

Chemotherapy Protocol

HAEMATOLOGY – HSCT ALLOGRAFT

ALEMTUZUMAB-BUSULFAN (10 doses)-FLUDARABINE-METHOTREXATE (GvHD)

Volunteer Unrelated Donor (VUD) CONDITIONING

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

Regimen

- HSCT – Alemtuzumab-Busulfan(10)-Fludarabine (VUD)-Methotrexate (GvHD)

Indication

- Conditioning for reduced intensity haematopoietic stem cell transplant (HSCT) with a volunteer unrelated donor.

Toxicity

Drug	Adverse Effect
Alemtuzumab	Infusion-related reaction (fever, hypotension, chills, rashes), allergic/anaphylactic reaction, anaemia, leucopenia, thrombocytopenia.
Busulfan	Seizures, asthenia, chills, fever, chest pain, oedema, headache, tachycardia, headache.
Fludarabine	Vomiting, diarrhoea, nausea, fever, malaise.
Methotrexate	Headache, back or shoulder pain, fever, mucositis

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

Monitoring

Drugs

- FBC, LFTs and U&Es prior to initiating treatment
- GFR measurement done by Nuclear Medicine prior to first day of treatment
- LFTs and creatinine prior to methotrexate
- Evaluate mucositis prior to administration of methotrexate

Dose Modifications

The dose modifications listed are for liver and renal function. Dose adjustments may be necessary for other co-morbidities as well which will involve discussions with the Transplant Director or senior Transplant Clinician.

Haematological

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

Hepatic Impairment

No studies have been done in patients with hepatic dysfunction receiving alemtuzumab. Dose adjustment is a clinical decision but is unlikely to require reduction.

Caution is recommended in patients with severe hepatic impairment receiving busulphan. Consider dose reduction in patients with raised liver enzymes.

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

Serum Bilirubin level $\mu\text{mol/L}$	Methotrexate dose
less than or equal to 35	100% dose
36-50	50% dose
51-85	25% dose
greater than 85	omit dose

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Alemtuzumab	No studies have been conducted. No dose adjustment is recommended in renal impairment	
Busulfan	No dose adjustment is recommended in renal impairment	
Fludarabine	greater than 70ml/min	100%
	30 to 70ml/min	adjust towards 50%
	less than 30ml/min	contraindicated

Serum Creatinine level $\mu\text{mol/L}$	Methotrexate dose
less than or equal to 145	100% dose
146-165	50% dose
166-180	25% dose
greater than 180	omit dose

Other

Dose adjustments may be necessary for mucositis caused by the transplant conditioning schedule. If mucositis is NCI-CTC grade 3 or more on day +11 the methotrexate dose may be reduced or omitted. This should be discussed with the patient's transplant clinician.

Regimen

Drug	Dose	Days	Administration
Alemtuzumab	10mg	-8	Intravenous infusion in 100ml sodium chloride 0.9% over 6 to 8 hours
	20mg	-7, -6	
Busulfan	0.8mg/kg every 6 hours for 10 doses starting at 1000hrs day -8, finishing at 1600hrs day -6	-8,-7,-6	Intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% and given over 2 hours
Fludarabine	30mg/m ²	-7, -6, -5, -4, -3	Intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
GvHD Prophylaxis (ciclosporin prescribed separately on the in-patient prescribing system)			
Methotrexate	10mg/m ²	+3	Intravenous bolus over 5 minutes
Methotrexate	5mg/m ²	+6, +11	Intravenous bolus over 5 minutes

Dose Information

- Busulfan dose is rounded to nearest 3mg (down if halfway) in view of short expiry (15hours) and high level of toxicity of product.
- Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics.
- Fludarabine doses are rounded to the nearest 2.5mg (down if halfway). The national tables are not applicable in the transplant setting.
- Methotrexate will be dose rounded to the nearest 2.5mg (down if halfway). The most common doses are 5mg, 7.5mg, 10mg, 12.5mg and 15mg. Doses will normally be supplied as two individual syringes containing different amounts to allow dose adjustment on the day of administration that may fall on a weekend.

Administration Information

Extravasation

- Alemtuzumab – non-vesicant
- Busulfan – non-vesicant
- Fludarabine – non-vesicant

- Methotrexate – non-vesicant

Other

- It is the responsibility of the nurse administering the dose to ensure that the patient's transplant clinician has checked the bilirubin, creatinine and mucositis of the patient and documented the dose to be administered before each methotrexate dose is given.

