Inpatient Management of Patients Receiving Immune Effector Cells (Including CAR-T Cells)

Lead Organisation: iMATCH

Author: The Christie NHS Foundation Trust

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Author	
Revision	14.0
Changes from previous Version	Format Change + Appendix D on the middle bottom box (management of CRS) please change 'IL-6 antagonists at grade 2 or grade 1 by exception e.g. early onset CRS' (i.e. not all at grade 1) 2. We now record ICANS and CRS on CWP The paper forms in Appendices E/F can stay however this is now a business continuity contingency 3. Integrated changes of new CAR-T product

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1.0 Introduction & Scope

This document is intended to act as an outline guide for management of patients receiving immune effector cells and should be read in conjunction with detailed SOP regarding patient assessment and management of toxicities. Chimeric antigen receptor T cell therapy (CAR-T) is the main type of Immune effector cells in the clinical area. These patients by their disease nature and treatment regimes are or will be immunocompromised and will require careful management.

For patients participating in clinical trials the management of the inpatient stay 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 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.

. Where applicable :

- A Risk Minimisation Programme Representative (RR) must be nominated whose contact details are provided to the pharmaceutical company. (see document EXT-107)

Consultant and Registrars:

1.To initiate appropriate investigations and treatment with reference to the management of patients with Cytokine Release Syndrome (CRS), neurological toxicities or other IEC toxicities

2. To liaise and communicate with nursing staff, other medical staff, allied healthcare professionals with reference to the management of patients who have received cellular therapy

3. To undertake training and education pertinent to the requirements of this role

Junior Doctors: must be familiar with the assessment of patients undergoing treatment and diagnosis and immediate management of treatment related complications. See appendix A, B and C for specific patient management responsibilities on the clinical areas.

Cellular Therapy Matron: Have overall responsibility for ensuring nursing staff are trained in the management of patients receiving IECs. To ensure that key staff involved in the care pathway have received appropriate training as set out by JACIE standards and any additional risk minimisation material from product company or clinical trial which is not covered in existing training.

Nursing staff: the nursing team should be aware of the clinical care and risk of toxicities 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 A, B and C for specific patient management responsibilities on the clinical areas.

Quality Team: In coordination with key staff in the cellular therapy team, the quality team will ensure that all relevant pharmaceutical & clinical trial product handling guides, risk minimisation material and protocols are available on Q Pulse (see references)

3.0 Objectives

This document is intended to act as an outline guide for management of patients receiving immune effector cells.

Prior to implementation of any new or revised procedure there shall be a review and if considered appropriate training and competency shall be delivered prior to implementation of the procedure.

4.0 Procedural Statements

4.1 Pre-Treatment and Baseline Investigations

Acceptance criteria, pre-treatment and baseline investigations

For details on all pre-treatment and baseline investigations please refer to CLN-14 coordinating adoptive cell therapy: chimeric antigen receptor t-cell (car-t) therapy (including tcr, car-nk, immunotherapy)

4.2 Supportive Care During Treatment

Medication

Many immune effector cell protocols lead to prolonged (>1-2 weeks) of bone marrow suppression. In such cases, patients should receive anti-infective prophylaxis as per autologous stem cell transplantation (see SOP: Haematology Summary of Prophylaxis)

- Aciclovir 400mg po bd
- Fluconazole 200mg od
- Co-trimoxazole (Septrin) 960mg po od mon/wed/fri, if the patient has low counts Co-trimoxazole (septrin) is stopped and pentamidine nebuliser given on discharge
- Lansoprazole 30mg od

Consider leviracetam 500mg po bd for patients at high risk of neurological toxicity (to be discussed at MDT), to begin from the start of Lymphodepletion. Also for patients with prolonged CRS and/or ICANs greater than 0 with neurological symptoms, to begin from the start of prolonged CRS/ICANs.

Tumour lysis prophylaxis as per standard protocols. See SOP: Tumour Lysis Syndrome: Prophylaxis and Management Guidelines (WRD-60). Patients will be tested (as per CLN-14 coordinating adoptive cell therapy SOP) for G6PD deficiency if they are at high risk of TLS and have not received rasburicase previously.

Blood tests

Patients require daily blood tests with additional monitoring for treatment related complications (e.g. infection – CRP, coagulopathy – coag and fibrinogen, HLH – ferritin); see SOP: WRD-36 Palatine Ward routine samples**)**, or as per trial protocol).

The utility of CRP testing is limited if patient has received steroids or IL-6 antagonists. Consider use of other tests e.g. procalcitonin to assess for evidence of sepsis'

E.g. Daily FBC, Christie profile
Coagulation (Clauss fibrinogen), CRP, ferritin and magnesium three times weekly (Mon, Wed, Fri). If Clauss Fibrinogen is below 1.5 then supplement fibrinogen concentrate (post infusion only)

Glucose if patient on steroids or if clinically indicated

CMV PCR at baseline and prior to discharge on D+28

All blood results must be reviewed by the nursing and, any concerns escalated to medical team, The medical are also responsible for checking blood results and ensuring results are acted on.

Further specific investigations will be undertaken as clinically indicated and at the physicians discretion.

For investigations post discharge, please refer to CLN-99 chimeric antigen receptor t-cell therapy discharge and follow up SOP.

NEWS 2 Assessments – general

Vital signs assessment is essential in caring for patients undergoing IEC treatment. There is an increased risk of significant toxicities which can result in the patient's condition dramatically changing in a short space of time.

Monitoring of temperature, pulse, blood pressure, oxygen saturations and respirations is required for all in-patients. This will be recorded on the ward electronic NEWS2 and score calculated (see trust policy "National modified early warning signs (NEWS2) policy").

All inpatients must have observations recorded at the time frequency specified as a minimum in the trust NEWS2 policy unless there is concern of deterioration or a procedure or treatment requires it then observations will be carried out more frequently.

Clinical judgment must be used in conjunction with the NEWS2 score at all times) or for trial patients as per protocol if the requirement is more frequent.

More frequent observations will be performed according to patient's clinical condition.

For patients receiving IEC's or treatments where CRS is a risk, and development temperature above 37.5 degrees, a full set of observations should repeated hourly. Till stabilisation/ starting treatment of CRS/ICANS If the temperature remains high discuss with senior medical team (Registrar/Consultant). Seek advice from senior medical team prior to administering paracetamol.

Observations – Cytokine release syndrome

Patients will be monitored at least twice daily for evidence of cytokine release syndrome (CRS) or more frequently if clinical concern or as directed by medical staff or trial protocol). Routine monitoring will be undertaken by trained nursing staff or junior medical staff. CRS will be graded according to patient observations and recorded on CWP nursing assessment eform.

CRS typically occurs within 1-2 weeks of treatment and is more common in the following groups:

Advanced age
Co-morbidity
Pre-treatment organ dysfunction
Bulky disease
Certain CAR-T products (available data suggest that this is more common in patients treated with CD19 CARs than for other targets although patterns will become clearer with increased use)
Grade 3-4 CRS is more common in patients who develop evidence of CRS early (within 3 days) of initiation of treatment and earlier intervention should be considered

Observations – Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients will be monitored at least twice daily for evidence of neurotoxicity (Immune effector cell-associated neurotoxicity syndrome ICANS) or more frequently if clinical concern or as directed by medical staff or per trial protocol). Routine monitoring will be undertaken by trained nursing staff or junior medical staff. Neurotoxicity will be graded as per the ICE Score (Immune effector Cell associated Encephalopathy) system developed from the ASTCT ICANS consensus and recorded on CWP nursing assessment eform when available. See also SOP: Neurological Disease in Stem cell Transplantation and Cellular Therapy for more details. Nursing and junior medical staff

must seek medical attention and senior review for patients showing signs of potential neurological toxicity (grade 1 or above) or change in grade.

Neurotoxicity most frequently occurs within 1 week of IEC (e.g. CAR-T therapy) infusion often in combination with CRS however patients should also be monitored for later neurotoxicity which may occur without evidence of CRS

4.3 Treatment

Complications from immune effector cell therapy may have overlapping presentation. Comparison between some of the common features of toxicities (sepsis, HLH, thrombotic microangiopathy, cytokine release syndrome) are shown in appendix C. Patients with signs of clinical deterioration must have senior medical review (Registrar and or Consultant).

A treatment algorithm is shown in appendix D although treatment decisions must be taken in conjunction with senior medical review and advice from neurology and CCU medical teams as appropriate.

For patients participating in clinical trials procedures 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). The SOPs and trial protocol are used in conjunction where a patient is participating in a clinical trial.

