Indication: Primary Central Nervous System Lymphoma

Regimen details:
- Methotrexate 500mg/m² IV Day 1
- Methotrexate 3000mg/m² IV Day 1
- Cytarabine 2000mg/m² IV BD Days 2 and 3

Administration:
- Methotrexate: 500mg/m² IV infusion in sodium chloride 0.9% over 15 minutes immediately followed by
- Methotrexate: 3000mg/m² IV infusion in sodium chloride 0.9% over 3 hours
- Cytarabine: IV infusion in sodium chloride 0.9% over 1 hour. There is a 12 hour gap between the doses.

Premedication: None required

Frequency: Every 21 days for 4 cycles

Extravasation: Methotrexate is an irritant. Cytarabine is not a vesicant

Anti-emetics: High emetogenic potential (60%-90% incidence). Follow local anti-emetic policy

Supportive medication:
- Allopurinol for prevention of tumour lysis syndrome if necessary as per local policy
- Mouthcare as per local policy
- Antimicrobial prophylaxis whilst neutrophil count < 0.5 x 10⁹/L as per local policy
- PPI or H₂ receptor antagonist as per local policy.
- Urinary alkalisation before and after methotrexate, as per local practice, for example:
  - Pre-methotrexate: Potassium chloride 0.15% (20mmol) + sodium bicarbonate 50mmol in 1000ml sodium chloride 0.18% & glucose 4% over 4 hours x 2
  - Post-methotrexate: Potassium chloride 0.15% (20mmol) + sodium bicarbonate 50mmol in 1000ml sodium chloride 0.18% & glucose 4% over 6 hours repeated continuously until methotrexate cleared
- Folinic acid rescue after methotrexate 30mg IV (or oral if appropriate) every 6 hours starting 24 hours after the start of the methotrexate infusion. If the methotrexate level is > 2.0 micromol/L after 72 hours, the dose and frequency of folinic acid administration should be increased. Refer to table below for folinic acid dose information:
<table>
<thead>
<tr>
<th>Time after starting methotrexate</th>
<th>Methotrexate Plasma Concentration (micromol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours</td>
<td>None 15mg/m² q6hr 15mg/m² q6hr 10mg/m² q3hr 100mg/m² q3hr</td>
</tr>
<tr>
<td>72 hours</td>
<td>None 15mg/m² q6hr 10mg/m² q3hr 100mg/m² q3hr 1000mg/m² q3hr</td>
</tr>
<tr>
<td>96 hours</td>
<td>None 15mg/m² q6hr 10mg/m² q3hr 100mg/m² q3hr 1000mg/m² q3hr</td>
</tr>
<tr>
<td>120 hours</td>
<td>None 15mg/m² q6hr 10mg/m² q3hr 100mg/m² q3hr 1000mg/m² q3hr</td>
</tr>
</tbody>
</table>

The dose of folinic acid should also be increased by if serum creatinine increases > 50% from baseline.

Corticosteroid eye drops as per local formulary (e.g. prednisolone (Predsol®) 0.5% or dexamethasone (Maxidex®) 0.1%), during and for 3 days after completion of chemotherapy.

Regular investigations: Prior to day 1:
- FBC
- LFTs
- U&Es

Methotrexate levels starting at 48 hours after the start of the first methotrexate infusion, and then every 24 hours until methotrexate level < 0.1micromol/L.

NB. Ensure that processes are in place to enable methotrexate level monitoring outside of working hours / weekends if necessary.

It is important that methotrexate levels are recorded and acted upon, so that folinic acid doses can be adjusted accordingly.

Dose Modifications

Haematological Toxicity:

Neutrophils ≥ 1.0x10⁹/L and platelets ≥ 100x10⁹/L prior to each cycle.

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>% dose</th>
<th>Cytarabine</th>
<th>% dose</th>
<th>Methotrexate</th>
<th>% dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>100%</td>
<td>100% dose</td>
<td>100%</td>
<td>Discuss with Consultant</td>
<td></td>
</tr>
<tr>
<td>46 - 59</td>
<td>60%</td>
<td>60% dose</td>
<td>50%</td>
<td>Discuss with Consultant</td>
<td></td>
</tr>
<tr>
<td>31 - 45</td>
<td>50%</td>
<td>50% dose</td>
<td>50%</td>
<td>Discuss with Consultant</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason for Update: Network Protocol Development Approved by Consultant: Paul Fields
Version: 1 Approved by Chair Haem TWG: Majid Kazmi
Supersedes: All other versions Date: 02 Oct 2012
Prepared by: Laura Cameron Checked by (Network Pharmacist): Jacky Turner 19 Sept 2012
Hepatic Impairment

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (IU/L)</th>
<th>Cytarabine</th>
<th>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 34</td>
<td>≤ 180</td>
<td>100% dose</td>
<td>100% dose</td>
</tr>
<tr>
<td>34 - 50</td>
<td>≤ 180</td>
<td>50% dose</td>
<td>100% dose</td>
</tr>
<tr>
<td>51 - 85</td>
<td>&gt; 180</td>
<td>50% dose</td>
<td>75% dose</td>
</tr>
<tr>
<td>&gt; 85</td>
<td></td>
<td>50% dose</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

For both renal and hepatic impairment, confirm any dose reductions with the Consultant as in some circumstances 100% dose may be given.

Toxicities: Cytarabine: ocular pain, foreign body sensation, photophobia and blurred vision. Dizziness, headache, confusion, cerebellar toxicity. Skin freckling, itching, cellulites at injection site, rash, skin sloughing of the palmar and plantar surfaces. Myalgia and bone pain

Methotrexate: Renal failure; consider dose reductions for patients with renal impairment as above, Gastrointestinal; diarrhoea, stomatitis

Bone marrow suppression

Hepatotoxicity; risk is related to cumulative dose and prolonged exposure. Alcohol abuse, obesity, advanced age and diabetes may increase the risk

Pneumonitis, may occur at any time during therapy; monitor for pulmonary symptoms, particularly dry, non-productive cough

Photosensitivity and/or severe dermatologic reactions

Drug interactions: The co-administration of co-trimoxazole / trimethoprim and methotrexate should be avoided as it can result in increased haematological toxicity.

NSAIDs can reduce the clearance of methotrexate, resulting in increased toxicity.

Comments: If low Hb prior to treatment, blood transfusion should be completed prior to high dose methotrexate (transfusing after high dose methotrexate will delay the clearance of methotrexate)