Chemotherapy Protocol

HAEMATOLOGY – HSCT ALLOGRAFT

ALEMTUZUMAB-CYCLOPHOSPHAMIDE-TOTAL BODY IRRADIATION (TBI)-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- Cyclophosphamide-TBI (VUD)-Methotrexate (GvHD)

Indication

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

Toxicity

Drug	Adverse Effect
Alemtuzumab	Infusion-related reaction (fever, hypotension, chills, rashes), allergic / anaphylactic reaction, anaemia, leucopenia, thrombocytopenia.
Cyclophosphamide	Chemical haemorrhagic cystitis, leucopenia, nausea and vomiting, hepatic toxicity, altered carbohydrate metabolism, pancreatitis, hyper and hypoglycaemia, inappropriate secretion of antidiuretic hormone, interstitial pulmonary fibrosis.
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 it is unlikely to require reduction.

Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected.

The dose must be reduced in patients with severe hepatic impairment. A dose reduction of 25% is recommended in patients with serum bilirubin concentrations of 53 to 86micromol/l.

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	
Cyclophosphamide	greater than 50	100%
	30-50	75%
	less than 30	High dose therapy and stem cell transplantation generally not undertaken

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	
Cyclophosphamide	60mg/kg	-6, -5	Intravenous infusion in 1000ml sodium chloride 0.9% over 2 hours
Total body irradiation (TBI)	165cGy	-3, -2, -1, 0	Twice a day
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

- Cyclophosphamide will be dose banded in accordance with national dose banding table (20mg/ml)
- Mesna dose will be rounded to nearest 100mg and prescribed on the inpatient system
- 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 of 10mg and above 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
- Cyclophosphamide – 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 cyclophosphamide

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

Priot to total body irradiation

- dexamethasone 4mg or equivalent intravenous
- ondansetron 8mg oral or intravenous

- Prior to the administration of the alemtuzumb and stem cells

  - chlorpheniramine 10mg intravenous
  - paracetamol 1000mg oral

  Pethidine 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 cyclophosphamide infusion prescribed on inpatient prescribing system or using paper proforma (appendix 1)

  Day – 7

  2200 sodium chloride 0.9% 1000ml over 12 hours

  Day – 6

  1000 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours
  1600 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours
  2200 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours

  Day -5

  0400 glucose 5% 1000ml over 6 hours
  1000 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours
  1600 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours
  2200 sodium chloride 0.9% 1000ml with potassium chloride 0.2% over 6 hours

  Day -4

  0400 glucose 5% 1000ml over 6 hours

  Prescribe furosemide 40mg oral or intravenous to be administered if fluid overload occurs.

- Mesna 24mg/kg (rounded up to the nearest 100mg) to be given at:

Day – 6:

1000 (dose on ARIA immediately before cyclophosphamide), 1300, 1600, 1900, 2200

Day – 5

0200, 0600,1000,1300, 1600, 1900, 2200

Day -4

0200, 0600

- Mouthwashes including;

  - nystatin 1ml four times a day
  - sodium chloride 0.9% 10ml four times a day

- TBI specific premedication includes lorazepam 1mg oral twice a day starting the night before radiotherapy and continued until radiotherapy is complete.

- 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 – 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-17 Wessex Blood and Marrow Transplant – Cy/TBI Conditioning regimen policy. Version 1.3
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 Cyclophosphamide (Sandoz) – last updated 04 Dec 2014
6. Renal drug database (https://www.renaldrugdatabase.com) Mesna last reviewed 18/06/2014
7. Handbook of Systemic Treatments for Cancer 7th Edition 2012 Lilly Oncology
8. National Dose Banding Tables: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/

REGIMEN SUMMARY

Alemtuzumab-Cyclophosphamide-TBI (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 describes 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 medcines

   1. Hydration to start at 2200hrs on day -7 (Appendix 1)
   2. Mesna 24mg/kg intravenous at:
   Day –6: 1300hrs, 1600hrs, 1900hrs, 2200hrs
   Day –5: 0200hrs, 0600hrs, 1300hrs, 1600hrs, 1900hrs, 2200hrs
   Day -4: 0200hrs, 0600hrs.
   3. Antibacterials, including gut decontamination, in accordance with the individual transplant schedule
   4. Antifungals in accordance with the individual transplant schedule
   5. Antivirals in accordance with the individual transplant schedule
   6. Lorazepam 1mg twice a day to start the evening before the radiotherapy and continued until radiotherapy is complete
   7. Metoclopramide 10mg three times a day oral or intravenous
   8. Ondansetron 8mg twice a day oral or intravenous
   9. Nystatin mouthwash 1ml four times a day
   10. Sodium chloride 0.9% mouthwash 10ml four times a day
   11. Dexamethasone 3.3mg or equivalent dose intravenous twice a day at 0730 and 1600hrs before TBI (days -3, -2, -1)
   12. Ciclosporin in accordance with the individual transplant schedule
   13. Calcium folinate 30mg intravenous bolus six hourly for four doses on days +4, +7, +12
   14. Chlorphenamine 10mg intravenous when required
   15. Paracetamol 1000mg when required oral
   16. Furosemide 20mg four times a day when required for the treatment of fluid overload oral or intravenous
   17. Gastric protection
   18. Heparin line lock in accordance with Trust central venous access device management procedure
   19. Reminders for chemotherapy administration including methotrexate and stem cells

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

3. Paracetamol 1000mg oral
   Administration Instructions
   Administer 30 minutes prior to alemtuzumab. Check to ensure the patient has not already been administered paracetamol. The maximum dose is 4000mg/24 hours

4. 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 25mg intravenous following a verbal instruction from a doctor

Day -7

5. Chlophenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to alemtuzumab. 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 alemtuzumab. Check to ensure the patient has not already been administered paracetamol.

