

# BC Cancer Protocol Summary for Central Nervous System Prophylaxis with High Dose Methotrexate, CHOP and ritUXimab in Diffuse Large B-Cell Lymphoma

**Protocol Code**

LYCHOPRMTX

**Tumour Group**

Lymphoma

**Contact Physician**

Dr. Diego Villa

## ELIGIBILITY:

Patients must fit the following criteria:

1. Age: 16 y or greater,
2. Performance status: ECOG 0-3,
3. **Diagnosis:** biopsy-proven diffuse large B-cell lymphoma with high risk of CNS involvement, but no established CNS disease
  - a. All stages of testicular DLBCL
  - b. Advanced stage DLBCL with renal involvement, or
  - c. Advanced stage DLBCL with other high-risk features for CNS relapse

Patients should have:

Acceptable hematologic, renal and hepatic function

## EXCLUSIONS:

Patients must not have:

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, or
3. AST, ALT, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

## TESTS:

- **Baseline and Pretreatment:**
  - Baseline Only (required, but results do not have to be available to proceed with treatment; results must be checked before proceeding with cycle 2): LDH, HBsAg, HBcoreAb
  - CBC & diff, platelets, serum creatinine, sodium, potassium, ALT, bilirubin, alkaline phosphatase, LDH
  - urine pH
  - chest radiograph
  - Baseline Folstein mini mental status exam (MMSE) (see Appendix 1)
  - ECOG performance status

- During Methotrexate Treatment:
  - Immediately pre-methotrexate and q6h: urine pH
  - Daily every morning during methotrexate treatment: serum creatinine, electrolytes panel,
  - If clinically indicated starting on Day 11 (i.e. post methotrexate): daily ALT, bilirubin, alkaline phosphatase, LDH, GGT
  - **At hour 48** (from start of methotrexate infusion), **or morning of day 12** (day 10= day of methotrexate infusion) **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.)
  - Folstein mini mental status exam (MMSE) at 4<sup>th</sup> dose

## PREMEDICATIONS:

For CHOP portion

Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

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
  - predniSONE as ordered for the LYCHOPRMTX protocol
- For subcutaneous injection:
  - diphenhydrAMINE 50 mg PO prior to riTUXimab subcutaneous
  - acetaminophen 650-975 mg PO prior to riTUXimab subcutaneous
  - predniSONE as ordered for the LYCHOPRMTX protocol

For methotrexate portion:

ondansetron 8 mg PO or IV pre-chemotherapy

prochlorperazine 10 mg PO after methotrexate infusion completed and then 10 mg PO q6h PRN

## SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily 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.

**TREATMENT:**

Note that riTUXimab is given once with each dose of CHOP, not weekly as when used as single agent.

Drug	Dose	BC Cancer Administration Guideline
<b>DAY 1</b>		
DOXOrubicin	50 mg/m <sup>2</sup> on day 1	IV push
vinCRIStine	1.4 mg/m <sup>2</sup> on day 1 (no cap on dose)	IV in 50 mL NS over 15 minutes
cyclophosphamide	750 mg/m <sup>2</sup> on day 1	IV in 100 to 250* mL NS over 20 minutes to 1 hour (*use 250 mL for doses greater than 1000 mg)
predniSONE	45 mg/m <sup>2</sup> on days 1-5 (round off dose to nearest 25 mg)	PO in am with food (the predniSONE dose for that day should be taken on the morning of the riTUXimab infusion)
riTUXimab**†	375 mg/m <sup>2</sup> on day 1 or 2 whenever possible but not later than 72 h after CHOP	IV in 250 to 500 mL NS over 1 hour 30 minutes to 8 hours*
	<b>If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration</b>	
	1400 mg (fixed dose in 11.7 mL) on day 1 or 2 whenever possible but not later than 72 h after CHOP	subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
<b>DAY 10^^</b>		
<b>START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE:</b>		
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 or equal to 7 before starting methotrexate.		
methotrexate	3.5 grams/m <sup>2</sup> on day 10	IV in 1000 mL NS over 4 hours See "Dose Modifications" section below.
leucovorin	25 mg q6h start on day 11	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^^^

**Note: One staff Physician signature is required. Methotrexate orders written by other providers MUST be co-signed.**

\*Start the riTUXimab (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.