Sepsis

Patients with evidence of sepsis will be treated according to the sepsis and NEWS2 policies (SOP: Guidelines for the management of sepsis, SOP: National Early Warning score (NEWS2) policy) however it is very important to recognise that other complications of immune effector cell therapy (e.g. cytokine release syndrome, thrombotic microangiopathy, HLH) can also present with similar symptoms such as fever, neurological changes and organ dysfunction)

Cytokine release syndrome (CRS)

Management of CRS is as detailed in SOP: Guidelines for management of cytokine release syndrome.

- Particular care should be taken with patients who have high tumour bulk, co-morbidities, abnormal organ function or who develop early CRS (within 3 days of initiation of treatment). In this patient group the risk of developing more significant CRS is greater and a lower threshold for initiation of anti IL6 therapy (tocilizumab) should be considered. This is 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

Neurological toxicity - Immune effector cell-associated neurotoxicity syndrome ICANS

Principles for management are as below, see SOP: Neurological disease in stem cell transplantation and cellular therapy for more detailed information

- Supportive care, close monitoring (including MRI, LP, EEG) for grade 1 disease
- Neurology opinion for patients with toxicity ≥ grade 2 or deteriorating patients
- Treat co-existent CRS as per protocol
- Anti-convulsants for seizures
- Steroids for grade 2 or greater disease
- CCU transfer considered for grade 2 and mandated for grade 3-4 disease. Patients with uncontrolled status epilepticus or raised intracranial pressure should be considered for transfer to neurological ITU at Salford

HLH

Patients with suspected HLH and grade ≥3 organ dysfunction should be treated with CRS protocol and consider use of etoposide and intrathecal chemotherapy for patients resistant to therapy and evidence of CNS disease respectively. See SOP: HLH and Macrophage Activation Syndrome for more information.

Adverse Events: Inform MHRA/HTA of any suspected adverse events reported at any time via yellow card system and the pharmaceutical company (

4.4 Discharge and Follow Up

Inpatient discharge will occur approximately day +12 to Day +30:

- Day 12 onwards, as assessed by attending haematology consultant when patient is fit to be discharged to ambulatory care. To be seen by the Haematology CNS or Cellular Therapy co-ordinator to confirm follow up arrangements if possible
- On discharge patients will remain under the care of ambulatory care until day 30+.
- Patients will attend ambulatory care for Mon/Wed/Fri bloods, post treatment nursing review and ICANS assessment and bloods as per ambulatory care nursing protocol.
- Patients will have a clinic review (Tuesday PM) After D+28
- Please contact the cellular therapy co-ordinators on 0161 446 8011 if needed, who will co-ordinate day 30+ restaging and clinic appointment
- Ensure the patient has received a Christie hotline card in case of any issues post discharge.

Full follow up details can be found in CLN-99 CAR-T follow up and CLN-14 coordinating adoptive cell therapy: chimeric antigen receptor t-cell (car-t) therapy (including tcr, car-nk, immunotherapy) SOP.

All patients must have received a Christie hotline card in case of any issues post discharge and where relevant product specific patient card.

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

CLN-99 CAR-T follow up and CLN-14 coordinating adoptive cell therapy: chimeric antigen receptor t-cell (car-t) therapy (including tcr, car-nk, immunotherapy) SOP.

SOP: HLH and Macrophage Activation Syndrome for more information.

PHA-14 Joint Pharmacy/Pathology Management of Advanced Therapy Medicinal Products (ATMPS)

Ext-102 - Lisocabtagene maraleucel Healthcare Professional Guide

Ext- 104 Lisocabtagene maraleucel Clinician GuideEXT- 107 Standard Operating Procedure (SOP) for CAR T (idecabtagene vicleucel and lisocabtagene maraleucel) Risk Minimisation Programme (RMinP) Requirements

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.

9.0 Appendices

9.1 Appendix A - Comparison of Serious Toxicities Following Immune Effector Cell Therapy (for Trial Patients Refer to the Protocol for Toxicity Management)

The table below compares some of the clinical and laboratory parameters encountered in patients following immune effector cell therapy. This is not exhaustive and should not be relied on in isolation to make a diagnosis. Some patients may present with more than one syndrome at the same time and there is significant overlap between these (notably HLH and cytokine release syndrome which may be best regarded as being on the same spectrum of disorders).

