Infusion of CAR T cells

PURPOSE

To infuse CAR T cells which are autologous or allogeneic T cells that have been genetically modified to allow them to recognise and kill certain types of cancer. They may be given as a licenced cellular product or within a trial and regulated by MHRA as a type of Advanced Therapy Investigational Medicinal Product (ATIMP).

RESPONSIBILITY

The consultant responsible for treating CAR T cell eligible patients, Trial Principal Investigator (PI) or Investigator's designee should ensure the patient is eligible to receive the CAR T cell product infusion and ensure the relevant study related pre-infusion investigations, treatments and consent have been performed. It is their responsibility to:

- To confirm the total dose of product to be infused to the patient.
- To ensure the thawing of CAR T cells will be performed by experienced HTL staff who are trained in thawing of cellular therapy products.
- To ensure the infusion of CAR T cells will be performed by experienced BMT CNS staff who are trained in infusing of cellular therapy products.

RESTRICTIONS

This document should be used in conjunction with trial specific study protocols.

DEFINITIONS

CAR T cells – Chimeric Antigen Receptor T cells
MHRA – Medicines and Healthcare products Regulatory Agency
ATMP – Advanced Therapy Medicinal Product
PI – Principle Investigator
DMSO – Dimethylsulphoxide Cryoprotectant
N Saline – Sodium Chloride 0.9%

APPLICABLE DOCUMENTS

HTL/F/131 – request for CAR T cells
HTL/F/125 – request for trial specific cellular products
HTL/O/031 – Thawing and Infusion of Cryopreserved Products
Trial Specific Forms as supplied by the Sponsor

ITEMS REQUIRED

- 1 x 100ml bag N Saline for IV infusion
- 1 x 500ml bag N Saline
- IV non filter blood infusion set as supplied from Haematology Transplant Laboratory
- 10ml syringes
- Green needles
- CAR T cells as supplied from Haematology Transplant Laboratory
- Chlorphenamine IV 10mg
- Oral paracetamol 1gram
- IV antiemetic choice
- IV N Saline flush
- Sterile Gloves
- Antiseptic wipes

- Sterile gloves
- Drip Stand
- Equipment for monitoring BP, pulse and oxygen saturation
- Equipment to deliver oxygen and suction

STEP	DETAILS	INFORMATION
	PI and trained designees	
1. Request CAR T cells	**1.1.** Confirm CAR T cells are available from haematology transplant laboratory	Some patients have sufficient CAR T cells stored for more than single use
	1.2 Confirm with PI/Senior Medical Designee responsible for patient, the dose of CAR T cells for infusion	
	1.3 Check completion time of chemotherapy and calculate time delay required before infusion of CAR T cells considering:- • Chemotherapy drugs given • Renal function	Confirm with PI/Senior Medical Staff, the date for infusion. Most protocols involve chemotherapy and at least 24 hours from completion is required before infusion of CAR T cells. This may be longer depending on which chemotherapy drugs have been given and where there is renal insufficiency
	1.4 Ensure delivery of request form to haematology transplant laboratory. .	**HTL/F/131**, **HTL/F/125** or trial specific prescription paperwork as supplied by sponsor to complete request
	1.5 Prescribe IV Chlorphenamine and oral Paracetamol to be administered 30 minutes before infusion of CAR T cells	NO STEROIDS TO BE PRESCRIBED ROUTINELY

NOTE

DO NOT CONFIRM CAR T CELLS FOR DELIVERY TO WARD UNTIL CONDITIONING CHEMOTHERAPY HAS BEEN CONFIRMED COMPLETED AND RENAL FUNCTION HAS BEEN REVIEWED

