BCCA Protocol Summary for Treatment of Leptomeningeal Lymphoma or Recurrent Intracerebral Lymphoma with High Dose Methotrexate

Protocol Code: LYHDMTXR

Tumour Group: Lymphoma

Contact Physician: Dr. Diego Villa

ELIGIBILITY:
1. Age: 16 y or greater
2. Performance status: ECOG 0-3
3. Diagnosis: Leptomeningeal lymphoma or recurrent intracerebral lymphoma
4. Acceptable hematologic, renal and hepatic function

EXCLUSIONS:
1. Estimated glomerular filtration rate (GFR) or estimated creatinine clearance (CrCl) below 60 mL/min

\[
\text{Estimated creatinine clearance: } = \frac{N (140 \text{ - age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L) }}
\]

\[
N = 1.23 \text{ male} \\
1.04 \text{ female}
\]

2. Pleural effusion, ascites, full extremity edema.
3. Hemoglobin less than 90 g/L; neutrophils less than 1.5 x 10^9/L; platelets less than 75 x 10^9/L
4. AST, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

TESTS:
- **Baseline and pretreatment:**
  - CBC & diff, platelets, serum creatinine, lytes, bilirubin, AST, ALT, alkaline phosphatase, LDH
  - urine pH
  - Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2: HBsAg, HBcoreAb
  - chest radiograph

- **During Treatment:**
  - Immediately pre-methotrexate and q6h: urine pH
  - Daily q am during treatment: serum creatinine, lytes
  - Daily q am starting day 2 (day of Methotrexate = day 1) Methotrexate levels (until less than 0.1 micromol/L; note date and time of withdrawal on the specimen)

PREMEDICATIONS:
- ondansetron 8 mg PO or IV before Methotrexate
- prochlorperazine 10 mg PO after Methotrexate infusion completed and then 10 mg PO q4h PRN
SUPPORTIVE MEDICATIONS:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>BCCA ADMINISTRATION GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td>4 mg QID x 1 week, followed by taper over 1 month as long as patient is clinically improving. (4 mg TID x 1 week, 4 mg BID x 1 week, 2mg BID x 1 week)</td>
<td>PO</td>
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<tr>
<td>ranitidine</td>
<td>150 mg BID while on dexamethasone</td>
<td>PO</td>
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<tr>
<td>cotrimoxazole</td>
<td>1 DS tablet BID 3 x each week while on dexamethasone. Discontinue cotrimoxazole 48 hours before beginning chemotherapy and resume when the plasma methotrexate is, or is projected to be, less than 0.1 X 10^-6 molar (note: µmoles/L = 10^-6 molar). If allergic, do not use any antibiotic prophylaxis.</td>
<td>PO</td>
</tr>
<tr>
<td>lamiVUDine (if HBsAg or HBcoreAb positive)</td>
<td>100 mg/day for the duration of chemotherapy and for six months afterwards</td>
<td>PO</td>
</tr>
</tbody>
</table>

TREATMENT:

Patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalization to maintain urine pH above 7. (NOTE: use the same renal function measure throughout the treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and not CrCl)

ALKALINIZING REGIMEN AND PREHYDRATION:

- IV 2/3 : 1/3 with sodium bicarbonate100 mEq/L and potassium chloride 20 mEq/L at 125 ml/h x 4 h pre-methotrexate
- Oral sodium bicarbonate 3000 mg PO q4h until methotrexate level IS LESS THAN 0.1 micromol/L (start on admission to hospital or 0800 h of day planned for Methotrexate if already in hospital)
- Check urine pH before starting methotrexate. If pH less than 7, continue alkalizing regimen until urine pH greater than or equal to 7 before starting methotrexate.

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<tr>
<td>methotrexate (Cycle 1 to 4)</td>
<td>8 grams/m² (Day 1) prorated* to GFR or CrCl between 60 to 100 mL/min**</td>
<td>IV in 1000mL NS over 4 hours</td>
</tr>
<tr>
<td>methotrexate (Cycle 5 to 8, if necessary, see below)</td>
<td>3.5 grams/m² (Day 1)</td>
<td>IV in 1000mL NS over 4 hours</td>
</tr>
<tr>
<td>leucovorin</td>
<td>25 mg q6h (start Day 2)</td>
<td>Starting exactly 24 hours after start of methotrexate infusion; IV for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L*</td>
</tr>
</tbody>
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POST HYDRATION:

IV 2/3 : 1/3 with sodium bicarbonate100 mEq/L and potassium chloride 20 mEq/L at 125 mL/h for 48 h after Methotrexate

NOTE: One staff Physician signature is required. Orders written by residents and fellows MUST be co-signed.

