BC Cancer Protocol Summary for the Treatment of Hairy Cell Leukemia with Cladribine and riTUXimab

Protocol Code	*LYCLADR*
Tumour Group	*Lymphoma*
Contact Physician	*LY Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Relapsed or refractory hairy cell leukemia (HCL), or
- Previously untreated, relapsed or refractory hairy cell leukemia variant (HCLv), and
- Symptomatic disease requiring systemic therapy.

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, total bilirubin, ALT, LDH
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Week 3 treatment): HBsAg, HBsAb, HBcoreAb
- Before each weekly treatment (results do not have to be available to proceed with treatment. Provider to review results and provide supportive care as required, no dose modifications indicated for bloodwork): CBC & Diff
- If clinically indicated: HBV viral load, ALT (see protocol SCHBV)

PREMEDICATIONS:

Cladribine: None

riTUXimab: (Note: patients should bring their own supply)

- For intravenous infusion:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab IV and then* q4h during the IV infusion, *if the infusion exceeds 4 hours*
  acetaminophen 650-975 mg PO *prior to riTUXimab IV and then* q4h during the IV infusion, *if the infusion exceeds 4 hours*

- For subcutaneous injection:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab subcutaneous*
  acetaminophen 650-975mg 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.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV), unless contraindicated (valACYclovir 500 mg PO daily). Continue for duration of treatment and for 6 months afterwards or until adequate neutrophil and lymphocyte recovery.

TREATMENT:

WEEK 1:

Drug	Dose	BC Cancer Administration Guideline
cladribine	0.15 mg/kg/day	IV in 500 mL NS over 2 hours daily for 5 consecutive days on Days 1 to 5
	OR	
	0.15 mg/kg/day	Subcutaneous daily for 5 consecutive days¥‡ on Days 1 to 5
riTUXimab**†	375 mg/m^2*** on Day 1 only	IV in 250 to 500 mL NS over 90 minutes to 8 hours*
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL)	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

WEEKS 2 to 8: Day 1 only

Drug	Dose	BC Cancer Administration Guideline
riTUXimab**†	375 mg/m^2***	IV in 250 to 500 mL NS over 90 minutes to 8 hours*
	If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration	
	1400 mg (fixed dose in 11.7 mL)	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. The subsequent infusions may start at 100 mg/h and be increased by 100 mg/h every 30 minutes until a rate of 400 mg/h is reached. 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.

***Select dose per Dose Banding Table (appendix).

†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).

¥In Canada, cladribine is provided as 1 mg/mL concentration only. As a result, subcutaneous administration requires several syringes to be administered. Therefore, IV route may be preferred.

Treatment duration:

- Cladribine is given for 5 consecutive days during Week 1 only (i.e. on Days 1 to 5).
- riTUXimab is given weekly on Day 1 of each week (i.e. Week 1 Day 1, