coordinated by

Guidelines for Management of Cytokine Release Syndrome

Author	
Revision	9.0
Changes from previous version	Format Change + Delete 'The highest incidence of CRS has been reported with anti-CD19 CAR-T where more than 50% of patients may be expected to develop evidence of CRS with 15-25% of patients developing ≥3 toxicity.' 'Incidence and timing , changed to - bispecific T-cell engagers (BiTe) - The incidence of CRS is variable between products although severity is generally less than observed with CAR-T therapy. Summary of Product Information or trial protocols should be consulted for guidance on treatment which varies between products.' Treatment bullet point 5 to 'Prophylactic treatment e.g. steroids is often used for patients being treated with BiTe therapy'. Delete the figure comparing CART therapy and Blinatumumab

Table of Contents

1.0 Introduction & Scope

Cytokine release syndrome (CRS) is a serious and potentially life-threatening complication associated with cancer immunotherapies. This is the most common serious toxicity of cellular immunotherapy triggered by activation of T-cells on engagement with target antigen leading to release of inflammatory cytokines and chemokines (including IL-2, soluble IL-2α receptor, IL-6, INF-γ, GM-CSF) and activation of immune effector cells (including macrophages, monocytes and dendritic cells).

For patients treated with CAR-T therapy, IL-6 plays a pivotal role in the development of CRS. Treatments which have be associated with development of CRS are as listed below and this document focuses on management of CRS with cellular therapies (notably CAR-T cells) and bi-specific T cell engaging antibodies (e.g. blinatumomab).

Immune checkpoint inhibitors	Anti-CTLA4 – ipilimumab Anti-PD(L)1 – nivolumab, pembrolizumab, avelumab
CD3/CD19 bispecific antibodies	Blinatumumab
Genetically unmodified cytotoxic T cells (CTL) therapy	Tumour-Infiltrating lymphocytes (TIL) EBV-specific CTL
Chimeric Antigen Receptor Therapy (CAR-T)	Most common with anti-CD19
Others	High dose IL-2, alemtuzumab, donor lymphocyte infusion, Haplo-identical transplant

For patients participating in clinical trials the management of cytokine release syndrome may be defined within the trial protocol. It is a regulatory requirement that clinical trials are approved by the national competent authority, MHRA and a research ethics committee.

In addition clinical trial protocols must undergo a local capacity and capability review to ensure the research can be conducted in accordance with the protocol (Approving apheresis and high risk immune effector cell trials SOP (QM-11) and R&D001.000 Study Set Up - Capacity and Capability Process). This SOP and trial protocol should be used in conjunction where a patient is participating in a clinical trial.

2.0 Responsibilities

The Programme Director, Quality Manager and Ward Nursing Leads are responsible for ensuring staff who are required to carry out activities described in this document receive a copy via the Q Pulse document distribution system.

All staff who are required to undertake activities described in this document must read and acknowledge receipt of this document, and where training is required shall not undertake described activities unsupervised until relevant training has been delivered.

Medical staff: must be familiar with the assessment of patients undergoing treatment and diagnosis and immediate management of treatment related complications. See appendix G and H for specific patient management responsibilities on the clinical areas.

Nursing staff: the nursing team should be aware of the needs of patient undergoing immune effector cell treatment and recognition and assessment of treatment related complications. Student nurses and HCA should be supervised and seek guidance when attending to patients undergoing immune effector cell treatment. See appendix G and H for specific patient management responsibilities on the clinical areas.

3.0 Objectives

This document is intended to act as an outline guide for management of patients with cytokine release syndrome following transplant.

4.0 Procedural Statements

4.1 Clinical Presentation

Incidence and timing – CAR-T therapy

The reported incidence of CRS is variable and depends on the CAR construct and the therapeutic target.

Serious CRS is observed more frequently in

- Increased tumour bulk
- Elderly patients
- Patients with impaired organ function or co-morbidity
- Early onset CRS (within 3 days of infusion)

