High dose METHOTREXATE, high dose CYTARABINE, RITUXIMAB and THIOTEPA (MATRix - for Primary CNS lymphoma)

INDICATION
CNS Lymphoma.

TREATMENT INTENT
Curative.

PRE-ASSESSMENT

1. Ensure histology is confirmed and documented in the notes. Although it is sometimes difficult to obtain tissue in cases of primary CNS lymphoma, treatment should NOT be given without this.

2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis) or PET-CT, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.

3. A number of drugs can interfere with renal tubular secretion of methotrexate. These include penicillins, aspirin, co-trimoxazole 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.

4. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save. **Note:** The risk of primary CNS lymphoma is raised several thousand fold by the presence of HIV infection.

5. Consider lumbar puncture to ascertain for the presence of leptomeningeal involvement by flow cytometry and CSF protein (raised level is a poor prognostic factor). **Note:** Contra-indicated in the presence of space occupying lesion associated with raised intracranial pressure.

6. MRI brain with gadolinium to accurately ascertain extent of disease (multiple lesions and deep lesions represent poor prognostic features).

7. Consider testicular ultrasound in older men.

8. Slit lamp examination of both eyes. If presence of intraocular disease confirmed, consider radiotherapy to orbits at end of treatment.

9. Record the prognostic score. 1 point for each of: age >60 years, ECOG performance status >1, raised serum LDH, raised CSF protein, deep brain structures involved.

10. 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.
11. ECG +/- Echo - if clinically indicated.
12. Record performance status and cognitive state including MMS.
13. Record height and weight.
14. 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.
15. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice (see fertility guidelines).
16. Ensure patient has a creatinine clearance of >50 ml/min.
17. Patients MUST NOT receive co-trimoxazole in the week before the first methotrexate infusion. Consider pentamidine treatment if considered at risk from *Pneumocystis* infection. Restart co-trimoxazole once methotrexate level is <0.1 micromol/L and neutrophil count recovery.
18. T = 0 is the time of the start of the methotrexate infusion.
19. 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.
20. Dipstick urine every 2 hrs to check pH >7. If pH <7, give additional bicarbonate as in point 19.
21. Methotrexate infusion must aim to be given over 3 hours, although may be continued for longer if technical problems restrict flow rate.
22. Treatment should be agreed in the relevant MDT.

**When used for priming and harvesting:**
23. Liaise with BMT nurse co-ordinator for timing of harvest and possible transplant slot.
24. Venous access should be assessed well in advance of collection. Every effort should be made not to use antecubital fossa veins in the run up to harvest.
25. If good antecubital fossa veins, insert power PICC. Apheresis line to be inserted if poor antecubital veins.
26. Treatment should be agreed in the relevant MDT.
27. Ensure the peripheral stem cell harvest / final donor clearance form (form FRM3721/1) is sent within 30 days of scheduled harvest date, via nhs.net mail to NHSBT STS, to confirm eligibility for PBSCH.

**NB:** Infective agent screen. Peripheral blood stem cells for autologous transplant are cryopreserved in liquid nitrogen. In order to eliminate the risk of transmitting infective agents during the storage of marrow, virology testing is mandatory within 30 days of the harvesting procedure and results must be known before priming. Bottles and consent form provided by NHSBT Oxford. Please send to the stem cell laboratory Oxford. Address provided on consent form.
**Lymphoma group**

