**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 based on the following risk factors (CNS-IPI score):

- Age > 60 years
- Serum LDH > ULN
- Ann Arbor Stage III or IV disease
- ECOG Performance status > 1
- >1 extranodal sites of disease
- Renal or adrenal involvement

In addition, the following extranodal sites are deemed high risk, irrespective of other risk factors:

- Testes
- Epidural *
- Breast

* These patients require careful discussion at MDT, given the proximity to the CNS, on whether to treat as CNS involvement.

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

These specific disease entities are also considered high risk, irrespective of other risk factors:

- Double hit lymphoma
- Adult T-cell leukaemia/lymphoma

All high grade T cell lymphomas should be risk assessed in a similar manner to high grade B cell lymphoma, albeit in the absence of research relating specifically to this setting.

Please note the above indications are for guidance only and local approval/agreement should be sought.

**ICD-10 codes**

C82.4, C83.3, C84.4

**Regimen details**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methotrexate</td>
<td>500mg/m²</td>
<td>IV infusion</td>
</tr>
<tr>
<td>1</td>
<td>Methotrexate</td>
<td>3g/m²</td>
<td>IV infusion</td>
</tr>
</tbody>
</table>

Pre and post hydration required, to commence as below.
Please discuss with consultant for patients aged ≥ 70 years or with significant co-morbidities.
**Cycle frequency**
If planned to be given alongside chemotherapy for systemic disease (e.g. R-CHOP), patients should aim to start high dose methotrexate around day 10 of each cycle. Chemotherapy for systemic disease should **NOT** be delayed for CNS prophylaxis. Alternatively, high dose methotrexate can be given at the end of chemotherapy for systemic disease depending on local policy/consultant preference. Discuss any delays to treatment with the responsible consultant.

**Number of cycles**
2-4 cycles

**Administration**

**Methotrexate pre and post hydration:**
1000mL sodium chloride 0.45%/dextrose 5% with 20mmol potassium chloride and 50mmol sodium bicarbonate should be commenced 8 hours prior to methotrexate at a suggested rate of 1000mL over 4 hours and continued concurrently during methotrexate infusion and until calcium folinate rescue is no longer required.

Full dose methotrexate should only be given in the presence of a normal serum creatinine and CrCl ≥ 80mL/min. See below for dose reductions in renal impairment.

Prior to commencing methotrexate, patients must have a urine pH ≥ 7.0 and a urine output ≥ 100mL/hour. This should be maintained during treatment and until calcium folinate rescue is no longer required. Fluid balance should be closely monitored and urine pH measured hourly. Additional sodium bicarbonate (either added to fluids or given orally) may be required to maintain urine pH ≥ 7.0.

**Methotrexate** is given in 2 separate doses. Methotrexate 500mg/m² is administered in 250mL sodium chloride 0.9% over 15 minutes. This is then immediately followed by the 3g/m² dose administered in 1000mL sodium chloride 0.9% over 3 hours.

**Calcium folinate** is commenced 24 hours after the start of the first methotrexate infusion at a dose of 15mg/m² every 3 hours for 6-8 doses. It is administered as an IV bolus or IV infusion in 100mL glucose 5% over 30 minutes. Calcium folinate is then given every 6 hours until serum methotrexate level < 0.1μmol/L. It may be given orally after the first 24 hours if the patient is compliant, not vomiting and otherwise without complication. Calcium folinate is available as 15mg and 30mg tablets.

Serum methotrexate levels should be taken 48 hours after the start of the methotrexate infusion and then every 24 hours. If the 48 hour level is > 2.0μmol/L, the dose of calcium folinate should be doubled. Serum methotrexate levels and U+Es must be checked every 24 hours, and urine output and pH every hour. Calcium folinate rescue and urine pH should be maintained at ≥ 7.0 until the methotrexate level is < 0.1μmol/L. The dose of calcium folinate should also be increased if serum creatinine increases > 50% from baseline.

