High-dose Methotrexate (3.5g/m²) for CNS Lymphoma

Indication: Central Nervous System Lymphoma

Regimen details:
- Methotrexate 500mg/m² IV Day 1
- Methotrexate 3000mg/m² IV Day 1

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

Premedication: None required

Frequency: Every 14 days for 4 cycles

Extravasation: Methotrexate is an irritant.

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>Methotrexate Plasma Concentration (micromol/L)</th>
<th>Time after starting methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>48 hours</td>
<td>None</td>
</tr>
<tr>
<td>72 hours</td>
<td>None</td>
</tr>
<tr>
<td>96 hours</td>
<td>None</td>
</tr>
<tr>
<td>120 hours</td>
<td>None</td>
</tr>
</tbody>
</table>

Reason for Update: Network Protocol Development
Version: 1
Supersedes: All other versions
Date: 02 Oct 2012
Prepared by: Laura Cameron
Checked by (Network Pharmacist): Jacky Turner
19 Sept 2012
The dose of folinic acid should also be increased by if serum creatinine increases > 50% from baseline.

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>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100% dose</td>
</tr>
<tr>
<td>20 - 49</td>
<td>50% dose</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Discuss with Consultant</td>
</tr>
</tbody>
</table>

Hepatic Impairment

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

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

Toxicities: 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).

References: British Neuro-Oncology Society / National Cancer Action Team Rare Brain and CNS Tumour Guidelines June 2011.