STEP	DETAILS	INFORMATION
PI DESIGNATED STAFF INFUSING CAR T CELLS		
2. Inform patient details of CAR T cell infusion	**2.1** Explain procedure for CAR T cell infusion:- • Need for two sites for IV access • Chlorphenamine and antiemetic to be given IV • Oral paracetamol **2.2** Explain side effects of DMSO:- • Taste/nausea • Smell from DMSO on breath • Cough/tickly throat/chest tightness • Sedation from chlorphenamine **2.3** Confirm patient understands possibility of cytokine release syndrome, requirement for ITU and possible neurological effects	Chlorphenamine IV and oral paracetamol to be given 30 minutes before infusion Similar to tinned tomatoes/sweetcorn Contact PI or designee if patient needs further information/discussion
3. Prepare for infusion of CAR T cells	**3.1** Check patient is ready for CAR T cell infusion:- • Check correct patient is at bed area • Enquire if nausea/vomiting • Check two good IV access sites are available **3.2** Prepare sterile tray with:- • 1 x 100ml bag N Saline • 1 x 500 ml bag N Saline • IV blood component giving set • IV Chlorphenamine • IV antiemetic if required • Normal saline flush • 10ml syringes • Green needles • Sterile gloves • Antiseptic wipes • Sterile gloves	Confirm full name, D.O.B, and hospital number with hospital notes of patient Check time of last antiemetic dose Check re allergies Central line flushes easily or insert peripheral venous access minimum 18 gauge for infusion of CAR T cells Second access site should be available in case of adverse effects IV non filter blood giving set to be supplied from Haematology Transplant Laboratory on delivery of CAR T cells. For Autolus study please see appendix with additional items required to flush CAR T product bag after product infusion

STEP	DETAILS	INFORMATION
	3.3 Record baseline observations on neurological NEWS chart • Pulse • Blood pressure • Temperature • Oxygen saturation • Baseline neurological assessment	
	3.4 Give oral paracetamol	Administer 30 minutes before infusion
	3.5. Give IV Chlorphenamine and antiemetic as appropriate	Administer 30 minutes before infusion
	3.6 Spike 100ml N Saline bag with infusion IV giving set	Check N Saline can flow freely. If not, establish new access before giving CAR T cells.

NOTE

Cryopreserved CAR T cells should be infused essentially in under thirty minutes since defrosting. Small gauge access may block during infusion. Access in hand/forearm may flow too slowly.

STEP	DETAILS	INFORMATION
4. Infuse CAR T cells	**4.1** Request haematology transplant laboratory staff to defrost a bag of CAR T cells.	
	4.2 Check identity of patient with identification of CAR T cell bag. • Ask patient to give name • Ask patient to give date of birth • Check against hospital notes, wristband, CAR T cell bag • Check patient identification detail on bag corresponds with hospital notes • Check bag detail corresponds with Request for Trial Specific Cellular Products form or CAR T cell request form	2 person checks with medical staff, nursing staff or stem cell laboratory staff. **HTL/F/125** or **HTL/F/131**
	4.3 Stop N Saline infusion, disconnect and insert spike of giving set into CAR T cell bag port	For small volumes of CAR T cells in patients weighing <50kg it may be preferred to draw all the CAR T cell bag contents into a syringe for direct administration over 5 to 10 minutes. Flush bag with N Saline to ensure all product drawn to infuse.
	4.4 Infuse initially slowly to observe reaction and provided stable increase to infuse over 5 to 15 minutes	Once a bag is defrosted it must be infused within 30 minutes
	4.5 Once almost completed, request any further bag of CAR T cells for defrost if available and patient has not had adverse reaction to first bag	Do not request thaw of further bags if patient unwell or technical issues with infusion Repeat identification checks in 4.2 with each bag given
	4.6 Once CAR T cell bag is empty, continue to next bag NOTE: for Autolus product, each bag must be flushed in addition to the infusion set. See appendix.	
	4.7 Once all requested bags infused attach 500 ml IV N Saline to clear line or for Autolus product, refer to appendix	Continue IV infusion with N Saline until line is as clear as possible.
	4.8 Flush patient IV access with N Saline if remaining in situ	
	4.9 Complete paperwork by signing receipt on request form and completing accompanying trial specific forms	**HTL/F/125** Trial specific paperwork

STEP	DETAILS	INFORMATION
5. Observe patient during infusion	**5.1** Consider volume intake **5.2**. Symptoms: • Chills • Urticaria • Fever • Flushing • Cough • Abdominal cramps • Hypotension • Hypertension • Bradycardia • Anaphylaxis **5.3** Observe pulse, BP, temp, oxygen saturations throughout procedure, checking after the first five minutes and thereafter at every fifteen minutes until completion. Record at completion of infusion. Continue regular observation for a minimum of 4 hours at regular intervals as defined in the trial management plan.	For mild reactions slow infusion and • Nausea vomiting – second line antiemetics eg cyclizine or prochlorperizine • Rigor/headache – consider Pethidine 12.5 to 25mg IV • Hives/pruritis – consider further chlorphenamine In the event of severe reaction call for medical assistance and advise patient consultant, PI or designees Emergency anaphylactic reaction which may cause stridor, wheeze, facial swelling, colour change, chest pain, tachycardia, hypotension, abdominal cramps – stop infusion, administer oxygen, N saline, consider adrenaline, chlorphenamine, hydrocortisone, salbutamol nebuliser.

NOTE

DAMAGE TO A CAR T CELL BAG WITH RISK OF LEAK OF PRODUCT CAN OCCASIONALLY OCCUR USUALLY WHEN INSERTING GIVING SET. DO NOT REMOVE GIVING SET AND COVER DAMAGE WITH A STERILE SWAB. CELLS CAN OFTEN BE RECOVERED BY HAEMATOLOGY TRANSPLANT LABORATORY STAFF DRAWING INTO A 50 ML SYRINGE. CONTACT CONSULTANT/PI/DESIGNEE AND REFER TO TRIAL SPECIFIC MANAGEMENT PLAN FOR ADVICE TO ADMINISTER. SAVE AN ALIQUOT TO SEND FOR MICROBIOLOGY. CONSIDER ANTIBIOTIC COVER. REPORT AS DATIX. REPORT TO MANUFACTURER.

6. Dispose of waste	**6.1** For licensed products please dispose of clinical waste according to Trust policy **6.2** For unlicensed product please dispose of all clinical waste according to Appendix 10	
7. Record infusion of CAR T cells	**7.1** Complete **HTL/F/125** or **HTL/F/131** and copy to patient notes with original to Haematology Transplant Laboratory **7.2** Document procedure in hospital notes **7.3** Complete trial specific paperwork	In the event of any incident or adverse event/ reaction this should be reported to PI/designee and DATIX within 24 hours. Additionally report to sponsor as specified in trial protocol /yellow card

8. Further Information/Exceptions

Refer to trial specific management plans.
In the unlikely situation of the DMSO dose exceeding 1ml DMSO/kg body weight the PI/designee should consider splitting the dose between early morning and late afternoon.

9. For further information refer to: Quality Management Staff QMU.I.021

Appendix I

Additional information to flush the product bag

1) Cellular Therapies will issue:
   - Needle free coupler
   - BAXTER non-filtered infusion set
   - Plasma transfer set
   - ATIMP

2) Spike 500ml N Saline for flushing the product bag with a needle free coupler

3) Clamp a plasma transfer set

4) Attach the luer lock of the plasma transfer set to the needle free coupler in the saline bag

5) Spike the ATIMP product bag with the free needle free coupler end of the plasma transfer set

6) Clamp the Baxter infusion set using the roller clamp

7) Spike the ATIMP product bag with the Baxter infusion set

8) Release the roller clamp on the Baxter infusion set and administer entire contents product bag

9) Clamp the Baxter infusion set using the roller clamp

10) Release the clamp on the plasma transfer set and flush 25mL of saline into the ATIMP product bag

11) Clamp the plasma transfer set

12) Flush the bag by gently mixing the saline around the product bag

13) Release the roller clamp and administer contents of the bag

14) Repeat points 10-14 two more times

Appendix II

Appendix for Waste disposal for unlicensed CAR T cell products

- **Prepare waste disposal as follows:**
  - Put the giving set with spike still within the empty product bag and saline bag, any cannula if removed and any additional product bags into a clinical waste container/bag
  - Seal the container/bag
  - Label as ' **CAR-T (GM class 1) waste**'

- **Contact microbiology to say there is CAR T GM waste for disposal by phoning 31019**

- **Waste container taken to main pathology Reception.**
  - Waste should be handed to microbiology staff, Graham Short, Robert Oxley, Michael Jones.

- **Waste autoclaved in Microbiology**