Chemotherapy Protocol

CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY
ALL – BREXUCEL – CYCLOPHOSPHAMIDE (900) – FLUDARABINE (25)

This regimen will only be available to prescribe at the Wessex Blood and Marrow Transplant Unit

Regimen

- Acute Lymphoblastic Leukaemia- Brexucabtagene autoleucel – Cyclophosphamide (900) – Fludarabine (25)

Indication

- CAR-T therapy with Brexucel (brexucabtagene autoleucel) for the treatment of adult patients 26 years of age and above with:
  - Relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

  (See separate Mantle Cell Lymphoma a protocol for use in MCL)
- Lymphodepleting chemotherapy must be administered prior to Brexucel. This protocol includes both lymphodepletion and CAR-T administration.
- For autologous use only.

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Chemical haemorrhagic cystitis, leucopenia, nausea and vomiting, hepatic toxicity, altered carbohydrate metabolism, pancreatitis, hyper and hypoglycaemia, inappropriate secretion of antidiuretic hormone, interstitial pulmonary fibrosis.
Fludarabine	Transfusion related GVHD, fever, malaise, neurotoxicity, opportunistic infections, GI disturbances -nausea, vomiting, diarrhoea.
Brexucel (brexucabtagene autoleucel)	Cytokine release syndrome (CRS), hepatic dysfunction, renal dysfunction, cardiac dysfunction, neurologic adverse reactions -immune effector cell-associated neurotoxicity syndrome (ICANS), opportunistic infections, febrile neutropenia, HBV reactivation, prolonged cytopenias, hypogammaglobulinaemia, tumour lysis syndrome (TLS), hypersensitivity reactions.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required, these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

Symptoms of CRS or ICANS can occur weeks after infusion and therefore the patient must be issued with an alert card to carry with them at all times.

Any suspected adverse reaction to a CAR-T cell infusion should be reported. Reporting forms and information can be found at – www.mhra.gov.uk/yellowcard. Consideration should also be given to reporting adverse events to the relevant manufacturer via their usual channels.

Monitoring

Regimen

- FBC, U&Es, renal, liver and bone, CRP, coagulation screen, ferritin and LDH prior to initiating treatment and daily thereafter.
- Screening for HBV, HCV and HIV must be performed before collection of cells for Brexucel manufacture.
- Echocardiogram and baseline measure of lung function must be taken prior to initiating lymphodepletion

Brexucel

Nearly all patients treated with Brexucel experience some degree of CRS, including life-threatening and fatal reactions. -See WBMT Policy P-G-1 and SOP P-P-78 and P-P-79 for monitoring requirements.

CRS:

- Symptoms: pyrexia, tiredness, cardiac failure, tachycardia, cardiac arrythmias, dyspnoea, hypoxia, capillary leak syndrome, chills, renal impairment, headache, malaise, transaminitis, nausea, diarrhoea, hypotension.
- Temperature, blood pressure and oxygen saturation monitored 4-hourly after Brexucel administration on Day 0 and then twice daily as directed in accordance with local procedures.
- This must be documented, and CRS graded on the WBMT CRS Assessment Form in the patient's notes.

ICANS:

- Symptoms: seizures, somnolence, headaches, confusion, agitation, speech disorders, tremor, encephalopathy, ataxia, memory impairment, mental status changes, hallucinations, depressed level of consciousness, delirium, dysmetria.
- ICE score of the patient must be assessed twice daily and documented on the WBMT ICE Assessment Form in the patient's notes.

Dose Modifications

As a cell-based therapy and based on the mechanism of action, renal and hepatic impairment is not expected to impact brexucabtagene autoleucel expansion and cellular kinetics; hence no formal renal and hepatic impairment studies have been performed.

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Confirm with consultant before proceeding if there are signs of possible disease relapse.

Hepatic Impairment

No dose modification is recommended for hepatic dysfunction in those receiving fludarabine.

Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Cyclophosphamide	Greater than 50	100%
	30-50	75%
	Less than 30	High dose therapy not generally undertaken
Fludarabine	Greater than 70	100%
	50-69	Reduce dose by 20%
	30-49	Reduce dose by 40%
	Less than 30	Contraindicated -do not use fludarabine (consider alternative lymphodepletion regimen)

Other

Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of the cellular therapy and therefore, they should not be administered

as part of the pre-medication. However, corticosteroids may be used in the treatment of CRS or ICANS under consultant advice.

Cautions with Brexucel treatment:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active GVHD.

