

BCCA Protocol Summary for Treatment of Primary Intracerebral Lymphoma with High Dose Methotrexate and Rituximab

Protocol Code *LYHDMRP (Primary)*

Tumour Group *Lymphoma*

Contact Physician *Dr. Tamara Shenkier*

ELIGIBILITY:

1. Age: 16 y or greater
2. Performance status: ECOG 0-3
3. **Diagnosis:** Biopsy proven diagnosis of primary CNS lymphoma (PCNSL) (with or without intraocular involvement) or classic radiologic picture with resolution on steroids.
4. Acceptable hematologic, renal and hepatic function
5. A "Class II Drug Registration Form" must be submitted at the time of initiation of treatment.
Rituximab must be used in combination with Methotrexate in order to be reimbursed by BCCA.

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
 - CT brain with contrast **or** MRI with contrast (unless allergic to contrast)
 - Ocular slit lamp exam (ophthalmology consultation)
 - Baseline Folstein mini mental status exam (see Appendix 1)
 - ECOG performance status
- 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)
- Follow Up After Completion of Treatment:

- Reassess every 2 months x 1 year then every 3 months x 2 years, then every 6 months with imaging for suspected recurrence only, based on symptoms.
- History, physical, ECOG, Mini Mental Status Exam (MMSE) (to prospectively assess for neurotoxicity)
- Record site of relapse: local, neuraxial, ocular, meningeal, systemic.

PREMEDICATIONS:

For **Methotrexate**:

Ondansetron 8 mg PO or IV before Methotrexate
 Prochlorperazine 10 mg PO after Methotrexate infusion completed and then 10 mg PO q4h PRN

For **Rituximab**:

Diphenhydramine 50 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h
 Acetaminophen 650 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h

SUPPORTIVE MEDICATIONS:

DRUG	DOSE	BCCA ADMINISTRATION GUIDELINES
Dexamethasone	4mg QID x 1 week, followed by taper over 1 month as long as patient is clinically improving. (4mg TID x 1 week, 4mg BID x 1 week, 2mg BID x 1 week)	PO
Ranitidine	150mg BID while on dexamethasone	PO
Cotrimoxazole	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 0.1×10^{-6} molar (note: micromoles/L = 10^{-6} molar). 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 7.¹

ALKALINIZING REGIMEN AND PRE HYDRATION:
<ul style="list-style-type: none"> ▪ IV 2/3 : 1/3 + 100 mEq sodium bicarbonate/L + 20 mEq KCL/L at 125 mL/hr x 4 hrs pre-methotrexate
<ul style="list-style-type: none"> ▪ 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)
<ul style="list-style-type: none"> ▪ Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than or equal to 7 before starting methotrexate.

DRUG	DOSE	BCCA ADMINISTRATION GUIDELINES
Methotrexate	8000 mg/m ² (Day 1) prorated* to GFR or CrCl between 60-100 mL/min**	IV in 1000 mL 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		
Rituximab	375 mg/m ² on day 1 or 2 whenever possible but not later than 72 h after Methotrexate (note: given q 2 weekly x 4 doses)	IV in 250 mL NS over 90 minutes-8 hours*** (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)

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/m²
- GFR 85 mL/min, give 85% of 8000 mg/m²
- GFR 60mL/min, give 60% of 8000 mg/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

***Start the initial infusion at 50 mg/h and, after 60 min, increase by 50 mg/h every 30 minutes until a rate of 400 mg/h is reached. *For all subsequent treatments*, infuse 50 mL (or 100 mL) of the dose over 30 minutes then infuse the remaining 200 mL (or 400 mL) (4/5) over 120 minutes (total infusion time = 150 minutes). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

If the peripheral blood lymphocyte count is above 30 x 10⁹/L, the Rituximab should be omitted from that cycle.

Cycles are administered every two weeks. Note: Rituximab is given for a total of 4 doses.

Repeat imaging should be done (CT or MRI) prior to 5th cycle.

