

# BC Cancer Protocol Summary for Treatment of relapsed Chronic Lymphocytic Leukemia using Cyclophosphamide, vinCRISTine, predniSONE and riTUXimab (CVP-R)

**Protocol Code**

LYCLLCVPR

**Tumour Group**

Lymphoma

**Contact Physicians**

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## ELIGIBILITY:

- Relapsed chronic lymphocytic leukemia /small lymphocytic lymphoma (note: small lymphocytic lymphoma is a variant of CLL, see LYCLLFLUDR)

## TESTS:

- Baseline (required before first treatment): CBC and 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): LDH, HBsAg, HBcoreAb
- Before each treatment: CBC and diff, platelets

## PREMEDICATIONS:

For CVP Portion:

ondansetron 8 mg PO pre-chemotherapy  
dexamethasone 12 mg PO pre-chemotherapy

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 LYCLLCVPR 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 LYCLLCVPR 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 CVP, not weekly as when used as single agent.

**Treatment:****CYCLE 1:**

Drug	Dose	BC Cancer Administration Guideline
vinCRiStine	1.4 mg/m <sup>2</sup> on day 1 (no maximum dose)	IV in 50 mL NS over 15 mins
cyclophosphamide	1000 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 dose greater than 1000 mg.
predniSONE	100 mg starting on day 1	PO daily in am with food x 5 consecutive days
riTUXimab**†	375 mg/m <sup>2</sup> on day 1 or 2 whenever possible but not later than 72 h after CVP	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*

**CYCLES 2 - 8**

Drug	Dose	BC Cancer Administration Guideline
vinCRiStine	1.4 mg/m <sup>2</sup> on day 1 (no maximum dose)	IV in 50 mL NS over 15 mins
cyclophosphamide	1000 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 dose greater than 1000 mg.
predniSONE	100 mg starting on day 1	PO daily in am with food x 5 consecutive days
riTUXimab**†	500 mg/m <sup>2</sup> on day 1 or 2 whenever possible but not later than 72 h after CVP	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>	
	1600 mg (fixed dose in 13.4 mL) on day 1 or 2 whenever possible but not later than 72 h after CVP	subcutaneous over 7 minutes into abdominal wall‡  Observe for 15 minutes after administration

\*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 of 250 mL bag (or 100 mL of 500 mL bag) of the dose over 30 minutes then infuse the remaining 200 mL of 250 mL bag (or 400 mL of 500 mL bag) (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 or 28 days (see dose modifications) for 8 cycles. For further use, CAP approval is required.

## DOSE MODIFICATIONS:

### 1. Hematological:

ANC (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Dose Modification
less than 1.2	or	less than 100	delay x 1 week

### 2. Neurotoxicity: vinCRISTine only

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

### 3. Hepatotoxicity: vinCRISTine only

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

## PRECAUTIONS:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Extravasation:** vinCRISTine causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. **Hypersensitivity:** 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).
4. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 2 hours of initiating the first ritUXimab 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 and 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.
5. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, ritUXimab should be discontinued.
6. **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.
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. **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 or 1600mg/13.4mL ready-to-use solution which contains hyaluronidase to facilitate injection.
9. **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 H. Sehn, Dr. Gerrie or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

#### REFERENCES:

1. Byrd JC, Peterson BL, et al. Randomized phase II 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 9712. *Blood* 2003; 101:6-14. (re: shortened rituximab infusion duration)

2. O'Brien SM, Kantarjian H, Thomas DA, et al: Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19(8):2165-70.