

Chemotherapy Protocol

LYMPHOMA

LOMUSTINE-CYTARABINE-ETOPOSIDE (split)-MELPHALAN

(LEAM)

Ambulatory Regimen

This regimen is for AMBULATORY CARE pathway use only and will only be available to prescribe at units which carry out autograft transplantation.

[Regimen](#)

Lymphoma – AmB-LEAM (split)-Lomustine-Cytarabine-Etoposide-Melphalan

[Indication](#)

- Conditioning for autologous peripheral blood stem cell transplant (PBSCT) / bone marrow transplant in individuals with either Non Hodgkin Lymphoma (NHL) or Hodgkin Lymphoma

[Toxicity](#)

Drug	Adverse Effect
Lomustine	Pulmonary toxicity
Cytarabine	CNS toxicity, conjunctivitis, flu-like syndrome, pulmonary toxicity, gastro-intestinal toxicity
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Melphalan	Gastro-intestinal disturbances, stomatitis

Patients treated with LEAM are at risk of transfusion-associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive irradiated blood products for the 1 week prior to harvest and for at least 12 weeks after the transplant has taken place. Patients with Hodgkin lymphoma carry a lifelong risk of graft versus host disease and must always receive irradiated blood products. Local blood transfusion departments must be notified as soon as a diagnosis is made and the patient must be issued with an alert card to carry with them at all times.

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

Monitoring

Drugs

- FBC, LFTs (including albumin) and U&Es prior to day one of treatment
- EDTA or calculated creatinine clearance prior to each melphalan infusion
- Monitor the fluid balance during the administration of melphalan, including throughout the administration of the pre and post hydration. Ensure the urine output is more than 250ml/hour immediately prior to the administration of melphalan

Dose Modifications

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

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Treatment will be given regardless of blood results.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. Irradiated blood products must be used.

Hepatic Impairment

Please note that the approach may be different if abnormal liver function tests are due to disease involvement.

Drug	Bilirubin μmol/L		AST/ALT units/L	Dose (% of original dose)
Lomustine	N/A		N/A	No dose adjustment necessary
Cytarabine	more than 34			50% The dose may be escalated dependent on toxicity
Etoposide	30-51	or	60-180	Consider dose reducing to 50%
	more than 51	or	more than 180	Clinical decision
Melphalan	N/A		N/A	No dose adjustment necessary

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Lomustine	more 60	100%
	45-60	75%
	30-<45	50%
	less than 30	Clinical decision
Cytarabine	N/A	No dose adjustment necessary
Etoposide	more than 50	100%
	15-50	75%
	less than 15	50%
Melphalan	more than 50	100%
	30-50	75%
	less than 30	Clinical decision

Other

Lomustine

It may be necessary to reduce the dose of lomustine in patients with reduced pulmonary function. Lomustine dose reductions in this situation are to be made at the discretion of the consultant oncologist/haematologist only.

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

Regimen

1 cycle will be set in Aria

Drug	Dose	Days	Administration
Lomustine	200mg/m ²	-6	Oral
Cytarabine	1600 mg/m ² (8 doses of 200mg/m ² every 12 hours)	200mg/m ² BD Every 12 hours at 9am and 9pm. -5,-4,-3,-2 (8 doses total)	Administer via CADD Solis VIP pump. Each CADD cassette contains 8 doses (240ml total volume). Connect cassette on day -5 and disconnect on day -1 (AM) Each dose: IV infusion of 200mg/m ² in 30ml of sodium chloride 0.9% over 15 minutes at 120ml/hr.
Etoposide	200mg/m ²	-5,-4,-3,-2	Intravenous infusion in 2000ml sodium chloride 0.9% over 120 minutes (this will be administered as two infusions of 100mg/m ² in 1000ml sodium chloride 0.9% over 60 minutes administered

			sequentially)
Melphalan	140mg/m ²	-1	Intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Dose Information

- Lomustine will be dose rounded to the nearest 40mg (down if halfway)
- Cytarabine will be dose banded in accordance with the national dose bands (100mg/ml)
- Etoposide will be dose banded in accordance with the national dose bands (20mg/ml)
- The melphalan dose will be dose rounded to the nearest 10mg (down if halfway). The National Dose Banding Team have advised not to use dose banding tables for this product in view of the 90 minute expiry (must be made locally for individual patient), the 50mg vial size and frequent stock shortages.