Parameter	Sepsis	HLH	Thrombotic microangiopathy	Cytokine release syndrome[1]
Fever	Yes	Yes	Yes	Yes
Tachycardia	Yes	Yes	No	Yes
Hypotension	Yes	Yes	No	Yes
Neurology	Non-specific findings (e.g. drowsiness) maybe observed but significant neurology uncommon (unless CNS infection)	Non-specific including ataxia, confusion and seizures	Wide range of symptoms including headache, confusion, change in personality (including irritability) and seizures.	May lead to associated encephalopathy syndrome
Renal	May complicate sepsis due to hypoperfusion	Renal dysfunction common. Low Na due to SIADH frequent	Renal disease common especially in HUS like presentation	Common related to hypoperfusion. Electrolyte disturbance (low Na, K, PO4 common)
Liver	Not characteristically affected	Hepatic dysfunction very common	Not characteristically elevated	Hepatic dysfunction common

Rash	Not characteristically present	Yes – rash and bleeding	Not typical	Yes – less common than with HLH
CRP	Elevated	Elevated	Not typically elevated	Typically elevated (although not seen in all cases) and high values(>150 mg/l) typical for grade 3-4 disease.
LDH	Not characteristically effected	Typically elevated	Characteristic abrupt rise in LDH	Typically elevated and high values (>1500 iu/l) in grade 3-4 disease
Ferritin	Elevated	Markedly elevated (maybe >10000 ng/ml)	Not typically elevated	Typically elevated (although not seen in all cases) especially with grade 3-4 disease (maybe >10000 ng/ml)
Blood count	Raised white count although may not be observed in patients following chemotherapy	Pancytopenia is characteristic	Thrombocytopenia, and microangiopathic haemolysis leading to red cell fragmentation (schistocytes on blood film)	No specific abnormalities – counts may be low due to conditioning chemotherapy
Clotting	DIC may be seen in severe cases	Low fibrinogen and coagulopathy. DIC is common	Normal	May develop DIC picture but less common than with HLH
Other	Wide range of clinical presentation depending on the site and severity of infection	May cause significant respiratory distress. Bone marrow shows evidence of haemophagocytosis	Decreased haptoglobin,Direct Antiglobin Test (DAT or Coomb's test)negative	Severe respiratory distress in up to 15% of patients.

[1]Teachey DT *et al.* Cancer Discov 2016;6:664

9.2 Appendix B - Assessment of Neurological Status for patients receiving immune effector cells (Complete The E-Form on CWP, Paper Form to Be used if CWP Outage)

(CAR-T, TCR) ICANS Immune Effector Cell-Associated Encephalopathy (for trial patients refer to the protocol for neurological status assessments)

Name										**Hospital Number**				
	Year	Month	City	Where are we	Follows command	Name object 1	Name object 2	Name object 3	Serial 10s	ICE Score	ICE Grade	Seizure Grade	Conscious Level Grade	Overall Grade
Date and time														
Name	**Sentence**													
Date and time														
Name	**Sentence**													

ICE Score	**ICE grade**	**Seizure grade**	**Conscious level grade**	**Overall grade**
Score 1 point for correct answer to each of 9 questions and correctly writing any sentence. The total (maximum 10) is the ICE score used to calculate the ICE grade	Grade 0 – ICE score 10 Grade 1 – ICE score 7-9 Grade 2 – ICE score 3-6 Grade 3 – ICE score 0-2 Grade 4 – unresponsive	Grade 0 – no seizures Grade 3 – seizures that resolve rapidly Grade 4 – seizures that take >5 mins to resolve	Grade 0 – AVPU Awake Grade 2 – AVPU Verbal Grade 3 – AVPU Pain Grade 4 – AVPU Unresponsive	Highest grade (ICE, seizure, conscious level)

Seek senior medical review if clinical concerns, changes to grade/symptoms or overall grade ≥1

9.3 Appendix C - Assessment of Cytokine Release Syndrome Complete the E-Form on CWP, Paper Form to be Used if CWP outage)

(For trial patients refer to the protocol for neurological status assessments)

Assessment for cytokine release syndrome (CRS)								
Patient name and number or addressograph	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time	Date and time
	Name	Name	Name	Name	Name	Name	Name	Name
	Grade	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**	**Grade**
Temperature 0- None 1- ≥38C or has received antipyretics or tocilizumab for CRS								
WITH								
Blood Pressure support 0- None 2- Low blood pressure requiring iv fluids not requiring vasopressors 3- Requiring a vasopressor with or without vasopressin								
AND/OR								
Breathing 0- None 2- Requiring low-flow oxygen < 6l / minute 3- Requiring high-flow oxygen >6l / minute, non-rebreather mask or venturi mask 4- Requiring positive pressure (eg.CPAP, BiPAP intubation or mechanical ventilation)								
Overall Grade The **MAXIMUM** grade recorded								

Patients require medical review if they develop any signs of CRS.

