SOP: CAR-T therapy discharge and follow up. CAR-T service pathway – post infusion

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STANDARD OPERATING PROCEDURE (SOP)

TITLE: CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY DISCHARGE AND FOLLOW UP. CAR-T SERVICE PATHWAY – POST INFUSION

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1.0 INDICATIONS OF PRACTICE

This document reflects the international consensus recommendations from EBMT, JACIE and ASTCT, and complies with the NHS England CAR-T service specification for allogeneic transplant centres commissioned as CAR-T therapy centres with attending transplant physicians.

This procedure ensures safe discharge and follow-up for patients following Chimeric Antigen Receptor (CAR) T-cell therapy. It defines the expected treatments, tests, medical and nursing care at the required timescale according to the individual patient's condition and protocol. Patients treated within a clinical trial will also follow the relevant trial protocol.

In contrast to post autologous and allogeneic transplant patients, little is known about the long-term effects of CAR T cell therapy beyond 1-2 years. Only a small cohort of patients has been followed for more than 2 years. The identified complications include prolonged cytopaenias, hypogammaglobulinemia, delayed B and T cell immune reconstitution with consequent atypical infection. Other longer term toxicities may emerge with longer term follow up of larger cohorts of patients.

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2.0 AUTHORISED PERSONNEL/TRAINING REQUIRED

Ambulatory Care Nursing and Clerical Teams are responsible for the organisation of visits and nursing care for the first 28 days post CAR-T infusion.

Auto/CAR-T Therapy Coordinator/Haematology CNS is responsible for ensuring the patient has been appropriately informed of all relevant information prior to commencing shared care arrangements. To liaise with referring teams with regarding patient needs and to act as a point of support and reference for patients. Undertake annual reviews to meet JACIE, EBMT, NCCP and NHS England service specifications.

Cellular/CAR-T Therapies Clinical Lead will provide oversight of the overall clinical care and data returns of patients and once clinically appropriate, authorise shared care arrangements of the patient with the referring Consultant, supporting long-term follow-up by The Christie nursing and referring consultant teams.

Transplant Program Lead takes overall responsibility for cellular therapies including CART treatment.

3.0 HOSPITAL DISCHARGE

Exact timing of discharge will be based on the clinical condition of the patient, availability of carers, pre-existing co-morbidities, distance from home to hospital and suitability for ambulatory discharge care. The Palatine attending haematology consultant will be responsible for assessing the suitability of the patient discharge supported by the CAR-T Lead.

3.1 Duration of admission and timing of discharge

Patients undergoing CAR-T therapy will be closely followed up as inpatients or in ambulatory care until day+28.

- All patients will remain inpatients until at least day+14 or as directed by a relevant trial protocol
- Selected patients who are clinically stable with no evidence of significant treatment related complications beyond asymptomatic bone marrow suppression may be considered for discharge to home or ambulatory care at day+14
- Patients who are unstable, or who develop significant complications (eg treatment related or disease progression) may require longer time in hospital or ambulatory care as directed by the Attending Consultant or CAR-T lead.

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3.2 Discharge planning

All patients must remain within a 1 hour drive of The Christie Hospital until at least day+28 (or longer as above). This can be either from home, remaining as an inpatient, or be accommodated at the StayCity Piccadilly hotel. Where patients are discharged before day+28

- Patients who are stable with no should only be discharged mon-thurs and not on public holidays.
- All patients should have a carer available to stay with them until day+28 or resolution of neurotoxicity/ICANS whichever is longer.
- Patients must be aware of the requirements for life long irradiated blood products
- Patients must monitor their temperature regularly and to report fever or any symptoms of being unwell to the Hotline.
- Patients must have contact details for the Hotline, Cellular Therapy Team, Ambulatory care unit
- Patients must be made aware of the potential symptoms of delayed neurological toxicity and advised that they should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks post infusion or until resolution of neurologic adverse reactions if longer. Patients experiencing a seizure should inform the DVLA and refrain from driving until authorised.

Discharge will be facilitated by the ward nurses, CNS team and CAR-T/transplant coordinators

3.3 Patient monitoring in ambulatory care

Patients discharged before day+28 will be monitored in ambulatory care on mon/wed/fri and will require the following assessments

- ICANS and CRS assessment
- Weight and observations
- Blood tests - FBC and Christie profile, CRP, Ferritin, coagulation monitoring

All patients will be reviewed by nursing staff. A medical review is indicated in the vent that patients are unwell, deteriorating, exhibiting new symptoms, have observations or blood tests out of normal range or where nursing team or patients have any concerns.

Patients will also be reviewed on a weekly basis in the Tuesday pm cellular therapies clinic.

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3.4 Patient monitoring beyond day+28

Patients can be discharged home and out of ambulatory care without restrictions on distance from The Christie if they are stable with no evidence of any significant treatment related toxicity.

Day+28 to day+100

Patients will be followed up in the Tuesday pm Cellular Therapies Clinic to Regular day+100; the frequency of appointments (generally every 1-4 weeks) will be determine on an individual patient basis. Shared care arrangements with local referring centres should be considered for patients travelling significant distances to the Christie; a documented plan of care must be in place with the referring team. Extended intensive follow up may be needed per section 3.3 for patients with significant treatment related complications or those discharged from the ward after day+28.

