High dose METHOTREXATE (high grade NHL CNS prophylaxis)

INDICATION
HIGH GRADE LYMPHOMA WITH HIGH RISK OF CNS INVOLVEMENT [ICD-10 codes: C82-C84]

[Licensed / NHSE funded]

- Definition of high-risk disease for diffuse large B-cell lymphoma is a score 5 or 6 based on the following risk factors:
  - Age > 60
  - Raised serum LDH
  - Stage III or IV
  - Performance status > 1
  - Multiple extranodal sites (2 or more)
  - Renal or adrenal involvement
- In addition, the following extranodal sites are deemed high risk:
  - Testes
  - Breast
  - Renal or adrenal

NB. The following sites are NOT deemed high risk: tonsil, isolated bone marrow involvement, epidural, cranio-facial involvement unless erosion through base of skull.

Caution in patients over 70 years of age, and/or with significant co-morbidities.

TREATMENT INTENT
Used as prophylaxis alongside a curative regimen

PRE-ASSESSMENT
1. Blood tests - FBC, creatinine, LFTs, urate, calcium, magnesium, creatinine, LFTs, glucose, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, group and save.
2. Assess creatinine clearance before prescribing. Methotrexate may cause renal damage primarily due to the precipitation of methotrexate and its metabolites in the renal tubules. Consider measured GFR (for example, $^{51}$Cr-EDTA) in patients at higher risk of methotrexate toxicity, for example patients >65 years, and/or other significant co-morbidities (see below).
3. Confirm medication history. Counsel patients they MUST NOT take co-trimoxazole in the week before the high dose methotrexate infusion until adequate clearance of methotrexate from the blood due to increased risk of renal toxicity. NSAIDs and penicillin antibiotics should also be avoided before and during methotrexate infusion (see INTERACTIONS below).

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4. ECG +/- Echo - if clinically indicated.
5. Record performance status (WHO/ECOG).
6. Record height and weight.
7. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
8. Fertility - it is very important the patient understands the potential risk of infertility; all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
9. A fluid space, e.g., pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.
10. Asses the risk of tumour lysis syndrome. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8).
11. Urine pregnancy test - before cycle 1 of each chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
12. Treatment should be agreed in the relevant MDT.

**DRUG REGIMEN**

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration details</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 12hrs</td>
<td>Pre-hydration and alkalization</td>
<td></td>
<td></td>
<td>See table below</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>METHOTREXATE</td>
<td>3g/m²</td>
<td>IV infusion</td>
<td>in 500mL sodium chloride 0.9% over 3 hours</td>
</tr>
<tr>
<td>1</td>
<td>+3hrs</td>
<td>Post-hydration and alkalization</td>
<td></td>
<td></td>
<td>See table below</td>
</tr>
<tr>
<td>2</td>
<td>+24hrs</td>
<td>Calcium folinate (Folinic acid)</td>
<td></td>
<td></td>
<td>See table below</td>
</tr>
</tbody>
</table>

**CYCLE FREQUENCY:** 21 days  
**DURATION:** 2 – 4 cycles *

* Normally 2 cycles of intravenous methotrexate would be administered, after a full course of R-CHOP chemotherapy (typically 6 cycles). R-CHOP chemotherapy should not be interrupted for administration of IV methotrexate (unless for intravascular DLBCL). 2-4 doses of intrathecal methotrexate may also form part of the CNS prophylaxis regimen in particular high risk cases such as testicular lymphoma, to be administered with the first few courses of R-CHOP (or equivalent chemotherapy).

**Pre-hydration and alkalization**

- Start 12 hours before methotrexate infusion
- IV continuous infusion: 1000mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20mmol and sodium bicarbonate 100mmol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6m²). Duration: continuous infusion for 15 hours (run concurrently with methotrexate infusion).
- PO: Sodium bicarbonate 1500mg four times daily.
- Dipstick urine every 2 hours to check if pH over 7. If pH under 7, give additional sodium bicarbonate (PO) 1500mg.
**Urine output**
- Check: Every 4 hours.
- Aim: 400 mL/m²/4 hours (approximately 700 mL over 4 hours).
- Furosemide: Administer 20-40 mg to maintain urine output.

**Post-hydration and alkalinization**
- Start immediately at the end of methotrexate infusion.
- IV continuous infusion: 1000mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20mMol and sodium bicarbonate 50mMol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6m²). Duration: continuous infusion until methotrexate level < 0.1 micromol/L.
- PO: Sodium bicarbonate 1500mg four times daily.
- Dipstick urine every 2 hours to check if pH over 7. If pH under 7, give additional sodium bicarbonate (PO) 1500mg. Review the need for regular sodium bicarbonate at the end of methotrexate infusion and continue as appropriate until methotrexate levels < 0.1 micromol/L.