**Pre-medication**
Pre-hydration as above

**Emetogenicity**
This regimen has moderate emetic potential

**Additional supportive medication**
H₂ antagonist
Antiviral prophylaxis (e.g. acyclovir) as per local policy
Antiemetics as per local policy
Antifungal prophylaxis as per local policy
G-CSF as per local policy, to start from day 4 until neutrophil recovery
Extravasation
Methotrexate is an inflamma[tant (Group 2)

Investigations - pre first cycle

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period (or as per local policy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>72 hours</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>72 hours</td>
</tr>
<tr>
<td>LFTs</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Consider echocardiogram and/or pulmonary function tests if clinically indicated.

Investigations - pre subsequent cycles

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>72 hours</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>72 hours</td>
</tr>
<tr>
<td>LFTs</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer must be given by prescriber/consultant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>( \geq 1.0 \times 10^9/L )</td>
</tr>
<tr>
<td>Platelets</td>
<td>( \geq 100 \times 10^9/L )</td>
</tr>
<tr>
<td>Creatinine Clearance (CrCl)</td>
<td>( \geq 80 \text{mL/min} )</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>( \leq 50 \text{µmol/L} )</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>( \leq 5 \times \text{ULN} )</td>
</tr>
</tbody>
</table>

Dose modifications

- **Haematological toxicity**
  If neutrophils \(<1.0 \times 10^9/L\) and/or platelets \(<100 \times 10^9/L\) delay treatment until count recovery; this may be reviewed when methotrexate is intercalated between courses of systemic chemotherapy.

- **Renal impairment**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Methotrexate dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 80 )</td>
<td>100%</td>
</tr>
<tr>
<td>60-79</td>
<td>65%</td>
</tr>
<tr>
<td>30-59</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

- **Hepatic impairment**
  Methotrexate should be administered with great caution to patients with significant current or previous liver disease.

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (x ULN)</th>
<th>Methotrexate dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 50 )</td>
<td>And ( \leq 5 )</td>
<td>100%</td>
</tr>
<tr>
<td>51-85</td>
<td>Or ( &gt; 5 )</td>
<td>75%</td>
</tr>
<tr>
<td>&gt;85</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

It is expected that patients receiving high dose methotrexate will develop hypertransaminasaemia and/or occasionally hyperbilirubinaemia. These elevations can last up to 2 weeks following the methotrexate infusion. Persistent hyperbilirubinaemia and/or grade 3-4 hypertransaminasaemia for longer than 3 weeks should result in discontinuation of treatment.
Other toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Grade 3-4</td>
<td>Interrupt treatment until resolved</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Grade 4</td>
<td>75% dose</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Grade 4</td>
<td>75% dose</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Grade 4</td>
<td>75% dose</td>
</tr>
</tbody>
</table>

Adverse effects - for full details consult product literature/ reference texts

- Serious side effects
  Myelosuppression
  Cardiotoxicity
  Neurotoxicity
  Acute pulmonary toxicity
  Nephrotoxicity
  Hepatotoxicity
  Visual disturbances
  Infertility

- Frequently occurring side effects
  Myelosuppression
  Diarrhoea
  Fatigue
  Headache
  Drowsiness
  Nausea/Vomiting
  Mucositis/Stomatitis
  Alopecia
  Skin changes including photosensitivity and rash

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Methotrexate:
Avoid all nephrotoxic agents:
- NSAIDS: increase risk of methotrexate toxicity - avoid
- Omeprazole: potential to increase methotrexate levels
- Co-trimoxazole: if used concurrently may cause severe bone marrow depression – avoid the week before the first methotrexate infusion. Only restart co-trimoxazole once methotrexate level is <0.1 micromol/L and neutrophil count recovery.
- Theophylline: may reduce theophylline clearance - avoid
- Acetretin: increased risk of hepatitis
- Penicillins (including Tazocin): may reduce excretion of methotrexate levels – avoid during methotrexate administration and until methotrexate level is <0.1 μmol/L and neutrophil count recovery.

Additional Comments

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 (creatinine >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 are at risk of life-threatening methotrexate-induced toxicities.
The recommended dose is a single intravenous injection of 50 units/kg.

---

References

- Schmitz N, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With RCHOP. Journal of Clinical Oncology, 2016. 34: 3150–3156