Chemotherapy Protocol

CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY
DLBCL/ FL – TISACEL – BENDAMUSTINE (90)

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

Regimen

- DLBCL/ FL - Tisagenlecleucel – Bendamustine (90)

Indication

- CAR-T therapy with Tisacel (Tisagenlecleucel) for the treatment of adult patients with:
  - Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
  - Relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

  (See separate B-cell Acute Lymphoblastic Leukaemia protocol for use in B-cell ALL)
- Lymphodepleting chemotherapy must be administered prior to Tisacel. This protocol includes both lymphodepletion and CAR-T administration.
- For autologous use only.
- This bendamustine lymphodepleting regimen may be considered with Tisacel, in preference to the *Tisacel – Fludarabine (25) – Cyclophosphamide (250),* if the patient has experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy.

Toxicity

Drug	Adverse Effect
Bendamustine	Transfusion related GVHD, gastro-intestinal disturbances, fatigue, insomnia, cardiac dysfunction, hypotension/ hypertension, hypersensitivity reactions, hypokalaemia.
Tisacel (tisagenlecleucel)	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 bendamustine 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 Tisagenlecleucel manufacture.
- Echocardiogram and baseline measure of lung function must be taken prior to initiating lymphodepletion

Tisacel

Nearly all patients treated with Tisacel 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 Tisacel 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 tisagenlecleucel 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

Drug	**Bilirubin (µmol/L)**	**Dose (% of original dose)**
Bendamustine	Less than 21	100%
	21-51	70%
	More than 51	No information

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Bendamustine	More than 10	100%
	10 or less	No information. Use with caution

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 Tisacel treatment:

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

Regimen

Drug	Dose	Days	Route
Bendamustine	90 mg/m^2	-4, -3	Intravenous infusion in sodium chloride 0.9% 500ml over 30-60 minutes
Tisacel (tisagenlecleucel) 1.2 x 10^6 – 6 x10^8 cells	Target dose: 0.6 to 6 x 10^8 cells	0	Intravenous infusion of one or more infusion bags within 30 minutes -see below

Dose Information

- Lymphodepleting regimen must only be started after availability of Tisacel is confirmed.

- Bendamustine will be dose banded according to the national dose band (2.5mg/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 a weekend.

- Tisacel has a target dose of 0.6 to 6 x 10^8 cells (non-weight based dosing). This is a dosing range and the dose will vary between patients.

Administration Information

Tisacel

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

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

- One individual treatment dose comprises 1 or more infusion bags. Each infusion bag may contain either 10-30ml (50ml bag) or 30-50ml (250ml bag) cell dispersion.

- 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 Baxter non-filtered giving set (/ latex-free without a leukocyte depleting filter) primed with sodium chloride 0.9%.

- The product should be administered immediately after thawing.

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

- Gently agitate the bag during infusion to prevent cell clumping.

- If the volume of Tisacel to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration.

- All contents of the infusion bag(s) should be infused. If more than one infusion bag has been received for the treatment dose, the next bag should only be thawed after the contents of the preceding bag have been infused.

- Once the full volume of Tisacel has been administered, rinse the tubing at the same rate with 10-30ml 0.9% sodium chloride solution to ensure all Tisacel is delivered. Once completed, the infusion bag(s) 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 Tisacel should be discarded in clinical waste, with their approval.

- A GM spill-kit must be transported with Tisacel 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 Tisacel must be decontaminated with approved disinfectants.

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

Bendamustine

Skin
Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis have been reported in patients who received bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

Potassium
In patients with cardiac dysfunction ensure the potassium remains above 3.5mmol/L during treatment with bendamustine.

Extravasation

- Bendamustine –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 Tisacel
  - 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 Tisacel or if the patient has a history of seizures.
  - Levetiracetam 500mg twice daily orally commencing on day 0 until day +30.
  - This may then be reduced to 250mg orally twice 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 Tisacel. 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 Tisacel infusion. TLS prophylaxis may include:
  - Allopurinol 300mg oral once a day
  - Rasburicase 7.5mg intravenous injection once a day

Additional Information

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, the potential for interaction with CYP1A2 exists. Always check for drug interactions.

References

1. Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group.J.Clin.Oncol. 2011 Sep 10;29(26):3559-66
2. P-P-78 Wessex Blood and Marrow Transplant – CAR-T and IEC infusion procedure Version 2
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 2.0
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 Kymriah cells dispersion for infusion (Novartis Pharmaceuticals UK Ltd) -Last updated 6 June 2023
8. Summary of Product Characteristics for Bendamustine hydrochloride 2.5mg/ml powder for concentrate for solution for infusion (Seacross Pharmaceuticals Ltd) -Last updated 18 November 2021
9. Renal Drug Database monograph for Bendamustine -Last updated 30 October 2017

REGIMEN SUMMARY

DLBCL/ FL – TISACEL – BENDAMUSTINE (90)

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. Levetiracetam 500mg twice daily oral
   15. Reminders for chemotherapy administration and Tisacel.

   Ensure patient has been issued with Tisacel treatment alert card.

2. Warning – Check blood transfusion status
   Administration instructions
   Patients treated with bendamustine 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. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Bendamustine may be given over 30-60 minutes

Day – 3

4. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Bendamustine may be given over 30-60 minutes

Day 0

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

6. Paracetamol 1000mg oral
   Administration Instructions

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

7. Tisacel (Tisagenlecleucel) 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 Baxter non-leukodepleting filter latex-free giving set primed with sodium chloride 0.9%.
Tisacel infusion should be infused within 30 minutes of thaw completion time.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2023	None	Madeleine Norbury Pharmacist	Dr Rob Lown 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.