BC Cancer Protocol Summary for Treatment of Primary and Secondary CNS Lymphoma with High Dose Methotrexate, riTUXimab and temozolomide

Protocol Code	*LYHDMRTEM*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Diego Villa*

ELIGIBILITY:

Patients must:

- Have primary or secondary CNS lymphoma, newly diagnosed or recurrent,
- Be 16 years of age or older, and
- Have an ECOG performance status of 0-3

EXCLUSIONS:

Patients must not have:

- 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 male
1.04 female

- Pleural effusion, ascites, or full extremity edema

CAUTIONS:

- Hemoglobin less than 90 g/L; neutrophils less than 1.5 x 10^9/L; platelets less than 75 x 10^9/L
- AST, ALT, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

TESTS:

Baseline and Pretreatment:

- CBC and differential, platelets, serum creatinine, electrolytes panel, 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 further treatment: HBsAg, HBcoreAb
- 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, electrolytes panel
- If clinically indicated post methotrexate: daily ALT, bilirubin, alkaline phosphatase, LDH, GGT
- **At hour 48** (from start of methotrexate infusion)**, or morning of day 3, then daily q am:** methotrexate levels (until less than 0.1 micromol/L; note date and time of withdrawal as well as start time of infusion on specimen.)

For cycles with temozolomide:

- CBC and differential prior to temozolomide (may be done between days 4 to 7)

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 q6h PRN

For **riTUXimab** portion

- For intravenous infusion:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 h*
  acetaminophen 650-975 mg PO *prior to riTUXimab IV and then* q 4 h during the IV infusion, *if the infusion exceeds 4 h*

- For subcutaneous injection:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab subcutaneous*
  acetaminophen 650-975 mg PO *prior to riTUXimab subcutaneous*

For **temozolomide**:

- ondansetron 8mg PO 30 minutes prior to each dose

SUPPORTIVE MEDICATIONS:

DRUG	DOSE	BC CANCER 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
famotidine	20 mg 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 X 10^{-6} molar (note: micromoles/L = 10^{-6} molar).** If allergic, do not use any antibiotic prophylaxis.	PO
lamiVUDine (if HBsAg or HBcoreAb positive)	100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.	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]

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.

DRUG	DOSE	BC CANCER ADMINISTRATION GUIDELINES
methotrexate	8 g/m^2 (Day 1)¥ prorated¶ to GFR or CrCl between 60 to 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 IS LESS THAN 0.1 micromol/L¶
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 to 8 hours* (doses between 500 to 1000 mg can be prepared in either 250 mL or 500 mL NS)
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL) on day 1 or 2 whenever possible but not later than 72 h after Methotrexate (note: given q 2 weekly x 4 doses)	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
temozolomide	150 mg/m^2 daily for 5 days (on days 7 to 11) on alternate cyclesϕ	PO, at bedtime

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

¥ Dose reductions should be strongly considered in elderly patients.

¶ Prorated dosing, e.g.
- GFR (or CrCl) greater than or equal to 100 mL/min, give 8 g/m^2
- GFR 85 mL/min, give 85% of 8 g/m^2
- GFR 60 mL/min, give 60% of 8 g/m^2

Note: Prorated dosing is not required if methotrexate dose is 3.5 g/m^2.

§ 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 (first dose) initial infusion at 50 mg/h and, after 1 hour, 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 1 hour (total infusion time = 1 hour 30 min). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

If the peripheral blood lymphocyte count is above 30 x 10^9/L, the riTUXimab should be omitted from that cycle.

†Patients must receive first dose by IV infusion (using the IV formulation) because the risk of reactions is highest with the first infusion. IV administration allows for better management of reactions by slowing or stopping the infusion.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.

ϕ Temozolomide initiation is recommended with cycle 2, but can start with earlier or later cycles according to physician discretion.

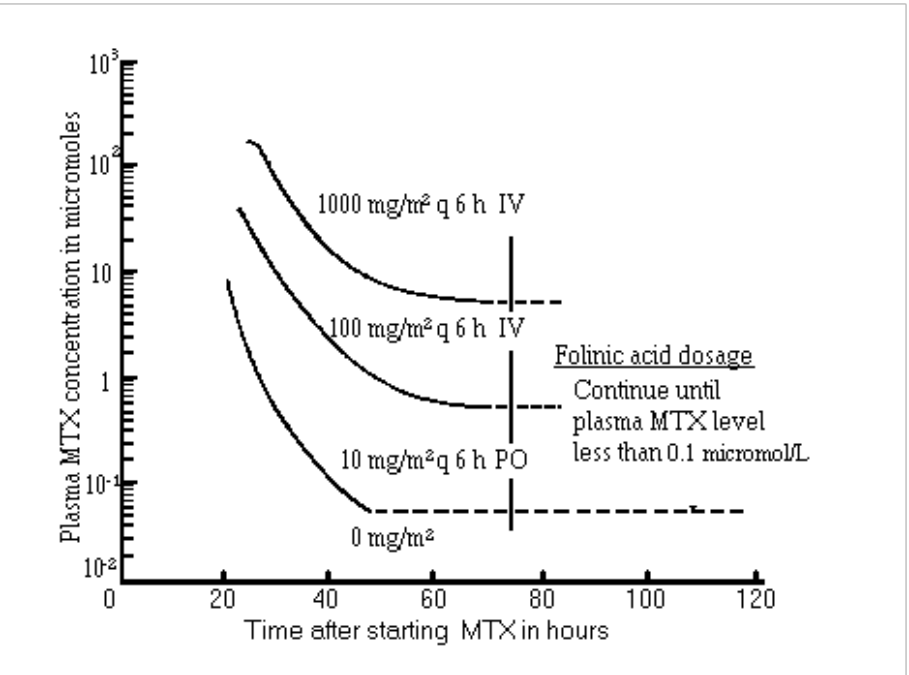
Cycles are administered every two weeks. Note: riTUXimab is given for a total of 4 doses. Temozolomide is given every 28 days for up to 4 cycles as tolerated.