Beyond day+100

Patients who are clinically stable and responding to treatment should be referred back to local teams for follow up. Requirements for monitoring (see section 3.5) and follow up must be shared with the referring team. Patients will also be followed up at the Christie (in person or remote consultation) every 6 months (year 1) and then annually in order to monitor progress and to collect data required for EBMT/BSBMT. Additional follow up appointments at the Christie may be required in the event of complications arising from treatment, suspected relapse or as requested by the referring team.

3.5 Schedule of assessments

Schedule for disease and CAR-T monitoring is as per the table below

Day	Disease/complication monitoring	CAR-T monitoring
+30	**NHL** – PET scan (and marrow or MRD if indicated **ALL** - marrow, MRD, imaging as indicated Ferritin/CRP/LDH Virology (parvovirus, JC/BK, HHV 6/7/8) if positive at consent visit	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins
+60	**ALL** - marrow, MRD, imaging as indicated Ferritin/CRP/LDH	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins
+100	**NHL** – PET scan (and marrow or MRD if indicated **ALL** - marrow, MRD, imaging as indicated	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins

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	Vitamin B12, vitamin D, folate	
Later follow up	**ALL** - marrow, MRD, imaging as indicated every 3 months until 24 months post treatment **NHL** - PET scan at 12 months and thereafter only if concerns about disease progression	Immune monitoring HIV viral load CMV/EBV PCR Immunoglobulins **All performed 3 monthly to 24 months post treatment**
Further specific investigations may be undertaken as clinically indicated		

3.6 Quality of Life assessments

Cellular Therapy Coordinator/Haematology CNS will provide quality of life assessments (FACT-BMT) to all CAR-T patients' pre admission (during consent visit), day +28 and day +100, the results will be reviewed and audited annually by the Haematology CNS team.

3.7 Prophylaxis and supportive medications

PCP prophylaxis - All patients will receive a dose of Pentamidine nebuliser pre hospital discharge with continuation of this method of PCP prophylaxis or switch to alternative medication such as Septrin or Atovaquone will be guided by the CAR-T Clinic and based on the patient's blood counts. PCP prophylaxis should ideally continue for at least 12 months or until lymphocyte count is consistently about 1 and CD4 count greater than 200, whichever is longer. Patients with Toxoplasma IgG exposure or patients with previously PCP infection should receive Atovaqone 750mg twice a day or septrin 960mg once a day on Mon/Wed/Fri.

Antiviral prophylaxis – aciclovir 400mg BD to be continued for a minimum of 12 months post CART therapy or until Lymphocyte count is consistently about 1 and CD4 count greater than 200, which ever is longer.

Levofloxacin is only required in patients where the neutrophil count is below 1.0, including those who require GCSF support.

Primary antifungal prophylaxis with fluconazole to continue until neutrophils are greater than 1.0, including those who require GCSF support.

Secondary antifungal prophylaxis or treatment with posaconazole to continue until neutrophils are greater than 1.0

GCSF support – Long term cytopenias are expected in this patient group and should be managed with GCSF support with aim of maintaining neutrophils >1-2x10^9/l

IVIG replacement is with 0.4-0.6 g/kg every 4-6 weeks will be considered from day+28 for deficiency secondary to CAR-T cell therapy, when IgG level is <3g/l and recurrent infections per NHSE guidance. Treatment will be discontinued after recovery of CD19 cells in the peripheral blood and IgG greater than 4.5 g/l.

3.8 Immunisations

CAR-T patients will be immunised one year post infusion at the clinicians discretion, full details are available in the DOC152 "Recommendations for Immunisation" and "SCT/INFCONTROL/S Travel and immunisation in stem cell transplant patients".

4.0 REFERENCES

DOC945 Coordinating a CAR-T therapy (including TCR)

DOC645 Inpatient management of patients receiving immune effector cells (including CAR-T cells)

DOC640 Neurological disease in stem cell transplantation and cellular therapy

AMB-23 Kymriah CAR-T - ALL Nursing Protocol for Haematology & TYA Ambulatory Care Unit

AMB-21 Kymriah CAR-T - DLBCL Nursing Protocol for Haematology & TYA Ambulatory Care Unit

AMB-22 Yescarta CAR-T - DLBCL Nursing Protocol for Haematology & TYA Ambulatory Care Unit

AMB-32 Nursing Protocol for: Tecartus CAR-T - mantle cell lymphoma (mcl) for Haematology & TYA Ambulatory Care Unit

NHS England CAR-T service specifications for Kymriah for DLBCL and ALL

NHS England CAR-T service specifications for Yescarta for DLBCL

NHS England CAR-T service specifications for Tecartus for MCL

SCT/APHE/L&E Allogeneic Transplant - Follow up and Late Effects

CAR-T DLBCL post transplant follow up worksheet

APH-68 CAR-T ALL post transplant follow up worksheet

Service specification for the delivery of Chimeric Antigen Receptor T Cell (CAR-T) Therapy (all indications, all ages)

Kymriah SPC https://www.medicines.org.uk/emc/product/9456

Yescarta SPC https://www.medicines.org.uk/emc/product/9439

Tecartus SPC https://www.medicines.org.uk/emc/product/11987/smpc#gref

http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf

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Management of adults and children undergoing chimeric antigen receptor T-cell therapy Haematologica 2018 Volume 105(2):297-316 I. Yakoub-Agha et al. https://haematologica.org/article/view/9515

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events | Journal for ImmunoTherapy of Cancer (bmj.com)