Administration Information

CADD pump

- Total 8 doses provided as one infusion bag in cassette of CADD pump, to be administered as intermittent infusion on day -5 to -2.
- Sodium chloride 0.9% 100ml to be run as continuous infusion to keep CADD infusion line patent.
- Administer concurrently with cytarabine via Y-site with at 0.5 mL/hour on days -5 to -1.

Extravasation

- Cytarabine – non-vesicant
- Etoposide – irritant
- Melphalan – irritant

Other

- Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes.
- Ensure the urine output is more than 250ml/hour immediately prior to the administration of melphalan

Additional Therapy

This regimen is to be administered in the ambulatory setting.

Please ensure all supportive and take home medicines are prescribed on the in-patient chart or general electronic prescribing system on admission. Please refer to the transplant schedule for each individual patient.

- **Antiemetics**

Starting 15-30 minutes prior to chemotherapy

- dexamethasone 2mg twice a day for 10 days oral or intravenous starting on day -6 of the cycle
- metoclopramide 10mg three times a day for 10 days oral or intravenous starting on day -6 of the cycle
- ondansetron 8mg twice a day for 10 days oral or intravenous
- aprepitant 125mg once only orally on the day of the melphalan infusion then 80mg once a day for the subsequent two days

- **Anti-infectives**

- aciclovir 400mg oral twice a day until day +180
- ciprofloxacin 250mg oral twice a day from day+1 (stop when neutrophils are greater than 1)
- pentamidine 300mg by nebuliser prior to discharge
- co-trimoxazole 960mg once a day on Monday, Wednesday and Friday (start from 28 days post discharge, if neutrophils are greater than 1 and platelets are greater than 50, and continue until day +180)
- fluconazole 100mg once a day oral (stop when neutrophils are greater than 1 unless the patient remains on corticosteroids)
- nystatin suspension 1ml four times a day oral (stop when neutrophils are greater than 1 unless the patient remains on corticosteroids)

- **Thromboprophylaxis**, continued until platelets are less than $50 \times 10^9/L$, or as directed by the consultant, according to local formulary choices;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

- **Growth factors** such as filgrastim biosimilar 30million units (300mcg) once a day subcutaneous from day +5 (stop when neutrophils are greater than $1 \times 10^9/L$ for at least 24 hours, or greater than 3 on any occasion)

- **Hormone replacement**

In menstruating women consider norethisterone 5mg three times a day oral to prevent menstruation. This may be stopped when the platelets are more than $50 \times 10^9/L$.

- **Mouthcare**

Commence oral cryotherapy approximately 15mins prior to melphalan infusion, replenishing to cover melphalan infusion and 75 mins afterwards.

Mouthcare for the prophylaxis or treatment of mucositis in accordance with local or national guidelines.

- **Gastric protection** with a proton pump inhibitor or a H₂ antagonist according to local formulary choice;
 - 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
- **Hydration**
 - Encourage 3L oral fluids daily. If ambulatory patients are unable to maintain this (e.g. due to nausea), they should be admitted for intravenous hydration.
 - Intravenous hydration before and after melphalan infusion should be prescribed on inpatient prescribing system or using paper proforma (Appendix 1)

Before and after melphalan infusion

- Encourage oral hydration at least 1 litre between 8pm and 8am the night before melphalan infusion.