**L. 33 High dose METHOTREXATE, High dose CYTARABINE, RITUXIMAB and THIOTEPA (MATRix – for Primary CNS lymphoma)**

**Authorised by Lymphoma Lead By: Dr Graham Collins**

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**Review date: May 2018**

**Version**

**3 of 8**

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**DRUG REGIMEN**

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><strong>Pre-med</strong> – paracetamol 1g po, chlorpheniramine 10mg iv, hydrocortisone 100mg iv 30 minutes before rituximab infusion</td>
</tr>
<tr>
<td>0</td>
<td><strong>RITUXIMAB</strong> 375mg/m² iv infusion in 500ml sodium chloride 0.9%</td>
</tr>
<tr>
<td>1</td>
<td><strong>Pre-med</strong> – paracetamol 1g po, chlorpheniramine 10mg iv, hydrocortisone 100mg iv 30 minutes before rituximab infusion</td>
</tr>
<tr>
<td>1</td>
<td><strong>RITUXIMAB</strong> 375mg/m² iv infusion in 500ml sodium chloride 0.9%</td>
</tr>
<tr>
<td>1</td>
<td><strong>Hydration / Alkalisation - Pre methotrexate</strong> (starting T= -12 hours; see below).</td>
</tr>
<tr>
<td>1</td>
<td><strong>METHOTREXATE</strong> 3.5 g/m² iv infusion [start at 10.00 hrs] Day 1 in exactly 500 ml sodium chloride 0.9% over 3 hrs.</td>
</tr>
<tr>
<td>2 (T=0)</td>
<td><strong>Calcium folinate (Folinic acid) post methotrexate</strong> (starting 24 hours from the start of methotrexate). Continue with fluids and folic acid rescue until methotrexate level &lt;0.1 micromol/L.</td>
</tr>
<tr>
<td>3 (T=+24 hr)</td>
<td><strong>CYTARABINE</strong> 2 g/m² iv infusion 12 hourly bd (at 24, 36, 48 and 60 hours after initiation of iv methotrexate) in 500 ml sodium chloride 0.9% over 1 hour.</td>
</tr>
<tr>
<td>5</td>
<td><strong>THIOTEPA</strong> 30mg/m² iv infusion in 50-100ml sodium chloride 0.9% over 30 minutes via a 0.22 micron filter</td>
</tr>
</tbody>
</table>

**When used for priming:**
- Days 6-12 (7 days) **Daily G-CSF** as per local policy (see mobilisation protocol).
- Aim to harvest on Days 11 – 13.

**When not used for priming:**
- Days 9-15 (7 days) **Daily G-CSF** as per local policy

Intrathecal chemotherapy is NOT a part of this regimen.

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**CYCLE FREQUENCY**

Cycle repeats every three weeks; Evidence suggests that the area under the curve for methotrexate (and therefore the tumour kill) is increased if the cycle frequency is every 3 weeks or less.

In most patients, the maximum number of cycles should be 4.

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**HARVESTING (if used for priming)**

Stem cell collection performed days 11, 12 & 13

Aim to collect minimum of 2.0 x 10⁶ with target of 4.0 x 10⁶ CD34-positive cells/kg
Intravenous hydration:

Start: T = -12 hours.
Fluid: 1000 ml glucose 2.5%, sodium chloride 0.45% with potassium chloride 20mmol and sodium bicarbonate 100mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50mmol/L.
Flow rate: 200 ml/hour (or 150 ml/hour if less than 1.6 m²).
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 (absolute maximum 6 hours).
Levels: Check 48 hours after the end 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 From 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.
DOSE MODIFICATIONS

Haematological toxicity
In case if inadequate bone marrow recovery (i.e. neutrophils < 1.5x10⁹/l and platelets < 90x10⁹/l on the intended day of re-treatment, delay cycle until counts satisfactory. Doses of the chemotherapy drugs in subsequent cycles is determined according to nadir neutrophil or platelet count of the previous course as follows:

<table>
<thead>
<tr>
<th>Nadir neutrophils (x10⁹/l)</th>
<th>Dose modifications</th>
<th>Nadir platelets (x10⁹/l)</th>
<th>Dose modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>Unchanged</td>
<td>≥ 125</td>
<td>Unchanged</td>
</tr>
<tr>
<td>1.5-1.9</td>
<td>Unchanged</td>
<td>75-124</td>
<td>Unchanged</td>
</tr>
<tr>
<td>1.0-1.4</td>
<td>Unchanged</td>
<td>50-74</td>
<td>Unchanged</td>
</tr>
<tr>
<td>0.5-0.9</td>
<td>Unchanged</td>
<td>25-49</td>
<td>Unchanged</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>Reduce cytarabine to 75% by omitting dose 4</td>
<td>&lt; 25</td>
<td>Reduce cytarabine to 75% (by omitting dose 4) AND thiotepa to 75%</td>
</tr>
</tbody>
</table>

Renal/Hepatic Impairment

Methotrexate:
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.

