ELIGIBILITY:
1. Age: 16 y or greater
2. Performance status: ECOG 0-3
3. Diagnosis: secondary CNS 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
   \[
   \text{Estimated creatinine clearance: } \frac{N (140 - \text{age wt (kg)})}{\text{serum creatinine (micromol/L)}}
   \]
   
   \[N = 1.23 \text{ male}
   \]
   
   \[1.04 \text{ female}
   \]
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. ALT, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

TESTS:
- **Baseline and pretreatment:**
  - CBC & diff, platelets, serum creatinine, sodium, potassium, bilirubin, 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, sodium, potassium
  - 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>BC CANCER 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>
</tr>
<tr>
<td>ranitidine</td>
<td>150 mg BID while on dexamethasone</td>
<td>PO</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>1 DS tablet BID 3 x each week while on dexamethasone. <strong>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).</strong> If allergic, do not use any antibiotic prophylaxis.</td>
<td>PO</td>
</tr>
<tr>
<td>lamivudine</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)

### START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE:

- Discontinue all other IV hydration before starting alkalinizing regimen.
- IV D5W with potassium chloride 20 mEq/L and sodium bicarbonate 150 mEq/L at 125 mL/h for at least 4 hours prior to methotrexate until urine pH is greater than 7. Hydration may be temporarily held during methotrexate infusion (per physician/nursing discretion). Continue hydration post-methotrexate infusion until methotrexate level is less than 0.1 micromol/L.
- Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than 7 before starting methotrexate.
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<tr>
<td>methotrexate</td>
<td>8 g/m² (Day 1)</td>
<td>IV in 1000 mL NS over 4 hours</td>
</tr>
<tr>
<td>(Cycle 1 to 4)</td>
<td>prorated* to GFR or CrCl between 60 to 100 mL/min**</td>
<td></td>
</tr>
<tr>
<td>methotrexate</td>
<td>3.5 g/m² (Day 1)</td>
<td>IV in 1000 mL NS over 4 hours</td>
</tr>
<tr>
<td>(Cycle 5 to 8, if necessary, see below)</td>
<td></td>
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</tr>
<tr>
<td>leucovorin</td>
<td>25 mg q6h</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>
<tr>
<td>(start Day 2)</td>
<td></td>
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</tbody>
</table>

NOTE: One staff Physician signature is required. Orders written by other providers MUST be co-signed.

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

**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 g/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).
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 (Septra®, 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.

**References:**


