

# BC Cancer Protocol Summary for Treatment of Lymphoma with DOXOrubicin, Cyclophosphamide, vinCRIStine, predniSONE and riTUXimab (CHOP-R)

**Protocol Code**

LYCHOPR

**Tumour Group**

Lymphoma

**Contact Physician**

Dr. Laurie H. Sehn

## ELIGIBILITY:

Patients must have:

- Newly diagnosed diffuse large B-cell lymphoma, any stage,
- Mantle cell lymphoma,
- Follicular lymphoma grade 3B, or
- Biopsy confirmed or clinically suspected transformed lymphoma

## CAUTION:

- Congestive cardiac failure requiring current treatment (LYCHOPR may be used but DOXOrubicin should be omitted, see cardiotoxicity below)

## TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, bilirubin, ALT
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Before each treatment: CBC and diff, platelets, (and serum bilirubin if elevated at baseline; serum bilirubin does not need to be requested before each treatment, after it has returned to normal)
- Reassess all sites of disease after cycles 4 and 6 to determine duration of treatment

## 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 LYCHOPR 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 LYCHOPR protocol

**SUPPORTIVE MEDICATIONS:**

If HBsAg or HBcoreAb positive, start lamivudine 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.

**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
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 mins
cyclophosphamide	750 mg/m <sup>2</sup> 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/m <sup>2</sup> 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/m <sup>2</sup> on day 1 or 2 whenever possible but not later than 72 h after CHOP (before or after chemotherapy)	IV in 250 to 500 mL NS over 1 hour 30 min 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 (before or after chemotherapy)	subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

\*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.

\*\*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<sup>9</sup> /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.

- 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.
- Limited stage: CHOP-R x 3 cycles, followed by radiation therapy
- Advanced stage: CHOP-R x 6 cycles. (Six cycles is generally considered the standard of care but may extend to 8 cycles if individual circumstances warrant continuation)
- **Discontinue if no response after 2 cycles.**

## 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:

ANC (x10 <sup>9</sup> /L)	Dose Modification
greater than or equal to 0.8	100%
less than 0.8	100% plus filgrastim* 5mcg / kg subcutaneous daily x 5 days, starting on day 7

*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 submit special authority request to Pharmacare for filgrastim coverage)*

\*Filgrastim 300 mcg: up to 75 kg

480 mcg: 76 kg to 110 kg

600 mcg: greater than 110 kg

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.

### 3. Neurotoxicity: vinCRISTine only:

Toxicity	Dose Modification
Dyesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	omit

4. **Hepatotoxicity:** For DOXOrubicin:

Bilirubin (micromol/L)	Dose Modification
2-35	100%
35-85	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. Serum bilirubin does not need to be requested before each treatment.

**Hepatotoxicity:** For vinCRISStine:

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

5. **Cardiotoxicity:** DOXOrubicin only:

When DOXOrubicin cannot be used due to proven cardiac dysfunction, it can be replaced by etoposide 50 mg/m<sup>2</sup> IV on day 1 (Use non-DEHP Equipment with in-line filter), 100 mg/m<sup>2</sup> PO on day 2 and 3.

**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 300 mg/m<sup>2</sup> of doxorubicin. (BC Cancer Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
3. **Extravasation:** DOXOrubicin and vinCRISStine 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 **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. **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.
10. **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. Laurie Sehn or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

#### References:

1. Fisher RI, Gaynor ER, Dahlborg S, Oken MM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;328:1002-6.
2. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, et al. Hydroxydaunomycin (Adriamycin) combination therapy in malignant lymphoma. *Cancer* 1976;38:484-93.
3. Coiffier B, Lepage E, Herbrecht R, Tilly H, et al. Mabthera (rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma (DLCL): interim results of a randomized GELA trial. *Blood* 2000;96(11):223a (abstract #950).
4. Byrd JC, Peterson BL, Morrison VA, Park K, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 2712. *Blood* 2003; 101:6-14. (re: shortened rituximab infusion)