**Calcium folinate (folinic acid)**
- Start 24 hours after the START of methotrexate infusion.
- 30mg IV injection every 3 hours for 4 doses, then 30mg IV injection (or tablets can be given orally if no nausea or vomiting) every 6 hours until methotrexate levels < 0.1 micromol/L.

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**RESTAGING**
On completion of 2 cycles of HD MTX

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**GLUCARPIDASE – reversal agent for methotrexate-induced renal dysfunction**

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m²)
- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria),
- Have toxic plasma methotrexate levels,
- Have been treated with all standard rescue and supportive measures,
- At risk of life-threatening methotrexate-induced toxicities

Administration of glucarpidase should optimally occur within 60 hours from the start of the HD MTX infusion, because life-threatening toxicities may not be preventable beyond this time point.

The recommended dose is one single intravenous injection of 50 units/kg. Multiple doses are not permitted under the NHSE Glucarpidase policy Refer to TVCA Glucarpidase guideline for full details.

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**DOSE MODIFICATIONS**

All dose modifications must be discussed with consultant.

**Haematological toxicities:**

Proceed with each cycle only if neutrophils > 1.0 x 10⁹/L and platelets > 75 x 10⁹/L.
Non-haematological toxicities:
Dose reduction should be considered in patients > 70 years due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR (calculated CrCl*):</td>
<td>Mild and moderate: caution required:</td>
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<tr>
<td></td>
<td>GFR &gt; 80mL/min: 100% dose</td>
<td>consider dose reduction or discontinue with</td>
</tr>
<tr>
<td></td>
<td>GFR 71-80mL/min: 75% dose</td>
<td>concomitant renal impairment or constant</td>
</tr>
<tr>
<td></td>
<td>GFR 60-70mL/min: 63% dose</td>
<td>increase in liver enzymes (see below**) –</td>
</tr>
<tr>
<td></td>
<td>GFR &lt; 60mL/min: contraindicated</td>
<td>clinical decision.</td>
</tr>
<tr>
<td></td>
<td>- use alternative therapy</td>
<td>Severe: contraindicated</td>
</tr>
</tbody>
</table>

*Consider measured GFR at consultant’s discretion (for example, $^{51}$Cr-EDTA) in patients >65 years, and/or with BMI ≥ 30 and other significant co-morbidities (for example, cardiac disease).

** It is expected that patients receiving high dose methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicity requiring discontinuation of repeated administration of methotrexate. Persistent hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients. Renal insufficiency (creatinine clearance less than 60 mL/min). Severe hepatic impairment. Refer to Summary of Product Characteristics (SmPC) for full details.

INVESTIGATIONS

- FBC, creatinine, LFTs,
- CXR

CONCURRENT MEDICATION

| Aciclovir | 200 mg three times a day for duration of treatment and for 3 months after completion |
| PJP prophylaxis | Co-trimoxazole should be stopped a week before the high-dose methotrexate infusion and must be held until methotrexate level is < 0.1 micromol/L and neutrophil count recovery, when it can be restarted (480-960mg three times a week, on Mon / Wed / Fri) |
| Pre- and post-hydration with sodium bicarbonate | See DRUG REGIMEN above |

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EMETIC RISK
Moderate

INTERACTIONS
(Consult with pharmacist and refer to SmPC for full details)

<table>
<thead>
<tr>
<th>Co-factor</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole</td>
<td>Avoid concomitant use. Acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofolic acid reductase can occur. Co-trimoxazole should be stopped a week before the start of methotrexate and held until methotrexate levels &lt; 0.1 micromol/L and neutrophil count recovery.</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Avoid concomitant use. Reduced renal clearance of methotrexate can occur. Tazocin (piperacillin with tazobactam) should NOT be used during high dose methotrexate administration until methotrexate levels &lt; 0.1 micromol/L. Consider using meropenem or another alternative.</td>
</tr>
<tr>
<td>NSAIDs and salicylates</td>
<td>Avoid concomitant use. Severe (including fatal) bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage).</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Avoid concomitant use. Delayed elimination and increased serum methotrexate can occur.</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>Insulin-dependent diabetes should be carefully monitored because liver cirrhosis and an increase in transaminases can occur.</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
(Consult with pharmacist and refer to SmPC for full details)

- Renal damage
- Hepatotoxic
- Interstitial pneumonitis (cough, dyspnoea, fever)
- Stomatitis, diarrhoea
- Skin changes and increased skin sensitivity to sun
- Gritty eyes
- Hair loss
- Neurotoxicity including headache, dizziness, blurred vision and loss of balance

EXTRAVASATION RISK
Methotrexate: inflammatory agent

TREATMENT RELATED MORTALITY
< 1%
REFERENCES


