Chemotherapy Protocol

HAEMATOLOGY – HSCT ALLOGRAFT

ALEMTUZUMAB-FLUDARABINE-MELPHALAN-METHOTREXATE (GvHD)

RELATED DONOR CONDITIONING

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

Regimen

- HSCT – Alemtuzumab-Fludarabine–Melphalan (Related Donor)-Methotrexate (GvHD)

Indication

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

Toxicity

Drug	Adverse Effect
Alemtuzumab	Infusion-related reaction (fever, hypotension, chills, rashes), allergic/anaphylactic reaction, aneamia, leucopenia, thrombocytopenia
Fludarabine	Vomiting, diarrhoea, nausea, fever, malaise
Melphalan	Nausea, vomiting, diarrhoea, stomatitis and alopecia.
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 which will involve discussions with the Transplant Director or senior Transplant Clinician.

Haematological

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

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

No information available is available on melphalan in hepatic impairment. No dose changes recommended.

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	
Fludarabine	greater than 70ml/min	100%
	30 to 70ml/min	Adjust towards 50%
	less than 30ml/min	contraindicated
Melphalan	greater than 50ml/min	100%
	30 – 50ml/min	50%
	less than 30 ml/min	Not generally recommended

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	-7	Intravenous infusion in 100ml sodium chloride 0.9% over 6 to 8 hours
	20mg	-6	
Fludarabine	30mg/m^2	-7, -6, -5, -4, -3	Intravenous infusion in 50ml sodium chloride 0.9% over 30 minutes
Melphalan	140mg/m^2	-2	Intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
GvHD Prophylaxis (ciclosporin prescribed separately on the in-patient prescribing system)			
Methotrexate	5mg/m^2	+3, +6, +11	Intravenous bolus over 5 minutes

Dose Information

- The melphalan dose is rounded to nearest 10mg. 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.
- Fludarabine doses are rounded to the nearest 2.5mg (down if halfway).
- 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
- Fludarabine – non-vesicant
- Melphalan – 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

  Prior to alemtuzumab, fludarabine and melphalan;

  - metoclopramide 10mg three times a day oral or intravenous
  - ondansetron 8mg twice a day oral or intravenous

  Prior to melphalan

  - aprepitant 125mg once a day prior to melphalan followed by 80mg once a day for the two days afterwards

- Prior to the administration of the alemtuzumb and stem cells

  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

  Pethidine 12.5mg-25mg intravenous 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

- Intravenous hydration before and after melphalan infusion prescribed on inpatient prescribing system (instruction) and using paper proforma (appendix 1)

  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

  0900hrs Start fluid chart and daily weights. Contact pharmacy to make melphalan infusion for delivery to ward at 1045hrs

  0930hrs 1000ml sodium chloride 0.9% intravenous infusion over 90 minutes

  1010hrs 20mg furosemide intravenous bolus

  1045hrs Measure urine output since 0900hrs

  - if more than 500ml continue with melphalan infusion

- if less than 500ml give furosemide 20mg intravenous, check urine output since 0900hrs again at **1100hrs**:

  - if more than 500ml go ahead with melphalan
  - if less than 500ml contact the prescriber.

1100hrs – give melphalan intravenous infusion over thirty minutes (this product has a short expiry so adhering to set timing is essential)

1130hrs - 1000ml sodium chloride 0.9% intravenous infusion over 120 minutes

1330hrs - 1000ml sodium chloride 0.9% with potassium chloride 27mmol intravenous infusion over 240 minutes

1730hrs - 1000ml sodium chloride 0.9% intravenous infusion over 360 minutes

2330hrs - 1000ml sodium chloride 0.9% with potassium chloride 27mmol intravenous infusion over 480 minutes

The day after melphalan infusion

0730hrs - 1000ml sodium chloride 0.9% intravenous infusion over 480 minutes then restart routine intravenous fluids

- 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 (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 – 71.5

- Delivery – Inpatient regimen

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 Melphalan (Aspen) – last updated 09 Dec 2014
7. Handbook of Systemic Treatments for Cancer 7th Edition 2012 Lilly Oncology
8. National Dose Banding Tables

REGIMEN SUMMARY

Alemtuzumab-Fludarabine–Melphalan (Related Donor)-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 describes the agents that must be prescribed on the in-patient chart or general electronic prescribing system.

Day -7

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. Metoclopramide 10mg three times a day oral or intravenous
   5. Ondansetron 8mg twice a day oral or intravenous
   6. Aprepitant 125mg once a day on the day of melphalan administration followed by 80mg once a day for two days afterwards
   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 for alemtuzumab
   12. Paracetamol 1000mg oral when required as a premedcation for alemtuzumab
   13. Pethidine 12.5 - 25mg intravenous when required for alemtuzumab rigors
   14. Furosemide 20mg four times a day when required for the treatment of fluid overload oral or intravenous
   15. Melphalan hydration as per paper chart
   16. Gastric protection
   17. Heparin line lock in accordance with Trust central venous access device management procedure
   18. Reminders for chemotherapy administration including methotrexate, calcium folinate and stem cells

2. Chlophenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered

3. Paracetamol 1000mg oral
   Administration Instructions
   Administer 30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered. Maximum dose is 4000mg per 24 hours

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

5. 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 12.5-25mg intravenous under the supervision of a doctor

Day -6

6. Chlophenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered

7. Paracetamol 1000mg oral
   Administration Instructions
   Administer 30 minutes prior to the alemtuzumab. Check in-patient prescribing system to ensure it has not been administered. Maximum dose is 4000mg per 24 hours

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

9. 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 12.5-25mg intravenous under the supervision of a doctor

