Chemotherapy Protocol

CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY
Large B-cell Lymphoma (LBL)
AmB- AXICEL – CYCLOPHOSPHAMIDE (500) – FLUDARABINE (30)

Ambulatory Regimen
This regimen is for AMBULATORY CARE pathway use only and will only be available to prescribe at the Wessex Blood and Marrow Transplant Unit

Regimen

- Lymphoma - AmB - Axicabtagene ciloleucel – Cyclophosphamide (500) – Fludarabine (30)

Indication

- CAR-T therapy with Axicel (axicabtagene ciloleucel) for the treatment of adult patients with:
  - Relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.
  - Primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
- Lymphodepleting chemotherapy must be administered prior to Axicel. This protocol includes both lymphodepletion and CAR-T administration.
- Lymphodepleting chemotherapy is given in Ambulatory Care setting and CAR-T product is administered as inpatient.
- 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.
Axicel (axicabtagene ciloleucel)	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 Axicel manufacture.
- Echocardiogram and baseline measure of lung function must be taken prior to initiating lymphodepletion

Axicel

Nearly all patients treated with Axicel 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 Axicel 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 axicabtagene ciloleucel 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 Axicel treatment:

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

Regimen

1 cycle will be set in ARIA -this is the complete treatment course.

Drug	Dose	Days	Route
Cyclophosphamide	500 mg/m^2	-5, -4, -3	Intravenous bolus over 10 minutes
Fludarabine	30mg/m^2	-5, -4, -3	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Axicel (axicabtagene ciloleucel)	Target dose: 2 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 Axicel is confirmed.

- Cyclophosphamide will be dose banded in accordance with national dose banding table (20mg/ml).

- 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.

- Axicel has a target dose of 2 $x10^6$ cells/ kg. However, there is a dosing range of 1 x 10^6 – 2 x 10^6 cells/kg, with a maximum dose of 2 $x10^8$ cells. The dose will vary between patients.

Administration Information

Axicel

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

- Axicel 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 primed with sodium chloride 0.9%.

- 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 Axicel has been administered, rinse the tubing at the same rate with 0.9% sodium chloride solution to ensure all Axicel 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 Axicel should be discarded in clinical waste, with their approval.

- A GM spill-kit must be transported with Axicel 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 Axicel 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
- 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

- 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 Axicel
  - 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 Axicel or if the patient has a history of seizures.
  - Levetiracetam 500mg twice daily orally commencing on day 0 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 Axicel. 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 Axicel infusion. TLS prophylaxis may include:
  - Allopurinol 300mg oral once a day
  - Rasburicase 3mg intravenous injection once a day

References

1. Dosage Adjustments for Cytotoxics in Hepatic Impairment January 2009 University College London Hospitals
2. NWS Cancer institute -Large B-cell lymphoma axicabtagene ciloleucel cellular therapy protocol – Last updated 30 June 2022
3. P-P-78 Wessex Blood and Marrow Transplant – CAR-T and IEC infusion procedure Version 1.3
4. P-P-79 Wessex Blood and Marrow Transplant – Immune effector cells including CAR-T cells policy Version 2.1
5. P-G-1 Wessex Blood and Marrow Transplant -Patient monitoring after CAR-T cell infusion Version 1.1
6. 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
7. Pan UK Pharmacy Working Group for ATMPs -Medication restrictions for patients having CAR-T cell therapy Version 4 July 2022
8. Summary of Product Characteristics for Yescarta (Gilead Sciences Ltd) -Last updated 10 August 2022
9. Summary of Product Characteristics for Fludarabine (Sanofi) -Last updated 18 March 2019
10. Summary of Product Characteristics for Cyclophosphamide (Sandoz Limited) -Last updated 6 April 2021

REGIMEN SUMMARY

LBL-AmB- AXICEL – CYCLOPHOSPHAMIDE (500) – FLUDARABINE (30)

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. Supportive care should be prescribed on ARIA and given to the patient on day -5. Supportive care should be transcribed to the electronic inpatient prescribing system on admission to hospital.

Day – 5

1. 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.
   Ensure patient has been issued with Axicel treatment alert card.

2. Ondansetron 8mg oral or intravenous

3. Metoclopramide 10mg oral or intravenous

4. Cyclophosphamide 500mg/m^2 intravenous bolus over 10 minutes

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

6. Furosemide 20mg injection bolus
   Administration instructions – to be given if required for fluid overload.

7. Warning -Ensure take home medicines are supplied

Take home medicines – To be taken home on Day -5

8. Ondansetron oral 8mg once a day in the evening for 3 days starting on day -5 the first day of chemotherapy. Then, starting on day -2, take 8mg twice a day for 2 days.

9. Metoclopramide oral 10mg twice a day in the afternoon and evening for 3 days starting on day -5 the first day of chemotherapy. Then, starting on day -2, take 10mg three times a day for 2 days. Then take three times a day when required.
   Administration instructions –Please supply 28 tablets or an original pack as appropriate

10. Aciclovir 400mg oral twice a day for 28 days
    Administration Instructions Please supply 28 days or an original pack if appropriate.

11. Fluconazole 100mg oral once a day for 14 days
    Administration instructions – please supply 14 days with no stop date

12. Nystatin 1ml four times a day
    Administration instructions – please supply 1 x OP

13. Paracetamol 1000mg oral four times a day when required.
Administration instructions please supply 1 x OP

14. Gastric Protection
    Administration Instructions The choice of gastric protection is dependent on local formulary choice and may include;
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    - ranitidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

15. Sodium Chloride 0.9% oral rinse 10mL four times a day
    Administration instructions – pharmacy please supply 50 x 10mL pods

16. Thromboprophylaxis according to local formulary choice and patient schedule.
    Continued until platelets are less than $50x10^9$/L, or as directed by the consultant, according to local formulary choices:
    - enoxaparin 40mg once a day subcutaneous injection
    - heparin 5000units twice a day subcutaneous injection

    Please supply 28 days or nearest original pack size.

17. Tumour lysis prophylaxis according to patient schedule.
    - Allopurinol 300mg oral once a day
    - Rasburicase 3mg intravenous injection once a day

Day – 4

18. Ondansetron 8mg oral or intravenous

19. Metoclopramide 10mg oral or intravenous

20. Cyclophosphamide 500mg/m^2 intravenous bolus over 10 minutes

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

22. Furosemide 20mg injection bolus
    Administration instructions – to be given if required for fluid overload.

Day – 3

23. Ondansetron 8mg oral or intravenous

24. Metoclopramide 10mg oral or intravenous

25. Cyclophosphamide 500mg/m^2 intravenous bolus over 10 minutes

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

27. Furosemide 20mg injection bolus
    Administration instructions – to be given if required for fluid overload.

Day 0 – Inpatient schedule

28. Warning – See paper chart for IV fluids to be administered pre- CAR-T.

29. Chlorphenamine 10mg intravenous

Administration Instructions
Administer 30 minutes prior to Axicel. Check on the in-patient system if the patient has already received a dose

30. Paracetamol 1000mg oral

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

31. Axicabtagene ciloleucel 1 dose intravenous infusion

Administration Instructions
Prescribed dose for this patient: ……
This is also known as AXICEL
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 primed with sodium chloride 0.9%.
Axicel infusion should commence within 30 minutes of thaw completion time.
Infuse over a maximum of 30 minutes.

32. 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. Levetiracetam 500mg twice daily oral
14. Heparin line lock in accordance with Trust central venous access device management procedure
15. Reminders for chemotherapy administration and Axicel.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	November 2023	New document	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.