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 concentration done on day 3 is used to plot the initial slope of the curve on the Bleyer diagram below and 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: micromoles/L = 10^{-6} molar).



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

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. Hematological:

On day 1 for methotrexate:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
greater than or equal to 1.5	and	greater than or equal to 75	Proceed
less than 1.5	or	less than 75	Delay*

Prior to temozolomide:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 50	100%
0.5 to less than 1.0	and	25 to less than 50	Reduce to 100 mg/m^2*
less than 0.5	or	less than 25	Discontinue or hold and reassess at the next even-numbered cycle**

* May re-escalate dose at next treatment

** Doses below 100 mg/m^2 not permitted

2. Renal Dysfunction

For methotrexate:

- 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
- If methotrexate is held for renal dysfunction, may consider proceeding with rituximab and temozolomide as scheduled

3. 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).

4. Hepatic dysfunction:

For methotrexate: At high doses, methotrexate can cause elevation of bilirubin and other liver enzymes. Even though these abnormalities are generally reversible, delaying treatment until liver enzymes significantly improve or return to near normal values before starting the next cycle is recommended. The table below may be used as a guide to dose reductions but more conservative dosing is strongly recommended for higher doses of methotrexate ($8g/m^2$) at physician discretion.

Bilirubin (micromol/L)		***AST or ALT(units/L)***	***Dose Modification***
2 to 49			100%
50 to 85	OR	3 x ULN	75%
Greater than 85			Omit

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 BC Cancer Hypersensitivity Guidelines.
4. **Fatal Cytokine Release Syndrome** has been reported with riTUXimab. It usually occurs within 1 to 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 during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. (Note: MSP does not cover more than 6 tests per calendar year). 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.
9. **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.
10. **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.
11. **Medication Safety:** riTUXimab is formulated differently for IV versus subcutaneous administration. Use caution during prescribing, product selection, preparation and administration. IV formulation is supplied as 10 mg/mL solution which must be diluted prior to administration. Subcutaneous formulation is supplied as a fixed dose of 1400 mg/11.7 mL ready-to-use solution which contains hyaluronidase to facilitate injection.
12. **Increased drug absorption by hyaluronidase:** other subcutaneous medications should not be injected at the same site as subcutaneous riTUXimab. Increased systemic effects are unlikely to be clinically significant with topical applications of EMLA, hydrocortisone, or diphenhydrAMINE.

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

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.
5. Ranchon F, Vantard N, Gouraud A, et al. Suspicion of drug-drug interaction between high-dose methotrexate and proton pump inhibitors: a case report – should the practice be changed? Chemotherapy 2011; 57 (3): 225-229.
6. Lexicomp Online®, Interaction Monograph, Methotrexate/Penicillins; 25 October 2016.
7. Rubenstein JL, Hsi ED, Johnson JL et al. Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202). JCO 2013; 31(25): 3061-8.
8. Kansara R, Shenkier T, Connors J et al. Rituximab with high-dose methotrexate in primary central nervous system lymphoma. Am J Hematol 2015; 90(12): 1149-54.

APPENDIX 1:

Folstein's Mini-Mental Status Exam

1. Orientation (10 pts)
   - Time – Date, Year, Month, Day, Season
   - Place – Hospital, Floor, City, Province, Country

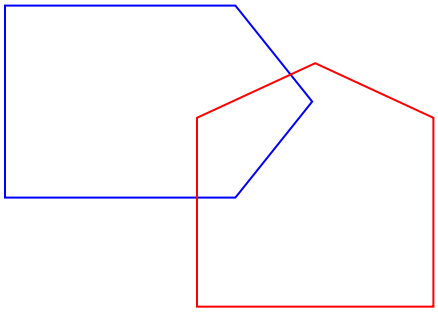
2. Registration (3 pts)
   - 3 objects – 1st repetition

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