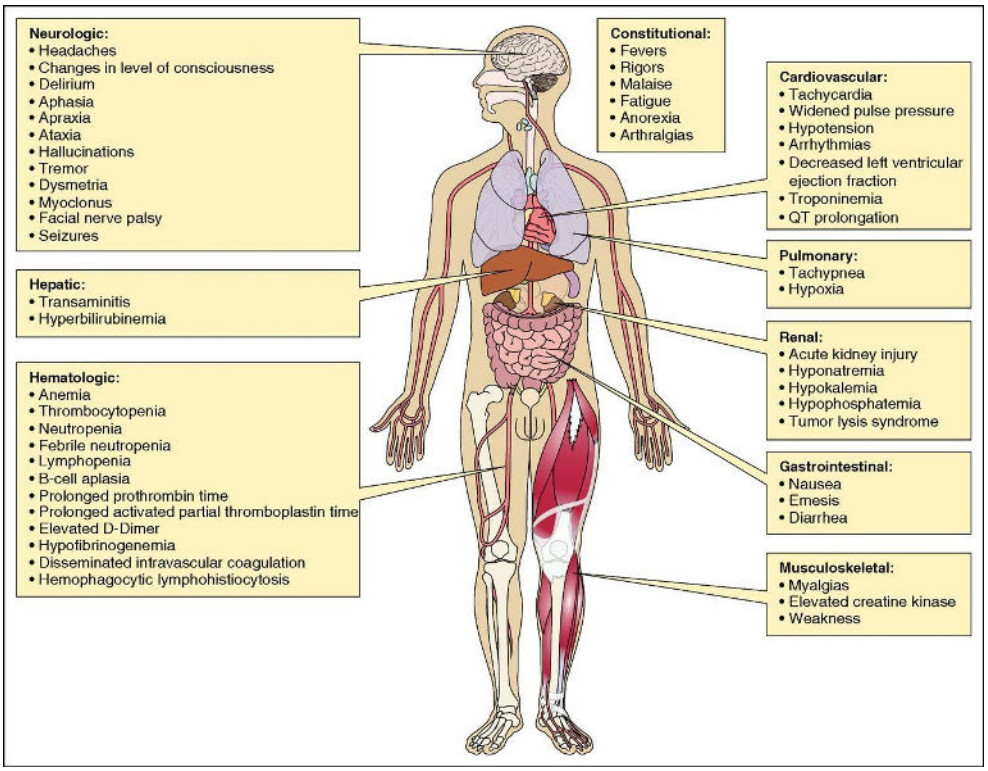
CRS is dependent on the engagement of T-cells with target antigen. The onset is dependent on the kinetics of T-cell activation and as such this varies with the CAR-T construct used (due to different T-cell co-stimulatory domains used). This is however usually observed within 14 days of treatment and is rarely observed more than 17 days after treatment.

Incidence and timing - blinatumomab

Bispecific T-cell engagers (BiTe) - The incidence of CRS is variable between products although severity is generally less than observed with CAR-T therapy. Summary of Product Information or trial protocols should be consulted for guidance on treatment which varies between products.'

Symptoms

A wide variety of symptoms have been reported. Early symptoms include fever (may be >40C), malaise, myalgia and anorexia. Progressive disease can affect any organ system.



Characteristic symptoms include

- Progressive fever
- Tachycardia
- Capillary leak syndrome leading to hypoxia and pulmonary infiltrates
- Hepato-renal dysfunction
- Hypofibrinogenaemia
- Hypotension which is the hallmark of disease severity

The clinical presentation of CRS also overlaps with other clinical syndromes (eg sepsis and HLH) which may co-exist. See SOP: Inpatient Management of patients receiving Immune Effector Cells (including Car-T Cells) for more information.

4.2 Monitoring

For guidance on inpatient assessment see SOP: Inpatient Management of patients receiving Immune Effector Cells (including Car-T Cells)

Observations

General observations (vital signs, NEWS2 score, VIP score, weight, skin assessment, mouth assessment, fluid balance, bowel assessment) will be performed according to the SOP: Nursing Observations for all Haematology and Stem Cell Transplant Patients) and Trust News2 policy (SOP: National Early Warning Score 2 (NEWS2) policy

- Vital signs will be recorded every 4 hours for all patients
- More frequent observations will be performed according to patient's clinical condition

Laboratory tests

Patients require daily blood tests with additional monitoring (CAR-T patients) for treatment related complications (e.g. infection – CRP, coagulopathy – coag and fibrinogen, HLH – ferritin); see SOP: Palatine Ward routine samples).

Additional blood testing is not generally recommended for patients treated with blinatumomab due to the significantly lower risk of serious CRS although may be indicated for selected high risk patients (e.g. those with high disease burden); this should be discussed with (Attending) Consultant. High risk testing schedule is as below:

- Daily FBC, Christie profile, coagulation (Clauss fibrinogen), CRP, ferritin, magnesium
- Glucose three times per week

Patients developing CRS will typically show laboratory evidence of acute inflammation (raised CRP and ferritin) and may develop Hypofibrinogenaemia (see SOP: Inpatient Management of patients receiving Immune Effector Cells (including CAR-T Cells).