Day – 5

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

Day – 4

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

Day -3

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

Day – 2

13. Warning – Check hydration and fluid balance
    Administration Instructions
    See separate hydration prescription chart for the pre hydration (Appendix 1):
    1. Overnight to be completed at 0930hrs on day of melphalan infusion, 1000ml sodium chloride 0.9% with potassium chloride 27mmol intravenous infusion
       The day of melphalan infusion:
    2. 0900hrs on the day of melphalan start fluid chart and daily weights. Contact pharmacy to make melphalan infusion for delivery to ward at 1045hrs
    3. 0930hrs 1000ml sodium chloride 0.9% intravenous infusion over 90 minutes
    4. 1010hrs 20mg furosemide intravenous bolus
    5. 1045hrs Measure urine output since 0900hrs
       If more than 500ml continue with melphalan infusion
       If less than 500ml give second furosemide 20mg dose intravenous bolus and recheck urine output since 0900hrs again at 1100hrs:
       - if more than 500ml go ahead with melphalan
       - if less than 500ml contact prescriber.

14. Time– Administer melphalan at 1100

15. Melphalan 140mg mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
    Administration Instructions - see separate hydration prescription chart for the post hydration (Appendix 1 of protocol)
    1. 1100hrs – give melphalan intravenous infusion over thirty minutes
    2. 1130hrs - 1000ml sodium chloride 0.9% intravenous infusion over two hours

3. 1330hrs - 1000ml sodium chloride 0.9% with potassium chloride 27mmol intravenous infusion over four hours
4. 1730hrs - 1000ml sodium chloride 0.9% intravenous infusion over six hours
5. 2330hrs - 1000ml sodium chloride 0.9% with potassium chloride 27mmol intravenous infusion over eight hours
6. The day after melphalan infusion: 0730hrs - 1000ml sodium chloride 0.9% intravenous infusion over eight hours and then restart routine intravenous fluids

Day +3, +6, +11

16. 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)

17. Time – Administer methotrexate at 1700

Administration Instructions
Administer the methotrexate at 1700

18. Methotrexate 5mg/m^2 intravenous bolus over 5 minutes

Administration Instructions
Administer at 1700

Check the patient's 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 Specialist Haematologist

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.

Unit no (affix hospital addressograph) Surname First name Date of Birth Ward Consultant	**Appendix 1**: WESSEX BLOOD AND MARROW TRANSPLANT – HYDRATION PRESCRIPTION FOR HIGH DOSE MELPHALAN CHEMOTHERAPY CONDITIONING FOR HSCT	**WARD**

DAY	DATE & TIME	DRUG	DOSE	INFUSION FLUID & VOLUME	ROUTE	INFUSION RATE	GIVEN/ CHECKED	START TIME	COMMENTS
	No later than midnight	HYDRATION FLUID	1000ml	Sodium chloride 0.9%	IV	To be completed at 0930hrs on day -1			Rate is variable and depends on time started
	0845	Contact Pharmacy on ext 5037 to inform them that the patient is present. Confirm that they have the melphalan prescription (on ARIA) ☐ Request melphalan to be on ward by 1045am ☐ Name of person you spoke to in pharmacy:..... at: .....hrs Nurse who phoned pharmacy:..... **0900hrs: start fluid balance sheet and start daily weight measurement**							
	0930	HYDRATION FLUID	1000 ml	Sodium chloride 0.9% 1000ml	IV	Infuse over 90 minutes at 667ml/hr			
	1000	Aprepitant Metoclopramide Ondansetron	Prescribed on inpatient prescribing system		Confirm that all of these have been administered on inpatient prescribing system:		:		
	1010	FUROSEMIDE	20mg		IV BOLUS	20mg over 5minutes			
	1045	FUROSEMIDE	20mg	Measure urine output since 0900hrs. If less than 500ml give this dose of furosemide and continue remeasure urine output before starting melphalan.	IV BOLUS	20mg over 5minutes			

Prescribed by : Date:

Unit no (affix hospital addressograph) Surname First name Date of Birth Ward Consultant	**Appendix 1**: WESSEX BLOOD AND MARROW TRANSPLANT –HYDRATION PRESCRIPTION FOR HIGH DOSE MELPHALAN CHEMOTHERAPY CONDITIONING FOR HSCT	***WARD***

DAY	DATE & TIME	DRUG	DOSE	INFUSION FLUID & VOLUME	ADDITIVES	ROUTE	INFUSION RATE	GIVEN/ CHECKED	START/ STOP	COMMENTS
	1100	**MELPHALAN - See ARIA prescription**					If urine output greater than 500ml since 0900hrs continue with melphalan If urine output less than 250ml since 0900hrs (despite two doses of furosemide 20mg iv) contact prescriber first			
	1130	HYDRATION FLUID	1000 ml	Sodium chloride 0.9% 1000ml		IV	Infuse over 2 hours at 500ml/hr			
	1330	HYDRATION FLUID	1000ml	Sodium chloride 0.9% Potassium chloride 0.2% (27mmol) 1000ml		IV	Infuse over 4 hours at 250ml/hr			
	1730	HYDRATION FLUID	1000 ml	Sodium chloride 0.9% 1000ml		IV	Infuse over 6 hours at 166ml/hr			
	2330	HYDRATION FLUID	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% (27mmol) 1000ml		IV	Infuse over 8 hours at 125ml/hr			
	0730	HYDRATION FLUID	1000 ml	Sodium chloride 0.9% 1000ml		IV	Infuse over 8 hours at 125ml/hr			

Prescribed by : Date: Pharmacist: Date: