High dose METHOTREXATE (high grade NHL CNS prophylaxis)

INDICATION

High grade lymphoma with high risk of CNS involvement

Definition of high risk disease for diffuse large B-cell lymphoma is a score 4 or 5 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
- Epidural
- Breast
- Renal or adrenal

The following sites are NOT deemed high risk: tonsil, isolated bone marrow involvement, 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. Assess creatinine clearance before prescribing.
2. A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.
3. Patients MUST NOT receive co-trimoxazole in the week before the first methotrexate infusion. Restart co-trimoxazole once methotrexate level is <0.1 micromol/L and neutrophil count recovery.
4. Blood tests - FBC, creatinine, LFTs, group and save.
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. Start oral sodium bicarbonate capsules at $T = -12$ hours. Administer $1.5 g$ four times a day + $1.5 g$ prn for 36 hours, then review. Review regular sodium bicarbonate requirements at the end of the methotrexate infusion, and continue as appropriate until methotrexate level <0.1 micromol/L.
11. Dipstick urine every 2 hours to check pH >7. If pH <7 give additional bicarbonate as in point 10.
12. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
13. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day 0

Hydration / Alkalisation - Pre methotrexate (starting $T = -12$ hours; see below).

Day 1 ($T=0$)

METHOTREXATE 3.0 g/m$^2$ IV infusion Day 1 in exactly 500 mL sodium chloride 0.9% over 3 hrs.

Calcium folinate (Folinic acid) post methotrexate (starting 24 hours after start of methotrexate).

Continue with fluids and folinic acid rescues until methotrexate level <0.1 micromol/L.
CYCLE FREQUENCY

Normally 2 courses 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. 2-4 courses of intrathecal methotrexate also forms part of the CNS prophylaxis regimen, to be administered with the first few courses of R-CHOP (or equivalent chemotherapy).

RESTAGING

On completion of 2 cycles of HD MTX.

INTRAVENTOUS HYDRATION

Start: \( T = -12 \) hours.

Fluid: 1000 mL glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50 mmol/L.

Flow rate: 200 mL/hour (or 150 mL/hour if less than \( 1.6 \text{ m}^2 \)).

Duration: Continue fluids during methotrexate infusion (run concurrently with methotrexate). Administer fluids until methotrexate level <0.1 micromol/L.

METHOTREXATE INTRAVENOUS INFUSION

Start: \( T = 0 \) (aim to start at 10.00 am)

Run infusion over 3 hours if possible. May run for longer if technical reasons limit flow rate (maximum 6 hours).

Levels: Check 48 hours after the start of the methotrexate infusion, and every 24 hours thereafter until methotrexate level less than 0.1 micromol/L.

URINE OUTPUT

Check: Every 4 hours.

Aim: 400 mL/m²/4 hours (approx. 700 mL over 4 hours).

Furosemide: Administer 20-40 mg to maintain urine output.
FOLINIC ACID RESCUE

Start: 24 hours after the start of methotrexate infusion.

Dose: 30 mg every 3 hours for 5 doses, then every 6 hours until methotrexate level is less than 0.1 micromol/L.

Administration: Give intravenous boluses for at least the first 4 doses, then change to oral if the patient is compliant and not vomiting.

GLUCARPIDASE – reversal agent

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) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

DOSE MODIFICATIONS

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Dose</th>
<th>Hepatic impairment</th>
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<tbody>
<tr>
<td>CrCl (mL/min)</td>
<td></td>
<td>Bilirubin micromol/L</td>
</tr>
<tr>
<td>&gt;80</td>
<td>100%</td>
<td>&lt;50</td>
</tr>
<tr>
<td>60-80</td>
<td>65%</td>
<td>51-85</td>
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<tr>
<td>45-59</td>
<td>50%</td>
<td>&gt;85</td>
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<tr>
<td>30-44</td>
<td>Discuss with Consultant</td>
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<tr>
<td>&lt;30</td>
<td>Contra-indicated</td>
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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.

Dose-reduce, particularly in patients with concomitantly impaired renal function.

Severe hepatic impairment – Contra-indicated
INVESTIGATIONS

- FBC, creatinine, LFTs,
- CXR

CONCURRENT MEDICATION

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<tr>
<th>Proton pump inhibitor</th>
<th>Daily for the duration of treatment</th>
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<tr>
<td>Aciclovir</td>
<td>200 mg three times a day for duration of treatment and for 3 months after completion</td>
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A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin, co-trimoxazole and NSAIDs. Tazocin (piperacillin with tazobactam) should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.

EMETIC RISK

Moderate.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- 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


Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
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<tbody>
<tr>
<td>Cheuk-kie Jackie Cheung</td>
<td>Removal of fluconazole in line with other first line DLBCL regimen</td>
<td>Dec 2019</td>
<td>1.6</td>
<td>May 2020</td>
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<td>Haematology Pharmacist</td>
<td></td>
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<tr>
<td>NSSG Lymphoma Group</td>
<td>Annual protocol review</td>
<td>Aug 2020</td>
<td>1.7</td>
<td>May 2022</td>
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