Regimen

Drug	Dose	Days	Route
Mesna	200 mg/m^2	-2	Intravenous bolus in 100ml sodium chloride 0.9% over 15 minutes to start at the same time as the cyclophosphamide infusion
Cyclophosphamide	900 mg/m^2	-2	Intravenous infusion in 1000ml sodium chloride over 60 minutes
Mesna	400 mg/m^2	-2	Oral for two doses taken at 2 and 6 hours after the start of the cyclophosphamide infusion
Fludarabine	25mg/m^2	-4, -3, -2	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Brexucel (brexucabtagene autoleucel)	Target dose: 1 x10^6 cells/ kg	0	Intravenous infusion of approx. 68ml within 30 minutes -see below

Dose Information

- Lymphodepleting regimen must only be started after availability of Brexucel is confirmed.
- Cyclophosphamide will be dose banded in accordance with national dose banding table (20mg/ml).
- Mesna (intravenous) will be dose banded according to the national dose bands (national dose banding table-mesna).
- Mesna (oral) will be rounded to the nearest 400mg (up if halfway)
- Fludarabine will be dose banded according to the national dose band (25mg/ml).
- A minimum period of time must elapse between last dose of conditioning chemotherapy and CAR-T infusion, and a longer period is required for patients with renal insufficiency. This information can be found on the patient's CAR-T cell schedule.
- CAR-T administration should not occur out of core hours or over the weekend.
- Brexucel has a target dose of 1 $x10^6$ cells/ kg. However, the maximum dose is 1 $x10^8$ cells for 100kg and above. The dose will vary between patients.

Administration Information

Brexucel

- Brexucel contains genetically modified human blood cells. Exposure to Brexucel must be avoided. Procedures for handling, personal protective equipment, spills and waste disposal must be adhered to.

- Brexucel cells are cryopreserved in a bag and require thawing prior to administration. -See WBMT SOP P-P-78.

- The cells must be administered gravimetrically and must **not** be administered via a volumetric pump, as there is no data to assure cell integrity is maintained via a pump.

- Administer via a giving set with a non-leukodepleting filter

- Cell infusion must begin within 30 minutes of thaw completion time.

- The infusion must be administered over a maximum of 30 minutes. The start and stop time of infusion must be documented.

- Gently agitate the bag during infusion to prevent cell clumping

- Once the full volume of Brexucel has been administered, rinse the tubing at the same rate with 0.9% sodium chloride solution to ensure all Brexucel is delivered. Once completed, the infusion bag and giving set must be disposed of in clinical waste, in accordance with Trust policy.

- If the bag is not fully administered, this must be documented and the consultant & pharmacist notified. The manufacturer must be informed and the remaining Brexucel should be discarded in clinical waste, with their approval.

- A GM spill-kit must be transported with Brexucel and available on the ward of administration. Local procedures must be followed in the event of a spill.

- Local guidelines on handling of waste of human-derived-materials must be followed in case of accidental exposure. Work surfaces and materials which have potentially been in contact with Brexucel must be decontaminated with approved disinfectants.

- See WBMT SOP P-P-78, P-P-79 and Policy P-G-1 for further administration direction.

Extravasation

- Cyclophosphamide – non-vesicant
- Mesna -neutral
- Fludarabine – non-vesicant

Additional Therapy

- Antiemetics
  - metoclopramide 10mg three times a day oral or intravenous
  - ondansetron 8mg twice a day oral or intravenous

- Anti-infective prophylaxis as follows:
  - Aciclovir 400mg oral twice a day
  - Fluconazole 100mg once a day
  - Pentamidine 300mg nebuliser during lymphodepletion. To be continued every 28 days until count recovery sufficient for co-trimoxazole use at consultant advice.
  - Posaconazole 300mg once daily if prolonged neutropenia or previous invasive fungal infection

- Gastric protection with a proton pump inhibitor or a H2 antagonist to commence on first day on lymphodepletion until platelet count >50 $x10^9$/L

- Mesna intravenous at the start of cyclophosphamide infusion.
  - Oral mesna 400mg/m^2 for two doses taken at 2 and 6 hours after the start of the cyclophosphamide infusion.

- Mouthwashes according to local or national policy on the treatment of mucositis. May include:
  - Nystatin 1ml four times a day
  - Sodium chloride 0.9% 10ml four times a day

- Prior to the administration of the Brexucel
  - Chlorphenamine 10mg intravenous
  - Paracetamol 1000mg oral

Pethidine 25mg intravenous can be administered under the supervision of a doctor for the treatment of rigors.

- Seizure prophylaxis may be considered due to the risk of neurotoxicity associated with Brexucel or if the patient has a history of seizures.
  - Levetiracetam 500mg twice daily orally commencing on the first day of lymphodepletion until day +30.
  - For weaning, this may then be reduced to 250mg orally twice daily for two weeks, then 250mg once daily for one week and then stopped.

