

BC Cancer Protocol Summary for Treatment of Chronic Lymphocytic Leukemia with Chlorambucil and riTUXimab

Protocol Code

LYCLLCHLR

Tumour Group

Lymphoma

Contact Physician

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ELIGIBILITY:

- Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

EXCLUSIONS:

- Uncontrolled active haemolytic anemia or immune-related thrombocytopenia

TESTS:

- Baseline (required before first treatment): CBC & Diff
- Baseline (required, but results do not have to be available to proceed with first treatment): HBsAg, HBsAb, HBcoreAb
- Before each cycle: CBC & Diff
- If clinically indicated: HBV viral load, ALT (see protocol [SCHBV](#))
- Reassess all sites of disease after cycles 4 and 6 to determine duration of treatment

PREMEDICATIONS:

For riTUXimab:

- 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

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per [SCHBV](#).

TREATMENT:

Two schedules of chlorambucil are available. Schedule 1 is preferred for most patients as it may be better tolerated. Rituximab is given with either schedule of chlorambucil.

Cycle 1:

Drug	Dose	BC Cancer Administration Guideline
chlorambucil	<u>Schedule 1</u> 0.4 mg/kg on Days 1 and 15. If ANC greater than $3.5 \times 10^9/L$, increase by 0.1 mg/kg to induce a response but not reduce ANC below $1.2 \times 10^9/L$. MAXIMUM: 0.8 mg/kg. OR <u>Schedule 2</u> 10 mg/m ² on Days 1 to 7 Round each dose to the nearest 2 mg. Administer on an empty stomach.	PO Dividing into 2-3 subdoses each day may improve tolerance
riTUXimab**	375 mg/m ² on Day 1 or 2 whenever possible but not later than 72 hours after Day 1 chlorambucil	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*

Cycle 2 onwards:

Drug	Dose	BC Cancer Administration Guideline
chlorambucil	<p><u>Schedule 1</u></p> <p>0.4 mg/kg on Days 1 and 15. If ANC greater than $3.5 \times 10^9/L$, increase by 0.1 mg/kg to induce a response but not reduce ANC below $1.2 \times 10^9/L$. MAXIMUM: 0.8 mg/kg.</p> <p>OR</p> <p><u>Schedule 2</u></p> <p>10 mg/m² on Days 1 to 7</p> <p>Round each dose to the nearest 2 mg. Administer on an empty stomach.</p>	<p>PO</p> <p>Dividing into 2-3 subdoses each day may improve tolerance</p>
riTUXimab**	500 mg/m ² on Day 1 or 2 whenever possible but not later than 72 hours after Day 1 chlorambucil	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1600 mg (fixed dose in 13.4 mL) on Days 1 or 2 whenever possible but no later than 72 h after Day 1 chlorambucil	Subcutaneous over 7 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 $50 \times 10^9/L$. 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. Allopurinol may also be considered for cycle 1 in patients with a lymphocyte count greater than 30 - $50 \times 10^9/L$.

†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. *IV first dose should also be given to patients previously treated more than 6 months ago.*

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible. *If restarting more than 6 months from prior subcutaneous rituximab, give first dose by IV infusion (using the IV formulation).*

Repeat every 28 days x 6 cycles. An additional 6 cycles of chlorambucil alone may be considered in patients with a continuing response.

DOSE MODIFICATIONS:

1. **Hematological:** chlorambucil (for low counts due to treatment, not disease)

ANC ($\times 10^9/L$)	Platelets ($\times 10^9/L$)	Dose Modification
greater than or equal to 1.2	Greater than or equal to 80	100%
less than 1.2	Less than 80	Delay until recovery

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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). See BC Cancer Hypersensitivity Guidelines.
3. **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.
4. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
5. **Hepatitis B Reactivation:** See [SCHBV protocol](#) for more details.
6. **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.

7. **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.
8. **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. Alina 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. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014; 370:1101-1110.
2. Hillmen P, Gribben JG, Follow GA et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukemia: Final analysis of an open-label phase II study. *J Clin Oncol* 2014; 32: 1236-1241.
3. Leblond V, Laribi K, Ilhan O et al. Rituximab in combination with bendamustine or chlorambucil for treating patients with chronic lymphocytic leukemia : interim results of a phase IIIb study (MaBLLe). *Blood (ASH Annual Meeting Abstracts)* 2012; 120: Abstract 2744.
4. 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.