These are not however present in all patients and laboratory parameters cannot be relied on in isolation to make a diagnosis. Inflammatory cytokine panels may be predictive of the onset and severity of CRS although are currently their use is restricted to clinical trials and they are not recommended for routine use.

Other investigations

Other investigations (ECG, echocardiogram, arterial blood gas monitoring, lactate, multi-site cultures, CXR or other imaging) should be requested according to clinical requirements.

CRS monitoring

All CAR-T patients and selected other high risk patients (eg high tumour burden patients treated with blinatumomab) will be monitored at least twice daily for evidence of CRS. More frequent monitoring is indicated for patients with evidence of clinical deterioration or as directed by Attending Consultant. For details and patient monitoring chart see SOP: Inpatient Management of patients receiving Immune Effector Cells (including Car-T Cells)

4.3 Staging

A number of staging systems have been described for CRS including adapted CTCAE and scales developed at MD Anderson Cancer Centre (MDACC) and University of Pennsylvania (Penn), and ASTCT (American society for Transplantation and Cellular Therapy, formally ASBMT) which are tabulated below. Although some trial protocols stipulate the use of a particular grading system, the **ASTCT consensus grading system** is recommended for routine use in order to harmonise toxicity grading for all patients.

Patients will be assessed and monitored at least twice per day and CRS graded according to the ASTCT staging system (see SOP: Inpatient Management of patients receiving Immune Effector Cells (including Car-T Cells).

Grade	ASTCT	MDACC	CTCAE	Penn
1	Temperature >38.0	Symptoms are not life-threatening and require symptomatic treatment only, e.g., fever, nausea, fatigue, headache, myalgias, malaise	Mild reaction; infusion interruption not indicated; intervention not indicated	Mild reaction: treated with supportive care such as antipyretics, antiemetics
2	Fever > 38.0 With Hypotension -not requiring Vasopressor And/or hypoxia requiring low flow nasal cannula (<6l/minute)	Symptoms require and respond to moderate intervention. Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Moderate reaction: some signs of organ dysfunction (e.g., grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including fevers with associated neutropenia, need for IV therapies (not including fluid resuscitation for hypotension)
3	Hypotension- Requiring vasopressors with or without vasopressin And/or Requiring high flow nasal cannula(> 6l/minute), facemask, non rebreather mask or venturi mask	Symptoms require and respond to aggressive intervention. Oxygen requirement ≥ 40% or hypotension requiring high-dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis	Prolonged reaction (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	More severe reaction: hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias; includes hypotension treated with intravenous fluids (defined as multiple fluid boluses for blood pressure support) or low-dose vasopressors, coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS

4	Requiring positive pressure (eg CPAP< BIPPAP, intubation and mechanical ventilation	Life-threatening symptoms. Requirements for ventilator support or grade 4 oxygen toxicity (excluding transaminitis)	Life-threatening consequences; pressor or ventilator support indicated	Life-threatening complications such as hypotension requiring high-dose vasopressors, a hypoxia requiring mechanical ventilation

- CRS grade is determined by the more severe event; hypotension or hypoxia not attributable to any other cause. For example a patient with a temp of 39.5, hypotension, and hypoxia requiring low-flow oxygen is classified as grade 2 CRS.
- Onset of CRS is defined by fevers with or without constitutional symptoms which are no a result of other causes (eg infection)
- Unstable hypotension is the hallmark of severe CRS

- Grading of high dose vs low dose inotropes is as below (not required for ASTCT grading)

Vasopressor	High dose definition
Noradrenaline monotherapy	Greater than or equal to 20 mcg/minute
Dopamine monotherapy	Greater than or equal to 10 mcg/kg/minute
Phenylephrine monotherapy	Greater than or equal to 200 mcg/minute
Adrenaline monotherapy	Greater than or equal to 10 mcg/minute
Vasopressin	Vasopressin + noradrenaline equivalent of greater than or equal to 10 mcg/minute
Combination therapy (not including vasopressin)	Noradrenaline equivalent of greater than or equal to 20 mcg/minute

4.4 Treatment

Treatment principles

Principles of treatment are as follows:

