**Chemotherapy Protocol**

## HAEMATOLOGY – HSCT ALLOGRAFT

**ALEMTUZUMAB-BUSULFAN (12 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(12)-Fludarabine (VUD)-Methotrexate (GvHD)

### Indication

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

### Toxicity

| Drug | Adverse Effect |
|---|---|
| Alemtuzumab | Infusion-related reaction (fever, hypotension, chills, rashes), allergic/anaphylactic reaction, aneamia, 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, mucosotis |

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 µmol/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 µmol/L** | **Methotrexate dose** |
|---|---|
| less than or equal to145 | 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 **12 doses** starting at 1000hrs day -8, finishing at 0400hrs day -5 | -8,-7,-6, -5 | 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 alemtuzumb (on ARIA) 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/$m^2$ 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 (12)-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 premedcation 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. 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.

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/m$^2$ 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
17. 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.

18. 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.

19. 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.

20. 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

21. Time – Administer busulfan at 1600

22. 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.

23. Time – Administer busulfan at 2200

24. 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**

25. Time – Administer busulfan at 0400

26. 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.

27. Fludarabine 30mg/$m^2$ intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

28. Time – Administer busulfan at 1000hrs

29. 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.

30. 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.

31. 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.

32. 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

33. Time – Administer busulfan at 1600

34. 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.

35. Time – Administer busulfan at 2200

36. 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**

37. Time – Administer busulfan at 0400

38. 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.

39. Fludarabine 30mg/$m^2$ intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

**Day -4**

40. Fludarabine 30mg/$m^2$ intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

**Day – 3**

41. Fludarabine 30mg/$m^2$ intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes

**Day +3**

42. 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)

43. Time – Administer methotrexate at 1700

44. Methotrexate 10mg/$m^2$ 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

45. 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)

46. Time – Administer Methotrexate at 1700

47. Methotrexate 5mg/$m^2$ 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<br>Pharmacist<br><br>Dr Deborah Wright<br>Pharmacist | Dr Deborah Richardson<br>Consultant<br>Haematologist<br><br>Dr Kate Hill<br>Associate Specialist<br>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.