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Dose</th>
<th>Hepatic impairment</th>
<th>Bilirubin</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (ml/min)</td>
<td></td>
<td></td>
<td>micromol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>100%</td>
<td></td>
<td>&lt;50</td>
<td>And &lt;180</td>
<td>100%</td>
</tr>
<tr>
<td>60</td>
<td>65%</td>
<td></td>
<td>51-85</td>
<td>Or &gt;180</td>
<td>75%</td>
</tr>
<tr>
<td>45</td>
<td>50%</td>
<td></td>
<td>&gt;85</td>
<td></td>
<td>Cl</td>
</tr>
<tr>
<td>&lt;30</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 – Cl
Cytarabine:

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For High dose 1-3 g/m² consider:</td>
<td>Bilirubin &gt;34 micromol/L give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td>46-60</td>
<td>60%</td>
</tr>
<tr>
<td>31-45</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>CI</td>
</tr>
</tbody>
</table>

Thiotepa:

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No formal studies. Dose modification is not recommended in patients with mild or moderate renal insufficiency. However, caution is recommended.</td>
<td>No formal studies. Thiotepa is mainly metabolized through the liver; caution needs to be exercised when thiotepa is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. Dose modification is not recommended for transient alterations of hepatic parameters</td>
</tr>
</tbody>
</table>

Other non-haematological toxicities

For grade 3-4 non-haematological, non renal / liver toxicities, the next cycle should be delayed until the grade of toxicity is 2 or less. The subsequent cycle should then be administered as follows:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Interruption</td>
<td>Interruption</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Unchanged</td>
<td>Reduce MTX, araC and thiotepa to 75%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Unchanged</td>
<td>Reduce MTX, araC and thiotepa to 75%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Unchanged</td>
<td>Reduce MTX, araC and thiotepa to 75%</td>
</tr>
</tbody>
</table>

EMETIC RISK

Moderate-High days 2, 3 and 4
Low emetic risk days 0, 1 and 5
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

**Rituximab:** Infusional reactions, reactivation of hepatitis B

**Methotrexate:** 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

**Cytarabine:** Fevers, chills, arthralgias, rash, conjunctivitis, cerebellar toxicity (rare but potentially devastating)

**Thiotepa:** Myelosuppression, nausea and vomiting, reduced fertility

CONCURRENT MEDICATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine (or PPI if specifically indicated - discuss with consultant)</td>
<td>Daily for the duration of treatment</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>50 mg daily for the duration of treatment</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>200 mg three times a day for duration of treatment and for 3 months after completion</td>
</tr>
<tr>
<td>Pentamidizne</td>
<td>4mg/kg iv (max dose 300mg) monthly. Patients MUST NOT receive co-trimoxazole in the week before the first methotrexate infusion. Consider pentamidizne treatment if considered at risk from Pneumocystis infection. Restart co-trimoxazole once methotrexate level is &lt;0.1 micromol/L and neutrophil count recovery.</td>
</tr>
<tr>
<td>Prednisolone eye drops 0.5% or 1% or Dexamethasone 0.1% eye drops (Mandatory) (depending on local formulary)</td>
<td>One drop to each eye QDS from day 2. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis, consider increasing the frequency to 2 hourly until resolution of symptoms. Liaison with ophthalmologists may be necessary in this situation.</td>
</tr>
<tr>
<td>GCSF</td>
<td>SC Daily from Day +6 (for priming cycle) or Day +9 (for non-priming cycle) as per local policy</td>
</tr>
</tbody>
</table>

A number of drugs can interfere with Tubular secretion of methotrexate. These include penicillins, aspirin, co-trimoxazole 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.
GLUCARPIDASE – REVERSAL AGENT

NHS England will fund Glucarpidase (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

EXTRAVASATION

Methotrexate is an inflammatant (Group 2)
Cytarabine is neutral (Group 1)
Thiotepa is neutral

TREATMENT RELATED MORTALITY

2-5%

REFERENCES

2. ILESG32 protocol version 1.3 August 2009.
3. MRC UKALL XII July 2002.