The maximum dose is 4000mg/24 hours

7. 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 25mg intravenous following a verbal instruction from a doctor

Day – 6

8. Mesna 24mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes starting 15 minutes before the cyclophosphamide infusion.
   Administration Instructions
   Administer 15 minutes before the start of the cyclophosphamide infusion

9. Time – Administer cyclophosphamide at 1015
   Administration Instructions
   The cyclophosphamide infusion should begin at 1015

10. Cyclophosphamide 60mg/kg intravenous infusion in 1000ml sodium chloride 0.9% over 2 hours.
    Administration Instructions
    The cyclophosphamide infusion should begin at 1015

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

12. Paracetamol 1000mg oral
    Administration Instructions

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

13. 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 25mg intravenous following a verbal instruction from a doctor

Day – 5

14. Mesna 24mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes starting 15 minutes before the cyclophosphamide infusion.
    Administration Instructions
    Administer 15 minutes before the start of the cyclophosphamide infusion

15. Time – Administer cyclophosphamide at 1015
    Administration Instructions
    The cyclophosphamide infusion should begin at 1015

16. Cyclophosphamide 60mg/kg intravenous infusion in 1000ml sodium chloride 0.9% over 2 hours.
    Administration Instructions
    The cyclophosphamide infusion should begin at 1015

Day +3

17. 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)

18. Time – Administer methotrexate at 1700
    Administration Instructions
    Administer the methotrexate at 1700

19. 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 of 10mg and above 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

20. 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)

21. Time – Administer methotrexate at 1700
    Administration Instructions
    Administer the methotrexate at 1700

22. 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 of 10mg and above 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	July 2017	None	Harriet Launders Haematology 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.

Unit no	(affix hospital addressograph)
Surname	
First name	
Date of Birth	
Ward	
Consultant	

Appendix 1: WESSEX BLOOD AND MARROW TRANSPLANT –HYDRATION PRESCRIPTION FOR CYCLOPHOSPHAMIDE CHEMOTHERAPY CONDITIONING FOR HSCT
Cyclophosphamide (prescribed on ARIA) and Mesna (prescribed on JAC) to be administered via line 2

LINE 1

HYDRATION

DAY	DATE & TIME	DRUG	DOSE	INFUSION FLUID & VOLUME	ADDITIVES	ROUTE	INFUSION RATE	LINE	GIVEN/ CHECKED BY	START/STOP TIME	COMMENTS
-7	2200	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9% 1000ml		IV	Infuse over 12 hours at 83ml/hr	1			FUROSEMIDE 20-40MG IV STAT may be required during treatment to maintain diuresis/ fluid balance
-6	1000	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			
-6	1600	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			FUROSEMIDE 20-40MG IV may be required to maintain fluid balance
-6	2200	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			
-5	0400	HYDRATION FLUID (1000ml)	1000 ml	Glucose 5%		IV	Infuse over 6 hours at 167ml/hr	1			

Prescribed by : Date: Pharmacist: Date:

Unit no (affix hospital addressograph) Surname First name Date of Birth Ward Consultant	**Appendix 1**: WESSEX BLOOD AND MARROW TRANSPLANT –HYDRATION PRESCRIPTION FOR CYCLOPHOSPHAMIDE CHEMOTHERAPY CONDITIONING FOR HSCT **Cyclophosphamide (prescribed on ARIA) and Mesna (prescribed on JAC) to be administered via line 2**	**LINE 1** **HYDRATION**

DAY	DATE & TIME	DRUG	DOSE	INFUSION FLUID & VOLUME	ADDITIVES	ROUTE	INFUSION RATE	LINE	GIVEN/ CHECKED BY	START/STOP TIME	COMMENTS
-5	1000	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			FUROSEMIDE 20-40MG IV may be required to maintain fluid balance
-5	1600	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			
-5	2200	HYDRATION FLUID (1000ml)	1000 ml	Sodium chloride 0.9%, Potassium chloride 0.2% 1000ml		IV	Infuse over 6 hours at 167ml/hr	1			FUROSEMIDE 20-40MG IV may be required to maintain fluid balance
-4	0400	HYDRATION FLUID (1000ml)	1000 ml	Glucose 5%		IV	Infuse over 6 hours at 167ml/hr	1			

FLUID PRESCRIPTION CONTINUES ON NORMAL FLUID PRESCRIPTION SHEET

TBI GIVEN DAYS –3 to –1 (see protocol)

Prescribed by : Date: Pharmacist: Date: