

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

**Protocol Code** *LYHDMTXR (Recurrent)*

**Tumour Group** *Lymphoma*

**Contact Physician** *Dr. Tamara Shenkier*

## 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

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

$$N = \begin{matrix} 1.23 \text{ male} \\ 1.04 \text{ female} \end{matrix}$$

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

## TESTS:

- Baseline and pretreatment:
  - CBC & diff, platelets, serum creatinine, lytes, AST, bilirubin, alkaline phosphatase, LDH, HBsAg, HBcoreAb
  - urine pH
  - 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** 0.05 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:**

DRUG	DOSE	BCCA ADMINISTRATION GUIDELINES
Dexamethasone	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, 2 mg BID x 1 week)	PO
Ranitidine	150 mg BID while on dexamethasone	PO
Cotrimoxazole	1 DS tablet BID 3x each week while on dexamethasone. <b>Discontinue cotrimoxazole 48 hours before beginning chemotherapy and resume when the plasma methotrexate is, or is projected to be, less than <math>0.1 \times 10^{-6}</math> molar (note: micromoles/L = <math>10^{-6}</math> molar).</b> If allergic, do not use any antibiotic prophylaxis.	PO

**TREATMENT:**

Patients must have GFR (or CrCl) **greater than** 60 mL/min and vigorous IV hydration and urine alkalinization 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:**

<ul style="list-style-type: none"> <li>IV 2/3 : 1/3 + 100 mEq sodium bicarbonate/L + 20 mEq KCL/L at 125 ml/hr x 4 hrs pre-methotrexate</li> </ul>
<ul style="list-style-type: none"> <li>Oral sodium bicarbonate 3000 mg PO q4h until methotrexate level 0.05 micromol/L (start on admission to hospital or 0800 h of day planned for Methotrexate if already in hospital)</li> </ul>
<ul style="list-style-type: none"> <li>Check urine pH before starting methotrexate. If pH <b>less than</b> 7, continue alkalinizing regimen until urine pH <b>greater than or equal to</b> 7 before starting methotrexate.</li> </ul>

DRUG	DOSE	BCCA ADMINISTRATION GUIDELINES
Methotrexate (Cycle 1-4)	8000 mg/m <sup>2</sup> (Day 1) prorated* to GFR or CrCl between 60-100 mL/min**	IV in 1L NS over 4 hours
Methotrexate (Cycle 5-8, if necessary, see below)	3500 mg/m <sup>2</sup> (Day 1)	IV in 1 L NS over 4 hours
Leucovorin	25 mg q6h (start Day 2)	Starting exactly 24 hours after start of Methotrexate infusion; IV for 4 doses then PO until Methotrexate level 0.05 micromol/L*

**POST HYDRATION:**

IV 2/3 : 1/3 + 100 mEq sodium bicarbonate/L + 20 mEq KCL/L at 125 mL/hr for 48 hours after Methotrexate
---

NOTE: Two physicians' signatures are required on the medication orders (one must be a medical oncologist).

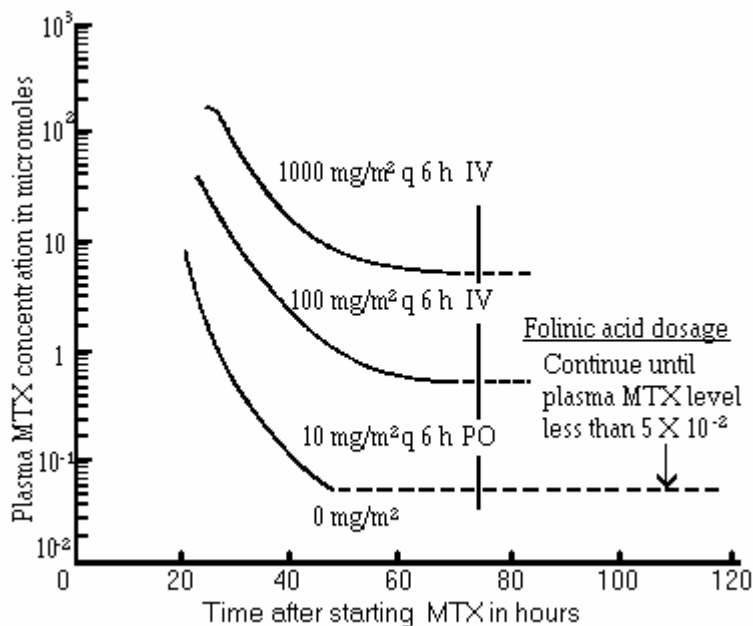
\* Prorated dosing, e.g.

- GFR (or CrCl) **greater than or equal to** 100 mL/min, give 8000 mg/m<sup>2</sup>
- GFR 85 mL/min, give 85% of 8000 mg/m<sup>2</sup>
- GFR 60 mL/min, give 60% of 8000 mg/m<sup>2</sup>

**\*\*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 5-8) are to be administered at a reduced dose of 3500 mg/m<sup>2</sup> 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 0.05 x 10<sup>-6</sup> molar (note: micromol/L = 10<sup>-6</sup> molar).



Reference: Bleyer WA. The clinical pharmacology of methotrexate – new applications of an old drug. Cancer 1978;41:36-51.

## 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 100 mg/day orally, for the entire duration of 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.

**Call Drs. Joseph Connors, Richard Klasa, Paul Hoskins, Laurie Sehn or Tamara Shenkier 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 2009 (unsafe abbreviations and symbols replaced)

## References:

1. Glantz MJ, Cole BF, Recht L, et al. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? *J Clin Oncol* 1998;16(4):1561-7.
2. Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev* 1977;4(2):87-101.
3. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol* 2003;21(6):1044-9.