0830hrs	Contact pharmacy on ext 5037 to inform them that the patient is present. Confirm that they have melphalan prescription (on ARIA). Request melphalan infusion to be on the ward by 11:30hrs. Start fluid chart and daily weights. Start fluid 1000ml sodium chloride 0.9% intravenous infusion over 90 minutes
0915hrs	Administer anti-emetics and supportive medication as per ARIA prescription
0930hrs	20mg furosemide intravenous bolus Warning – Check hydration and fluid balance
1000hrs	1000ml sodium chloride 0.9% intravenous infusion over 90 minutes
1030hrs	20mg furosemide intravenous bolus Measure urine output since 0900hrs <ul style="list-style-type: none"> - If more than 500ml continue with melphalan infusion - If less than 500ml give second furosemide 20mg dose

	intravenous bolus check urine output since 0900hrs again at 1100hrs: <ul style="list-style-type: none"> ○ if more than 500ml go ahead with melphalan ○ if less than 500ml contact the prescriber.
1130hrs	Give melphalan intravenous infusion over thirty minutes (This product has a short expiry so adhering to set timing is essential)
1200hrs	1000ml sodium chloride 0.9% intravenous infusion over 120 minutes
Thereafter	Encourage 2L oral fluid intake over subsequent 12 hours

Instruct patient to take all supportive medications with particular reference to antiemetics

Advise patient to drink 1000 ml of oral fluids over the evening

Emergency contact details for AOS given to patient

Patient and carer to return to C7 at 08:30 on day 0

- The day after melphalan infusion (Day 0):

0830hrs - 1000ml sodium chloride 0.9% intravenous infusion over 480 minutes then restart routine intravenous fluids

[Additional Information](#)

- Irradiated blood products must be used
- Autologous stem cells/ bone marrow will be infused on day 0, at least 24 hours after the melphalan infusion

References

1. Mills W, Chopra R, McMillan A et al. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol (1995);13(3): 588-95
2. Kelsey P, Pearce R, Perry J et al. Substituting carmustine for lomustine is safe and effective in the treatment of relapsed or refractory Lymphoma – a retrospective study from the BSBMT (BEAM versus LEAM)
3. Stabilis (manufacturers data) Stability of Alexan "Ebewe" infusion solutions. Ebewe Pharma 2007 from <http://www.stabilis.org/> (Date accessed: 03/07/23).

REGIMEN SUMMARY

AmB-LEAM (split)-Lomustine-Cytarabine-Etoposide (split)-Melphalan

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which 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 -6. Supportive care should be transcribed to the electronic inpatient prescribing system on admission to hospital.

Day -6

1. Warning – Check blood transfusion status

Administration Instructions

Patients treated with LEAM 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.

2. Dexamethasone 2mg oral or intravenous

3. Ondansetron 8mg oral or intravenous

4. Metoclopramide 10mg oral or intravenous

5. Lomustine 200mg/m² once a day for one day oral

Administration Instructions

This should be given before midday.

Swallow whole with a full glass of water. Do not open or chew

6. Warning -Ensure take home medicines are supplied

Take home medicines

7. Aprepitant 80mg once a day oral for 2 days starting the day after melphalan (i.e. start day 0).

8. Dexamethasone 2mg once a day in the afternoon for 6 days starting on day -6 the day of lomustine. Then take 2mg twice a day for 4 days.

9. Ondansetron 8mg once a day in the evening for 6 days starting on day -6 the day of lomustine. Then take 8mg twice a day for 4 days.

10. Metoclopramide 10mg twice a day in the afternoon and evening for 6 days starting on day -6 the day of lomustine. Then take 10mg three times a day for 4 days.

Administration instructions –Please supply 28 tablets or an original pack as appropriate

11. Aciclovir 400mg three times a day for 28 days

Administration Instructions Please supply 28 days or an original pack if appropriate.

12. Ciprofloxacin 250mg twice a day starting on day +1 (2 days after melphalan administration) for 14 days

Administration Instructions Please supply 14 days with no stop date

13. Fluconazole 100mg oral once a day for 14 days

Administration instructions – please supply 14 days with no stop date

14. Nystatin 1ml four times a day

Administration instructions – please supply 1 x OP

15. 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.

16. Sodium Chloride 0.9% oral rinse 10mL four times a day

Administration instructions – pharmacy please supply 50 x 10mL pods

17. Thromboprophylaxis according to local formulary choice

Continued until platelets are less than $50 \times 10^9/L$, or as directed by the consultant, according to local formulary choices:

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

Day -5

18. Dexamethasone 2mg oral or intravenous

19. Ondansetron 8mg oral or intravenous

20. Metoclopramide 10mg oral or intravenous

21. Warning – Cytarabine delivered via one CADD.

Administration Instructions

Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) via CADD pump. Sodium chloride infusion must be administered concurrently.

22. Cytarabine $1600\text{mg}/\text{m}^2$ intravenous infusion in 240ml sodium chloride 0.9% as intermittent infusions via CADD pump.

Administration Instructions

One dose: Cytarabine $200\text{mg}/\text{m}^2$ in 30ml sodium chloride 0.9% over 15 minutes at 120ml/hour.

Cytarabine is administered TWICE a day at 12 hour intervals (0900 and 2100) on days -5 to -2 (8 doses in total).

Connect cassette on day -5 and disconnect on day -1 (AM).

23. Sodium Chloride 0.9% 100ml continuous infusion at 0.5ml/hr.

Administration Instructions

Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr on Days -5 to -1.

To be connected via Y-site with CADD pump to maintain line patency.

Disconnect folfusor at the same time as disconnecting CADD cassette

24. Warning – Etoposide is TWO infusions

Administration Instructions

Due to the stability of etoposide the total dose of $200\text{mg}/\text{m}^2$ will be split into two infusions of $100\text{mg}/\text{m}^2$ in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes.

25. Etoposide 100mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes.

26. Etoposide 100mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes

Day -4, Day -3, Day -2

27. Dexamethasone 2mg oral or intravenous

28. Ondansetron 8mg oral or intravenous

29. Metoclopramide 10mg oral or intravenous

30. Warning – Etoposide is TWO infusions

Administration Instructions

Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes.

31. Etoposide 100mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes.

32. Etoposide 100mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

Due to the stability of etoposide the total dose of 200mg/m² will be split into two infusions of 100mg/m² in 1000ml sodium chloride 0.9% over 60 minutes. The two infusions are given sequentially, the second is started as soon as the first infusion is complete. The total duration of etoposide administration is 120minutes

Day -1

33. Warning – Check CADD pump and sodium chloride pump removal

34. Aprepitant 125mg oral

35. Dexamethasone 2mg oral or intravenous

36. Ondansetron 8mg oral or intravenous

37. Metoclopramide 10mg oral or intravenous

38. Furosemide 20mg injection bolus

Administration instructions – to be given if required for fluid overload.

39. Warning – Check hydration and fluid balance

Administration Instructions

See separate fluid prescription for the pre hydration:

The evening before melphalan infusion (to be completed by 0930 on the morning of the infusion)

Sodium chloride 0.9% with potassium chloride 27mmol 1000ml

The day of melphalan infusion:

0830hrs Contact Pharmacy on ext 5037 to inform them that the patient is present.

Confirm that they have melphalan prescription (on ARIA) ☐ Request melphalan to be on the ward by 11:30 ☐

Start fluid balance sheet and start daily weight measurement

0915hrs Administer anti-emetics and supportive medication as per ARIA prescription

0930hrs 20mg furosemide intravenous bolus

1000hrs 1000ml sodium chloride 0.9% intravenous infusion over 90 minutes

1030hrs 20mg furosemide intravenous bolus

Measure urine output since 0900hrs

If more than 500ml continue with melphalan infusion

If less than 500ml give second furosemide 20mg intravenous bolus dose and check urine output since 0900hrs again at **1100hrs**:

if more than 500ml go ahead with melphalan

if less than 500ml contact the prescriber.

1130hrs – give melphalan intravenous infusion over thirty minutes (this product has a short expiry so adhering to set timing is essential)

1200hrs - 1000ml sodium chloride 0.9% intravenous infusion over 120 minutes

40. Time– Administer melphalan at 1130hrs

41. Melphalan 140mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Administration Instructions - see separate fluid prescription for the post hydration requirements

Day 0

42. Chlorphenamine 10mg Intravenous bolus

Administration instructions – to be given pre stem cell infusion

43. Paracetamol 1000mg Tablet Oral

Administration instructions – to be given pre stem cell infusion

44. Stem Cell Return – see separate chart

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	August 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 -Wessex Blood and Marrow Transplant

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.