- Risk assess patient prior to treatment (age, comorbidity, disease bulk, treatment used)
- Monitor closely during high-risk period (for the first 14 days post infusion)
- Increased monitoring and escalation in the event of any deterioration. All patients need supportive care and some may require intensive supportive therapy but most organ dysfunction is reversible
- Consider alternative/co-existent pathologies (e.g. sepsis)
- Prophylactic treatment e.g. steroids is often used for patients being treated with BiTe therapy'
- Observe closely for evidence of additional neurotoxicity which may co-exist and requires earlier intervention with steroids.
- Early intervention should be considered in high-risk patients or those with early onset disease (eg within 3 days of CAR-T therapy)
- Unstable hypotension is the hallmark of severe CRS

Supportive therapy

All patients should receive supportive therapy

- Paracetamol for treatment of fever
- Analgesia if required
- Treat sepsis as per policy and investigate for source of infection (cultures, imaging as required)
- Intravenous fluids (maintenance hydration and normal saline boluses as required for management of hypotension)
- Supplementary oxygen if indicated to maintain SpO2 >90%

- Careful fluid balance
- Escalation (outreach, critical care) as per NEWS2 policy
- Monitoring as per CAR-T monitoring protocol (twice daily assessment or more frequently if deterioration, changes in condition or as directed by Consultant staff)
- Assess for neurotoxicity and treat accordingly

Additional treatment – CAR-T therapy

Additional treatment is as indicated by grade of toxicity. Additional guidance should also be used as indicated for patients in clinical trials in accordance with trial protocol.

ASTCT Grade	Symptom or sign	Management
1	Fever or organ toxicity[1]	• Vigilant supportive care • Monitor vital signs 4 hourly • Investigate for and treat potential infection • Administer IV fluids (keep well hydrated), antibiotics, paracetamol as clinically indicated • **If persistent for 3 days** administer Tocilizumab 8mg/kg IV (max 800mg)
2	Hypotension[1]	• Administer IV fluid bolus (10-30 mg/kg capped at 500-1000ml over 30-60 min). Fluid overload should be avoided. • Administer Tocilizumab 8mg/kg IV (max 800mg) • **Inform CCU Consultant and outreach team** • Assess BP response to fluid bolus. If patient fails to respond to IV fluid bolus (SBP<90mmHg) and if no response to 2 doses of tocilizumab or deteriorating condition then for administer dexamethasone[2] 10mg IV • If tocilizumab not available or persistent CRS after 4 doses, commence Anakinra 1-2 mg/kg SC (or IV) infusion (100 mg dose or 1 vial), increasing to a maximum dose of 10 mg/kg as required • If tocilizumab not available administer siltuxumab 11mg/kg single dose – cannot repeat in < 3 weeks • If siltuximab not available, administer Anakinra 1-2 mg/kg SC (or IV) infusion (100 mg dose or 1 vial), increasing to a maximum dose of 10 mg/kg as required • Discuss with attending or on-call Haematology consultant
	Hypoxia[1]	• As above for hypotension grade 2 • Administer Oxygen • Manage fluid overload if present. • Investigate for and treat potential infection • **Inform CCU Consultant and outreach team** • If higher doses are required consider humidified oxygen. If required escalate to a non-rebreather
3	Hypotension	• **Inform CCU Consultant and outreach team** • Admit to critical care. • Commence vasopressor therapy • Administer supportive treatment as in Grade 2 CRS • Administer Tocilizumab as per grade 2 CRS if not administered previously • Increase Anakinra dose up to 10 mg/kg SC (or IV) infusion (in 100 mg or 1 vial intervals) • Administer regular Dexamethasone 9.9mg (3ml) IV 6 hourly, increase to 19.8mg (6ml) IV 6 hourly if refractory • Continuous ECG monitoring & urgent echocardiogram, if feasible • Discuss with attending or on-call Haematology consultant

	Hypoxia	• As above for hypotension grade 3 • Administer high flow oxygen as in Grade 2 CRS • Manage fluid overload if present. • Investigate for and treat potential infection • Nasal/face mask high flow oxygen or non-invasive ventilation (should be avoided during COVID-19 pandemic to limit viral spread, if possible) • Consider intubation for invasive mechanical ventilation as per grade 4
4	Hypotension	• **Inform CCU Consultant and outreach team** • As above for hypotension grade 3 • Admit to critical care • Discuss with attending or on-call Haematology consultant • As per grade 3 and administer methylprednisolone IV 2 mg/kg/day in divided doses for up to 7 days. • Administer a higher dose of methylprednisolone IV (500-1000 mg/day) if no response • Consider anti T-cell therapy (eg cyclophosphamide 1.5g/m^2) if no response after discussion with cellular/CAR-T therapies consultant and attending Haematology consultant
	Hypoxia	• As above for hypotension grade 4 • Administer high flow oxygen as in Grade 3 CRS • Manage fluid overload if present. • Investigate for and treat potential infection • Nasal/face mask high flow oxygen or non-invasive ventilation (should be avoided during COVID-19 pandemic to limit viral spread, if possible) • Consider intubation for invasive mechanical ventilation

[1]Early intervention with IL-6 antagonists and steroids should be considered in high risk patients (CRS onset within 3 days of treatment, bulky disease, patients > 60 years or patients with co-morbidity or organ dysfunction

[2]Steroids are effective for treatment of CRS. Dexamethasone is first line therapy and where started should be continued for at least 3 days or until CRS resolution. Routine use (eg as pre-medication for transfusions or treatment of uncomplicated fever) should be avoided as steroids may impact on the efficacy of CAR-T treatment. In general steroids are therefore reserved for patients who don't respond to IL-6 antagonists

Patients with organ dysfunction (CTCAE grade 3 or above) attributable to CRS without other cause may also be considered for treatment with tocilizumab if this has not already been started. To be discussed with attending or on call consultant.

Additional treatment – blinatumomab

CRS following blinatumomab can generally be managed with pausing the infusion and additional doses of steroids (dexamethasone 10-20mg iv). Treatment may be re-started at reduced dose once CRS resolves for grade 3 toxicity but should be permanently discontinued for patients with grade 4 CRS as per drug SPC. In the event of patients not responding to steroids, then patients should be treated with tocilizumab as per CAR-T therapy.

4.5 Use of IL-6 Antagonists

IL-6 antagonists are the mainstay of treatment for CRS complicating CAR-T therapy requiring management beyond supportive care. Although CRS is associated with increased levels of a range of inflammatory cytokines, IL-6 is central to CRS pathogenesis.

Tocilizumab

IL-6 receptor antagonist used as first line therapy.

- 8mg/kg by iv bolus (maximum 800mg)
- Doses can be repeated every 6-8 hours (up to 3 doses in 24 hours) up to maximum of 4 doses
- Available as routine stock in pharmacy (via ward pharmacist) and ward stock on Palatine Treatment Centre/CCU.
- Out of hours available in emergency drugs cupboard via duty manager
- High response rates observed in CRS and does not affect CAR-T efficacy.
- Toxicities include infusion reactions, infection and hepatotoxicity (elevated AST).See SPC for more information. https://www.medicines.org.uk/emc/product/9086/smpc#

Anakinra (Kineret)

Human interleukin-1 receptor antagonist to be used as second line therapy at The Christie. This product is licenced for use in rheumatoid arthritis and other inflammatory syndromes but not currently licensed for cytokine release syndrome although has been used to successfully treat CRS.
To be considered as second line therapy for patients not responding to at least 2 previous doses of tocilizumab.

Anakinra will be stocked in critical care and must be agreed by the attending critical care and haematology consultants.

The dose of anakinra in CRS is 200mg once daily by subcutaneous injection continued until 24 hours after resolution of CRS. See SPC for more information https://www.medicines.org.uk/emc/product/559/smpc#

Available in 100 mg/0.67 ml solution for injection in pre-filled syringe.

5.0 Monitoring Compliance

Compliance to this document will be monitored by a combination of audit where appliable, non-conformance monitoring and Datix incident reporting.

6.0 Dissemination/ Distribution

This document will be distributed to staff members who need visibility of the document via Q Pulse.

7.0 References and Related Forms, Labels, Policies and Procedures

SOP: Inpatient Management of patients receiving Immune Effector Cells (including Car-T Cells)
SOP: Guidelines for the management of sepsis,
SOP: National Early Warning Score 2 (NEWS2) policy
SOP: Tumour lysis
SOP: Neurological disease in Stem Cell Transplantation and Cellular Therapy
Brudno JN & Kochenderfer JN Blood 2016;127:3321
Neelapu SS *et al.* Nat Rev Clin Oncol 2018;15:247
Porter D *et al*. J Hematol Oncol 2018;11:35
Teachey DT *et al*. Cancer Discov 2016;6:664
Frey NV Best Pract Res Clin Haematol. 2017;30:336
Lee D et al. (2018) 'ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells': Biology of Blood and Marrow Transplant

8.0 Approval Process & Review Process

All new procedures are approved by the Clinical Program Director or approved designate before implementation of the procedure.

Revisions to existing procedures will be approved by the Clinical Director or approved designate prior to implementation.

Procedures will be reviewed every 2 years as a minimum.