Urgent senior review is required if deteriorating, changes to CRS grade or CRS > grade 1

9.4 Appendix D - IEC Clinical Trial Patient Management on Palatine Ward

- This document outlines arrangements and responsibilities for the inpatient management of CART trial patients on Palatine Ward.
- Clinical trials of investigational medicinal products are regulated by the MHRA and the clinical trial protocol is a legal document. The trial protocol must be followed at all times.
- The trial PI will oversee all aspects of trial conduct at The Christie; all protocol related decisions must be made in consultation with the PI or delegated sub-I on their team.

Pre-treatment

Trial team	Haematology Transplant Team
Review trial protocols during the set-up phase as per the SOP QM-11 and in line with the CTRG process.	
Mandatory attendance at the ATMP R&I, trial SIV and related trial training sessions, as well as the weekly transplant MDT/scheduling meetings pre-admission.	
GCP and trial-specific training with designated roles and responsibilities listed on the signed trial delegation log (It is the responsibility of the PI/trials team to ensure the delegation log is maintained).	
All protocol mandated activities including but not limited to: • Patient identification and distribution of patient information sheet • Signed informed trial consent • Trial Screening • Confirmation of trial eligibility	
Written communication with apheresis and transplant teams, and support service leads (e.g. CCU, neurology etc)	Apheresis and admission scheduling at Transplant MDT as per co-ordination of CART SOP. Apheresis assessment, consent & procedure (as per trial protocol)
Clinical documentation review of trial patients at scheduled and unscheduled outpatient visits	
Co-ordination of the patient timeline including apheresis, LD chemotherapy and admission for C1D1 must be discussed on a case-by-case basis initiated by the trial team and the Sponsor, and discussed with apheresis and transplant teams (via the Transplant MDT) and support service leads (via written correspondence)	

Treatment (conditioning treatment, CART infusion and management of toxicities)

Trial team	Haematology Transplant Team
Patients will be admitted to PTW under the Attending Physician who will be responsible for the management of the patient according to the trial protocol and Trust polices where this is not specified in the protocol. All protocol-specified decisions must be discussed with the trial PI/delegated sub-I. The length of admission will be determined by the trial protocol and the medical condition of the patient. The treatment period also covers readmission for management of TEAEs e.g. late CRS/neurological toxicity and repatriation to PTW following escalation of care (e.g. to CCU)	
The PI/disease group Sub-I and Attending Physician will attend the weekly grand ward round to discuss patient management.	
Administration of conditioning treatment and ATIMP by trial research nurses	PTW ward nurses/CPF to support cellular therapy research nurses
Trial PI to maintain oversight of patient management	Patient management in accordance with the trial protocol and in discussion with the trial team including management of TEAEs
All protocol mandated activities including but not limited to: • Safety assessments and reporting of AE/SAE/SUSARs • Review of concomitant medications • Investigations (trial bloods, scans etc) • Response assessments • Study questionnaires	Non protocol mandated activities including but not limited to: • Management of unrelated medical complications or conditions • Physical examinations, ECOG score, neurological examinations, vital signs • Investigations as required
Escalation of care and referrals for supportive care (e.g. CCU/neurology) must be done in accordance with the trial protocol and discussed and agreed by the Attending Physician. Patients will be repatriated to PTW after admission for escalated care e.g. CCU.	

Post Treatment (discharge from PTW)

Trial team	Haematology Transplant Team
Follow-up per the trial protocol	Patient to be referred back to PI/DG consultant upon recovery. Post treatment day unit/ clinic visit if required[2]
	Collection of survival data for JACIE/EBMT

Notes:
1. Transplant MDT discussion, attendance required for initial discussion of suitability for therapy and subsequent scheduling of patients.
2. Acute Lymphoblastic Leukaemia patients – Dr Castleton Monday Pm clinic, lymphoma patients- Dr Bloor Friday am clinic