* Prorated dosing, e.g.
  - GFR (or CrCl) greater than or equal to 100 mL/min, give 8 grams/m²
  - GFR 85 mL/min, give 85% of 8 grams/m²
  - GFR 60 mL/min, give 60% of 8 grams/m²

BC Cancer Agency Protocol Summary LYHDMTXR
Activated: 1 Aug 2000 Revised: 1 May 2017
Warning: The information contained in these documents are a statement of consensus of BC Cancer Agency professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is at your own risk and is subject to BC Cancer Agency’s terms of use available at www.bccancer.bc.ca/legal.htm
**IMPORTANT NOTE:** use the **same** renal function measure throughout the treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and **not** CrCl.

If well tolerated, cycles are administered every 2 weeks for 4 cycles. If necessary for ongoing palliation, subsequent cycles (cycles 5 to 8) are to be administered at a reduced dose of 3.5 grams/m² every 2 weeks.

*Methotrexate must be given in a hospital where rapid reporting of methotrexate levels is available. Plasma Methotrexate levels are performed routinely each morning after starting the methotrexate infusion. At 24 hours, leucovorin rescue begins according to the protocol. A dose of leucovorin 25 mg q6h is used initially. The plasma Methotrexate concentrations done on day 2 and day 3 are used to plot the initial slope of the curve on the Bleyer diagram below, but only the Methotrexate concentration done on day 3 should be used to increase the dose of leucovorin, if necessary. Leucovorin is continued until the plasma methotrexate is, or is projected to be, less than 0.1 x 10⁻⁶ molar (note: micromol/L = 10⁻⁶ molar).


Note: New laboratory method has a higher limit of detection and inaccuracies have been reported with methotrexate levels below 0.1 micromol/L.

**DOSE MODIFICATIONS:**

1. **Renal Dysfunction:**
   - If GFR (or CrCl) less than 60 mL/min, reversible causes of renal dysfunction should be treated and the patient reassessed for suitability for this treatment once renal function improves.
   - Use the **same** renal function measure throughout the treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and **not** CrCl.

2. **Mucositis** greater than or equal to Grade 3 (painful erythema, edema or ulcers and cannot eat), reduce methotrexate to 80% or prolong routine rescue for 2 more days (unless abnormal methotrexate levels).
**PRECAUTIONS:**

1. **Third space fluids:** Patients with clinically or radiologically detectable third space fluid (e.g. pleural effusion, ascites, full extremity pitting edema) should NOT be given high dose methotrexate.

2. **Renal elimination:** Patients with elevated serum creatinine or calculated GFR (or CrCl) below 60 mL/min should NOT receive high dose methotrexate. Avoid concomitant use of drugs that may inhibit renal elimination of methotrexate such as non-steroidal anti-inflammatories (NSAIDs), salicylates and sulfa drugs.

3. **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBCab. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

4. **Cotrimoxazole Drug Interaction:** Cotrimoxazole (Septa®, Bactrim®, etc) may affect methotrexate toxicity, clearance or accurate measurement in assays of concentration. See instructions under Pre-medications above for dosing guidance.

5. **Possible interactions with proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole)** have been reported, resulting in elevated methotrexate levels and increased risk of methotrexate toxicity. Consider discontinuing proton pump inhibitors 1 day prior to methotrexate administration. If their use is required, closely monitor methotrexate levels and monitor for signs of methotrexate toxicity.

6. **Possible interaction with penicillins (e.g., amoxicillin, piperacillin, ticarcillin).** Penicillins compete with methotrexate for excretion sites in the renal tubules resulting in increased serum methotrexate and toxicity. Primarily a concern with high-dose methotrexate and thus the combination should be avoided if possible.

Call Dr. Diego Villa or tumour group designate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 01 Aug 2000 (replacing LYHDMTX)

Date revised: 01 May 2017 (Methotrexate/Penicillins drug interaction added)

**References:**


