Chemotherapy Protocol

HAEMATOLOGY – HSCT ALLOGRAFT

CYCLOPHOSPHAMIDE-TOTAL BODY IRRADIATION (TBI)-METHOTREXATE (GvHD)

Related Donor Conditioning

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

Regimen

- HSCT – Cyclophosphamide-TBI (Related Donor)-Methotrexate (GvHD)

Indication

- Conditioning for full intensity haematopoietic stem cell transplant (HSCT) from a related donor.

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Infusion-related reaction (fever, hypotension, chills, rashes), allergic/anaphylactic reaction, anemia, leucopenia, thrombocytopenia.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Chemical haemorrhagic cystitis, leucopenia, nausea and vomiting, hepatic toxicity, altered carbohydrate metabolism, pancreatitis, hyper and hypoglycaemia, inappropriate secretion of antidiuretic hormone, interstitial pulmonary fibrosis.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Headache, back or shoulder pain, fever, mucositis</td>
</tr>
</tbody>
</table>

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**

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 86 micromol/l.

<table>
<thead>
<tr>
<th>Serum Bilirubin level µmol/L</th>
<th>Methotrexate dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than or equal to 35</td>
<td>100% dose</td>
</tr>
<tr>
<td>36-50</td>
<td>50% dose</td>
</tr>
<tr>
<td>51-85</td>
<td>25% dose</td>
</tr>
<tr>
<td>greater than 85</td>
<td>omit dose</td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>greater than 50</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>less than 30</td>
<td>High dose therapy and stem cell transplantation generally not undertaken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Creatinine level µmol/L</th>
<th>Methotrexate dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than or equal to 145</td>
<td>100% dose</td>
</tr>
<tr>
<td>146-165</td>
<td>50% dose</td>
</tr>
<tr>
<td>166-180</td>
<td>25% dose</td>
</tr>
<tr>
<td>greater than 180</td>
<td>omit dose</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>60mg/kg</td>
<td>-6, -5</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 2 hours</td>
</tr>
<tr>
<td>Total body irradiation (TBI)</td>
<td>165cGy</td>
<td>-3, -2, -1, 0</td>
<td>Twice a day</td>
</tr>
<tr>
<td>GVHD Prophylaxis (ciclosporin prescribed separately on the in-patient prescribing system)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5mg/m²</td>
<td>+3, +6, +11</td>
<td>Intravenous bolus over 5 minutes</td>
</tr>
</tbody>
</table>

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

- 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

  Prior to total body irradiation
  - dexamethasone 4mg or equivalent intravenous
  - ondansetron 8mg oral or intravenous
• 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/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 – 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
5. Summary of Product Characteristics for Cyclophosphamide (Sandoz) – last updated 04 Dec 2014
REGIMEN SUMMARY

Cyclophosphamide-TBI (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 -6

1. Warning – Check supportive medication prescribed
   Administration instructions
   Please refer to the individual transplant schedule for full details of the required supportive medicines
   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. 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. 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

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

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

Day – 5

5. 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

6. Time – Administer at 1015
   Administration Instructions
   The cyclophosphamide infusion should begin at 1015
7. 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, +6, +11

8. 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 24 hours after the methotrexate, at 1700hrs, 2300hrs, 0500hrs, 1100hrs (days +4, +7, +12)

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

10. 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 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.
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.
### 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

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

Prescribed by:  
Date:  
Pharmacist:  
Date:
## Appendix 1: WESSEX BLOOD AND MARROW TRANSPLANT – HYDRATION PRESCRIPTION FOR CYCLOPHOSPHAMIDE CHEMOTHERAPY CONDITIONING FOR HSCT

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

**FLUID PRESCRIPTION CONTINUES ON NORMAL FLUID PRESCRIPTION SHEET**

_TBI GIVEN DAYS –3 to –1 (see protocol)_

Prescribed by: ___________________________ Date: ___________________________ Pharmacist: ___________________________ Date: ___________________________