Additional Therapy

- Antiemetics
 - metoclopramide 10mg three times a day oral or intravenous
 - ondansetron 8mg twice a day oral or intravenous
- Prior to the administration of the alemtuzumab and stem cells
 - chlorphenamine 10mg intravenous
 - paracetamol 1000mg oral

Pethidine intravenous 12.5-25mg can be administered under the supervision of a doctor for the treatment of alemtuzumab induced rigors.

- Antimicrobials should be prescribed according to the individual transplant schedule and may include;
 - gut decontamination
 - antifungal according to consultant preference
 - antivirals
 - antibacterials
- Clonazepam 500microgram oral twice a day to start the night before busulfan and continue until 3 days after last dose.
- Mouthwashes including;
 - nystatin 1ml four times a day
 - sodium chloride 0.9% 10ml four times a day
- Graft versus host disease (GVHD) prophylaxis is prescribed in accordance with the individual transplant schedule;
 - ciclosporin oral or intravenous
 - methotrexate intravenous bolus on days +3, +6 and +11 (included on ARIA)
- Calcium folinate 30mg (15mg/m² is the precise dose but in practice 30mg is given) intravenous bolus given six hourly for four doses starting 24 hours after each methotrexate bolus (+4, +7, +12)

Coding

- Procurement – X71.5
- Delivery – N/A

References

1. P-P-54 Wessex Blood and Marrow Transplant – Dose adjustments for stem cell transplant conditioning agents policy. Version 1.0
2. P-P-20 Wessex Blood and Marrow Transplant – Reduced toxicity conditioning regimens policy Version 1.2
3. Dosage Adjustments for Cytotoxics in Hepatic Impairment January 2009 University College London Hospitals
4. Summary of Product Characteristics for Alemtuzumab (Lemtrada) – last updated 28 Jun 2016
5. Summary of Product Characteristics for Fludarabine (Sandoz) – last updated 16 Jul 2015
6. Summary of Product Characteristics for Busulfan (Accord) – last updated 18 May 2016
7. Handbook of Systemic Treatments for Cancer 7th Edition 2012 Lilly Oncology
8. [National Dose Banding Tables](#)

REGIMEN SUMMARY

Alemtuzumab-Busulfan (10)-Fludarabine (VUD)-Methotrexate (GvHD)

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 -8

1. Warning – Check supportive medication prescribed

Administration instructions

Please refer to the individual transplant schedule for full details of the required supportive medicines

1. Antibacterials, including gut decontamination, in accordance with the individual transplant schedule
2. Antifungals in accordance with the individual transplant schedule
3. Antivirals in accordance with the individual transplant schedule
4. Clonazepam 500microgram twice a day to start the evening before the busulphan and continued until three days after the last dose of busulphan
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. Ciclosporin in accordance with the individual transplant schedule
10. Calcium folinate 30mg intravenous bolus six hourly for four doses on days +4, +7, +12
11. Chlorphenamine 10mg intravenous when required as a premedication
12. Pethidine 12.5-25mg intravenous when required for alemtuzumab rigors
13. Paracetamol 1000mg when required as a premedication oral
14. Furosemide 20mg four times a day when required for the treatment of fluid overload oral or intravenous
15. Gastric protection
16. Heparin line lock in accordance with Trust central venous access device management procedure
17. Reminders for chemotherapy administration including methotrexate and stem cells

2. Time – Administer busulfan at 1000

3. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours.

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

4. Chlorphenamine 10mg intravenous

Administration Instructions

Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.

5. Paracetamol 1000mg oral

Administration Instructions

Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.

6. Alemtuzumab 10mg intravenous infusion in 100ml sodium chloride 0.9% over 6 hours.

Administration Instructions

Alemtuzumab should be started 30 minutes after a premedication of chlorphenamine 10mg intravenous and paracetamol 1000mg oral

If rigors occur the infusion should be slowed, alemtuzumab may be administered over 8 hours. Administer pethidine 12.5mg-25mg intravenous under the supervision of a doctor

7. Time— Administer busulfan at 1600
8. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours
Administration Instructions
Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.
9. Time – Administer busulfan at 2200hrs
10. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours
Administration Instructions
Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

Day -7

11. Time – Administer busulfan at 0400hrs
12. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours
13. Administration Instructions
Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.
14. Fludarabine 30mg/m² intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
15. Time – Administer busulfan at 1000hrs
16. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours
Administration Instructions
Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.
17. Chlorphenamine 10mg intravenous
Administration Instructions
Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.
18. Paracetamol 1000mg oral
Administration Instructions
Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.
19. Alemtuzumab 20mg intravenous infusion in 100ml sodium chloride 0.9% over 6 hours
Administration Instructions
Alemtuzumab should be started 30 minutes after a premedication of chlorphenamine 10mg intravenous and paracetamol 1000mg oral

If rigors occur the infusion should be slowed, alemtuzumab may be administered over 8 hours. Administer pethidine 12.5mg-25mg intravenous under the supervision of a doctor

20. Time – Administer busulfan at 1600

21. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours.

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

22. Time – Administer busulfan to start at 2200

23. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours.

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

Day – 6

24. Time – Administer busulfan at 0400

25. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

26. Fludarabine 30mg/m² intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

27. Time – Administer busulfan at 1000hrs

28. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

29. Chlophenamine 10mg intravenous

Administration Instructions

Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.

30. Paracetamol 1000mg oral

Administration Instructions

Administer 15-30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered.

31. Alemtuzumab 20mg intravenous infusion in 100ml sodium chloride 0.9% over 6 hours

Administration Instructions

Alemtuzumab should be started 30 minutes after a premedication of chlorphenamine 10mg intravenous and paracetamol 1000mg oral

If rigors occur the infusion should be slowed, alemtuzumab may be administered over 8 hours. Administer pethidine 12.5mg-25mg intravenous under the supervision of a doctor

32. Time – Administer busulfan at 1600

33. Busulfan 0.8mg/kg intravenous infusion diluted to 0.5mg/ml in sodium chloride 0.9% over 2 hours.

Administration Instructions

Busulphan administration should start at the stated time

Busulfan dosing in obese patients dosing is based on adjusted ideal body weight as recommended in the Summary of Product Characteristics available.

Day – 5

34. Fludarabine 30mg/m² intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

Day -4

35. Fludarabine 30mg/m² intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

Day – 3

36. Fludarabine 30mg/m² intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

Day +3

37. Warning – Check calcium folinate prescribed

Administration instructions

Ensure that calcium folinate is prescribed on the inpatient prescribing system. Prescribe 30mg intravenous bolus every 6 hours for 4 doses starting 24hours after the methotrexate, at 1700hrs, 2300hrs, 0500hrs, 1100hrs (days +4, +7, +12)

38. Time – Administer methotrexate at 1700

39. Methotrexate 10mg/m² intravenous bolus over 5 minutes

Administration Instructions

Administer at 1700

Check the patient notes to confirm the dose to be prescribed

It is the responsibility of the nurse administering the dose to ensure that the patient's transplant clinician has checked the bilirubin, creatinine and mucositis of the patient and documented the dose to be given before each methotrexate dose is administered.

Methotrexate will be dose rounded to the nearest 2.5mg (down if halfway). The most common doses are 5mg, 7.5mg, 10mg, 12.5mg and 15mg. Doses will normally be supplied as two individual syringes containing different amounts to allow dose adjustment on the day of administration that may fall on a weekend.

Day +6, +11

40. Warning – Check calcium folinate prescribed

Administration instructions

Ensure that calcium folinate is prescribed on the inpatient prescribing system. Prescribe 30mg intravenous bolus every 6 hours for 4 doses starting 24hours after the methotrexate, at 1700hrs, 2300hrs, 0500hrs, 1100hrs (days +4, +7, +12)

41. Time – Administer methotrexate at 1700

42. Methotrexate 5mg/m² intravenous bolus over 5 minutes

Administration Instructions
Administer at 1700

Check the patients notes to confirm the dose to be prescribed

It is the responsibility of the nurse administering the dose to ensure that the patient's transplant clinician has checked the bilirubin, creatinine and mucositis of the patient and documented the dose to be given before each methotrexate dose is administered.

Methotrexate will be dose rounded to the nearest 2.5mg (down if halfway). The most common doses are 5mg, 7.5mg, 10mg, 12.5mg and 15mg. Doses will normally be supplied as two individual syringes containing different amounts to allow dose adjustment on the day of administration that may fall on a weekend.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Aug 2017	None	Harriet Launders Pharmacist Dr Deborah Wright Pharmacist	Dr Deborah Richardson Consultant Haematologist Dr Kate Hill Associate Specialist Haematology

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 that occur as a result of following these guidelines.