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:

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
   c. Advanced stage DLBCL with other high-risk features for CNS relapse
4. Acceptable hematologic, renal and hepatic function

EXCLUSIONS:

1. Estimated glomerular filtration rate (GFR) or estimated creatinine clearance (CrCl) below 60 mL/min

   N (140 - age) wt (kg)

   Estimated creatinine clearance: = ------------------------

   serum creatinine (micromol/L)

   N = 1.23 male

   = 1.04 female

2. Pleural effusion, ascites, full extremity edema.
3. AST, 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, lytes, AST, bilirubin, alkaline phosphatase,
  - urine pH
  - chest radiograph
  - Baseline Folstein mini mental status exam (see Appendix 1)
  - ECOG performance status

- **During Methotrexate Treatment:**
  - Immediately pre-methotrexate and q6h: urine pH
  - Daily every morning during methotrexate treatment: serum creatinine, lytes
  - Daily every morning starting on day 2 (day 1 = day of methotrexate treatment): methotrexate levels (until methotrexate level less than 0.1 micromol/L; note exact date and time methotrexate level was drawn)
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 SC
  - acetaminophen 650-975 mg PO prior to riTUXimab SC
  - 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 q4h PRN

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamivUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.
**TREATMENT:**
Note that riTUXimab is given once with each dose of CHOP, not weekly as when used as single agent.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOXorubicin</td>
<td>50 mg/m² on day 1</td>
<td>IV push</td>
</tr>
</tbody>
</table>
| vinCRISTine | 1.4 mg/m² on day 1  
(no cap on dose) | IV in 50 mL NS over 15 mins                                               |
| cyclophosphamide | 750 mg/m² on day 1      | IV in 100 to 250* mL NS over 20 min to 1 hour  
(*use 250 mL for doses greater than 1000 mg) |
| predniSONE | 45 mg/m² on days 1-5  
(round off dose to nearest 25mg) | PO in am with food  
(the predniSONE dose for that day should be taken on the morning of the riTUXimab infusion) |
| riTUXimab**† | 375 mg/m² on day 1 or 2  
(whenever possible but not later than 72 h after CHOP)  
(IV in 250 mL NS over 1 hour 30 min to 8 hours*  
(doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)) | If first IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by SC administration |
|           | 1400 mg (fixed dose in 11.7 mL) on day 1 or 2  
(whenever possible but not later than 72 h after CHOP)  
(SC over 5 minutes into abdominal wall‡  
Observe for 15 minutes after administration) |                                                                            |
| **DAY 10^^** |                                   |                                                                            |
| ALKALINIZING REGIMEN AND PRE HYDRATION: |                                                                            |
| IV 2/3 : 1/3 with sodium bicarbonate100 mEq/L and potassium chloride 20 mEq/L at 125 mL/h x 4 h pre-methotrexate |                                                                            |
| Oral sodium bicarbonate 3000 mg PO q4h until methotrexate level IS LESS THAN 0.1 micromol/L (start on admission to hospital or at 0800 h on day planned for methotrexate if already in hospital) |                                                                            |
| 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/m² on day 10  
(prorated to GFR or CrCl between 60 to 100 mL/min) | 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^^^ |
| **POST HYDRATION:** |                               |                                                                            |
| IV 2/3 : 1/3 with sodium bicarbonate100 mEq/L and potassium chloride 20 mEq/L at 125 mL/h for 48 h after Methotrexate |                                                                            |

**Note:** One staff Physician signature is required. Methotrexate orders written by residents and fellows 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 x 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 4th 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 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: micromoles/L = 10^-6 molar).
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: DOXOrubicin, cyclophosphamide and etoposide, if used, see below:

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 0.8</td>
<td>100%</td>
</tr>
</tbody>
</table>
| less than 0.8 | **For cycles with CHOPR only:** 100% plus filgrastim 300 mcg SC daily x 5 days, starting day 7  
**For cycles with CHOPR and methotrexate:** 100% plus filgrastim 300 mcg SC daily x 5 days starting day 11 |

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)

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 20 x 10^9/L.
3. **Neurotoxicity**: vinCRISTine only:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose Modification: vinCRISTine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysesthesias, areflexia only</td>
<td>100 %</td>
</tr>
<tr>
<td>Abnormal buttoning, writing</td>
<td>67%</td>
</tr>
<tr>
<td>Motor neuropathy, moderate</td>
<td>50%</td>
</tr>
<tr>
<td>Motor neuropathy, severe</td>
<td>Omit</td>
</tr>
</tbody>
</table>

4. **Hepatotoxicity**: DOXOrubicin and methotrexate:

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>Dose Modification: DOXOrubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-35</td>
<td>100%</td>
</tr>
<tr>
<td>35-85</td>
<td>50%</td>
</tr>
<tr>
<td>Greater than 85</td>
<td>Omit DOXOrubicin. <strong>ADD</strong> cyclophosphamide 350 mg/m² to the dose already planned.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>AST (units/L)</th>
<th>Dose Modification: methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-49</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>50-85</td>
<td>OR</td>
<td>75%</td>
</tr>
<tr>
<td>Greater than 85</td>
<td></td>
<td>Omit</td>
</tr>
</tbody>
</table>

Cardiotoxicity: DOXOrubicin only:

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

<table>
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<tr>
<td>etoposide</td>
<td>50 mg/m²/d on day 1</td>
<td>IV in 500 mL NS over 45 minutes, using non-DEHP bag and tubing with 0.22 micron or smaller in-line filter</td>
</tr>
<tr>
<td>etoposide</td>
<td>100 mg/m²/d on days 2 and 3</td>
<td>PO</td>
</tr>
</tbody>
</table>
5. **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 alkalization to maintain urine pH above 7.1

*** Prorated methotrexate dosing, e.g.
- GFR (or CrCl) greater than or equal to 100 mL/min, give 3.5 grams/m²
- GFR 85 mL/min, give 85% of 3.5 grams/m²
- GFR 60 mL/min, give 60% of 3.5 grams/m²

6. **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 lifelong dose of 450 mg/m² to be exceeded. (BC Cancer Drug Manual)

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 x 10⁹/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 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.

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 if 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:
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