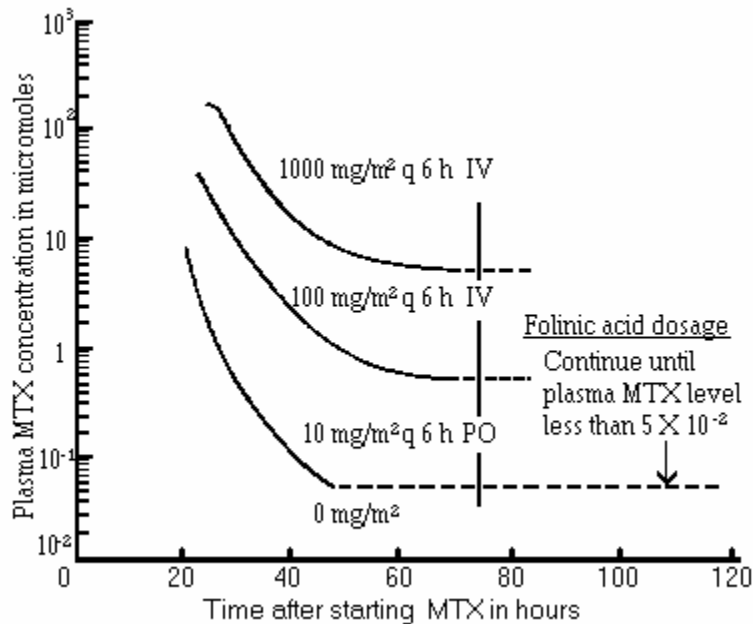
- If complete remission is demonstrated, two more cycles should be given (total cycles = 6)
- If a partial remission (greater than or equal to a 50% reduction in the sum of the products of the diameters of the lesion(s) is demonstrated, give two more cycles, then repeat imaging. If there is ongoing improvement, continue treatment until maximum response achieved or ten cycles administered, whichever comes first.
- If progressive disease or stable disease is demonstrated, patient should go off protocol and be referred for radiotherapy.

If vitreous involvement is present (either alone or in association with parenchymal disease), the patient should be reassessed by the ophthalmologist monthly while on treatment, in order to assess for ongoing response. If there is no response or progressive disease, the patient should receive eye XRT.

*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 0.05×10^{-6} molar (note: micromoles/L = 10^{-6} 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. **Hypersensitivity:** Rituximab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed. Vital signs are not required unless symptomatic. Because transient hypotension may occur during infusion, consider withholding antihypertensive medications 12 hours prior to Rituximab infusion. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. A reasonable guideline is as follows. After

recovery of symptoms, restart Rituximab infusion at one infusion rate below the rate at which the reaction occurred and continue with escalation of infusion rates on the appropriate schedule above. If the infusion must be stopped a second time, restart after clearance of symptoms, at one infusion rate lower and continue at that rate without further escalation. Fatal cytokine release syndrome can occur (see below). See BCCA Hypersensitivity Guidelines.

4. **Fatal Cytokine Release Syndrome** has been reported with Rituximab. It usually occurs within 1-2 hours of initiating the first infusion. Initially, it is characterized by severe dyspnea (often with bronchospasm and hypoxia) in addition to fever, chills, rigors, urticaria and angioedema. Pulmonary interstitial infiltrates or edema visible on chest x-ray may accompany acute respiratory failure. There may be features of tumour lysis syndrome such as hyperuricemia, hypocalcemia, acute renal failure and elevated LDH. For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
5. **Neutropenia:** **Fever or other evidence of infection must be assessed promptly and treated aggressively.**
6. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported with Rituximab. If such a reaction occurs, Rituximab should be discontinued.
7. **Gastrointestinal Obstruction or Perforation:** There have been rare reports of gastrointestinal obstruction or perforation, sometimes fatal, when Rituximab is given in combination with other chemotherapy, occurring 1 to 12 weeks after treatment. Symptoms possibly indicative of such complications should be carefully investigated and appropriately treated.
8. **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb. 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.

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 July 2007

Date revised: 01 Aug. 2010 (added neutropenia precaution)

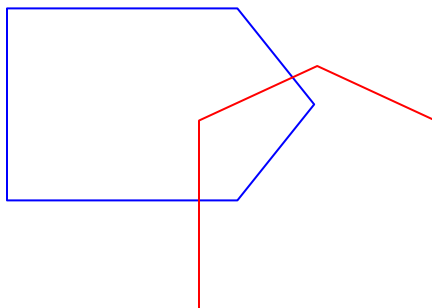
References:

1. Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev* 1977;4(2):87-101.
2. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. *Cancer* 1978;41(1):36-51.
3. 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.
4. 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.

APPENDIX 1:

Folstein's Mini-Mental Status Exam

1. Orientation (10 pts)
 - Time – Date, Year, Month, Day, Season
 - Place – Hospital, Floor, City, Province, Country
2. Registration (3 pts)
 - 3 objects – 1st repetition
3. Attention and Calculation (5 pts)
 - Serial 7's or spell "world" backwards
4. Recall (3 pts)
 - recall 3 objects
5. Language (8 pts)
 - Naming – watch and pencil (2 pts)
 - Repetition – "No if's, and's, or but's" (1 pt)
 - 3-stage command – "Take the paper in your right hand, fold it in half and put it on the floor" (3 pts)
 - Reading – "Close your eyes" (1 pt)
 - Writing – spontaneous sentence (1 pt)
6. Copying (1 pt)



TOTAL SCORE ____ / 30