\*\* The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than  $30$  to  $50 \times 10^9 /L$ . While there is no requirement to withhold ritUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to ritUXimab infusion or omit the ritUXimab from the first cycle of treatment.

†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.

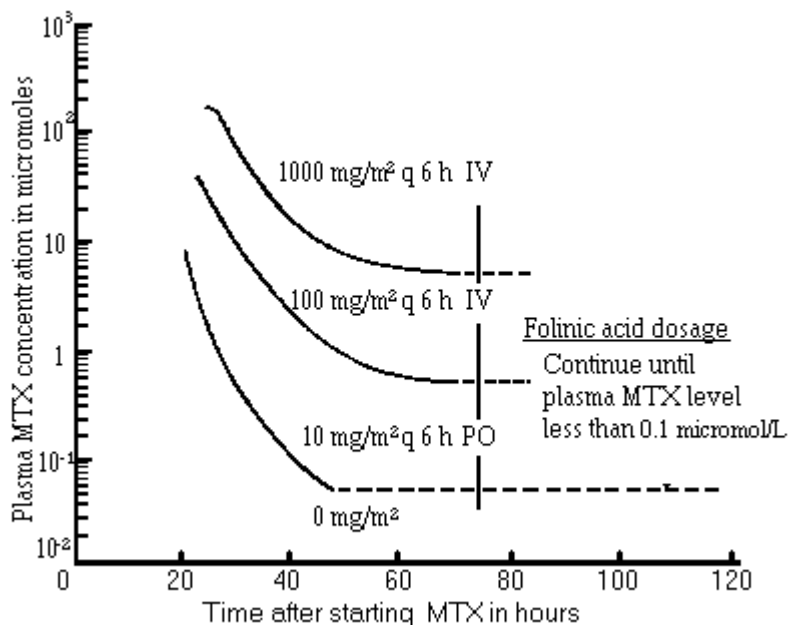
‡During treatment with subcutaneous ritUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.

**CHOPR:** Repeat every 21 days or when the neutrophil and platelet counts have recovered sufficiently to allow 100% dosing, if that is determined sooner than every 21 days. Treat for 6 cycles total.

**methotrexate:** Administer methotrexate with every second cycle of CHOPR, given on day 10. The recommended schedule is: day 10 of cycle 2, cycle 4 and cycle 6, followed by a final 4<sup>th</sup> dose 2-3 weeks later. However, the schedule may be adjusted by physician based on the patient.

^^The standard is to treat with methotrexate starting day 10 but treatment can be delayed up to day 20, based on patient tolerability of chemotherapy and according to treating physician's discretion.

^^^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 that is done at hour 48h from the start of the methotrexate infusion 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  $0.1 \times 10^{-6}$  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. Elderly Patients (age greater than 75 years):

Cycle 1 doses of cyclophosphamide and DOXOrubicin should be administered at 75% doses. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full 100% doses, but using the baseline experience with the 75% doses to guide these decisions.

### 2. Hematological:

For DOXOrubicin, cyclophosphamide and etoposide, if used, see below:

ANC (x10 <sup>9</sup> /L)	Dose Modification
greater than or equal to 0.8	100%
less than 0.8	<b>For cycles with CHOPR only:</b> 100% plus filgrastim±5mcg/kg subcutaneous daily x 5 days, starting day 7  <b>For cycles with CHOPR and methotrexate:</b> 100% plus filgrastim± 5mcg/kg subcutaneous daily x 5 days starting day 11

±Filgrastim 300 mcg: up to 75 kg  
480 mcg: 76kg to 110 kg  
600 mcg: greater than 110kg

*The patient should be treated with filgrastim (G-CSF) in doses sufficient to allow full dose treatment on a 21 day schedule, using the above dose modifications. Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate filgrastim (G-CSF) is required. (See Pharmacare guidelines and complete special authority form to Pharmacare for filgrastim coverage)*

Consider RBC transfusion support in individuals that have an expected hemoglobin nadir below 70 to 80 g/L and platelet transfusions to keep platelets greater than 20 x 10<sup>9</sup>/L.