- Tocilizumab must be prescribed as when required in advance of CAR-T infusion, in the event of CRS.
  - Tocilizumab 8mg/kg (maximum 800mg) intravenously 8-hourly if required. Maximum of four doses.
  - Four doses of tocilizumab must be available on the ward prior to infusion of Brexucel. Follow local procedures for administration.

- Tumour lysis syndrome (TLS) prophylaxis should be prescribed according to the individual patient TLS risk and at consultant review. This must start on the day of lymphodepletion and be re-reviewed on the day of Brexucel infusion. TLS prophylaxis may include:
  - Allopurinol 300mg oral once a day
  - Rasburicase 7.5mg intravenous injection once a day

References

1. Dosage Adjustments for Cytotoxics in Hepatic Impairment January 2009 University College London Hospitals
2. P-P-78 Wessex Blood and Marrow Transplant – CAR-T and IEC infusion procedure Version 1.3
3. P-P-79 Wessex Blood and Marrow Transplant – Immune effector cells including CAR-T cells policy Version 2.1
4. P-G-1 Wessex Blood and Marrow Transplant -Patient monitoring after CAR-T cell infusion Version 1.1
5. Pan UK Pharmacy Working Group for ATMPs -Supportive medications recommended for adults receiving licensed chimeric antigen receptor -T (CAR-T) cell therapy Version 1 May 2022
6. Pan UK Pharmacy Working Group for ATMPs -Medication restrictions for patients having CAR-T cell therapy Version 4 July 2022
7. Summary of Product Characteristics for Tecartus (Great Britain) (Gilead Sciences Ltd) -Last updated 1 February 2023
8. Summary of Product Characteristics for Fludarabine (Sanofi) -Last updated 18 March 2019
9. Summary of Product Characteristics for Cyclophosphamide (Sandoz Limited) -Last updated 6 April 2021

REGIMEN SUMMARY

ALL– BREXUCEL – CYCLOPHOSPHAMIDE (900) – FLUDARABINE (25)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describe the agents that must be prescribed on the in-patient chart or general electronic prescribing system.

Day – 4

1. Warning – Check supportive medication prescribed
   Administration instructions
   Please refer to the individual CAR-T schedule for full details of the required supportive medicines.
   1. Antibacterials in accordance with the individual CAR-T schedule
   2. Antifungals in accordance with the individual CAR-T schedule
   3. Antivirals in accordance with the individual CAR-T schedule
   4. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly when required in the event of CRS. Maximum four doses.
   5. Metoclopramide 10mg three times a day oral or intravenous
   6. Ondansetron 8mg twice a day oral or intravenous
   7. Nystatin mouthwash 1ml four times a day
   8. Sodium chloride 0.9% mouthwash 10ml four times a day
   9. Chlorphenamine 10mg intravenous when required as a premedication
   10. Paracetamol 1000mg when required as a premedication oral
   11. Furosemide 20mg four times a day when required for the treatment of fluid overload oral or intravenous
   12. Gastric protection
   13. Heparin line lock in accordance with Trust central venous access device management procedure
   14. Consider levetiracetam 500mg twice daily oral
   15. Mesna oral 400mg/m^2 for two doses to be taken at 2 and 6 hours after the start of the cyclophosphamide infusion on Day -2.
   16. Reminders for chemotherapy administration and Brexucel.

   Ensure patient has been issued with Brexucel treatment alert card.

2. Warning – Check blood transfusion status
   Administration instructions
   Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life. Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.

3. Fludarabine 25mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day – 3

4. Fludarabine 25mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day – 2

5. Mesna 200mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
   Administration Instructions
   The mesna infusion should begin at the same time as the cyclophosphamide infusion.
   Oral mesna 400mg/m^2 for two doses at 2 and 6 hours after the start of the cyclophosphamide infusion to be prescribed on in-patient chart. If the patient is vomiting please inform the medical staff and consider administering the mesna intravenously.

6. Cyclophosphamide 900mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

7. Fludarabine 25mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

Day 0

8. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to Brexucel. Check on the in-patient system if the patient has already received a dose

9. Paracetamol 1000mg oral
   Administration Instructions
   Administer 30 minutes prior to Brexucel. Check to ensure the patient has not already been administered paracetamol. The maximum dose is 4000mg/24 hours.

10. Brexucel (brexucabtagene autoleucel) 1 dose intravenous infusion
    Administration Instructions
    Prescribed dose for this patient: ……
    The cells must be administered **gravimetrically** and must not be administered via a volumetric pump.
    Administer via a giving set with a non-leukodepleting filter and primed with sodium chloride 0.9%.
    Brexucel infusion should commence within 30 minutes of thaw completion time.
    Infuse over a maximum of 30 minutes.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	August 2023	None	Madeleine Norbury Pharmacist	Hwai Jing Hiew Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

University Hospital Southampton NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.