For high dose methotrexate:

ANC (x10 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /L)	Dose Modification
greater than or equal to 1.0	and	greater than or equal to 75	Proceed with treatment
less than 1.0	or	less than 75	Delay

3. **Neurotoxicity:** vinCRISStine only:

<b>Toxicity</b>	<b>Dose Modification: vinCRISStine</b>
Dysesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

4. **Hepatotoxicity:** For DOXOrubicin:

<b>Bilirubin (micromol/L)</b>	<b>Dose Modification: DOXOrubicin</b>
2 to 35	100%
35 to 85	50%
Greater than 85	Omit DOXOrubicin. <b>ADD</b> cyclophosphamide 350 mg/m <sup>2</sup> to the dose already planned.

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs.

**Hepatotoxicity:** For vinCRISStine:

<b>Bilirubin (micromol/L)</b>	<b>Dose Modification</b>
Less than or equal to 25	100%
26 to 50	50%
Greater than 50	25%.

5. **Hepatic dysfunction:** 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 (8 g/m<sup>2</sup>) at physician discretion.

Methotrexate only:

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

## 6. .Cardiotoxicity: DOXOrubicin only:

When DOXOrubicin cannot be used due to proven cardiac dysfunction, it can be replaced by etoposide:

Drug	Dose	BC Cancer Administration Guideline
etoposide	50 mg/m <sup>2</sup> /d on day 1	IV in 500 mL NS over 45 minutes, using non-DEHP bag and tubing with 0.22 micron or smaller in-line filter
etoposide	100 mg/m <sup>2</sup> /d on days 2 and 3	PO

## 7. Renal Dysfunction: methotrexate only:

If GFR (or CrCl) less than 60 mL/min, reversible causes of renal dysfunction should be treated and the patient reassessed for suitability for methotrexate treatment once renal function improves.

\*\*\*\*IMPORTANT NOTE: Use the same renal function measure throughout the methotrexate treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and not CrCl

For methotrexate, patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7.<sup>1</sup>

## 8. Mucositis: methotrexate only:

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. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300mg/m<sup>2</sup> of DOXOrubicin (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
3. **Extravasation:** DOXOrubicin and vinCRistine cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Hypersensitivity:** If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to BC Cancer Hypersensitivity Guidelines. riTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. For first dose, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. For all subsequent doses, constant visual observation is not required. 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.
5. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1-2 hours of initiating the first infusion. Initially, it is characterised 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. The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than  $30$  to  $50 \times 10^9$  /L. While there is no requirement to withhold ritUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to ritUXimab infusion or omit the ritUXimab from the first cycle of treatment.

6. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, ritUXimab should be discontinued.
7. **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. 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.
8. **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.
9. **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.
10. **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.
11. **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.
12. **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.
13. **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.
14. **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 at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**



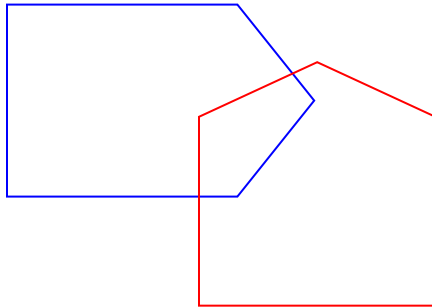
## References:

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): 225-9.
6. Villa D, Connors JM, Sehn LH, et al. Diffuse large B-cell lymphoma with renal involvement: outcome and risk of central nervous system relapse. *Haematologica* 2011;96(7):1002-07.
7. Villa D, Connors JM, Shenkier TN, et al. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. *Ann Oncol* 2010;5(21):1046-52.
8. Lexicomp Online®, Interaction Monograph, Methotrexate/Penicillins; 25 October 2016.
9. Cheah C.Y., Herbert K.E, O'Rourke K et al. A multicenter retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. *Br J Cancer* 2014;111(6):1072-9.
10. Abramson JS, Hellmann M, Barnes JA et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer* 2010;116(18):4283-90

## 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 – 1<sup>st</sup> 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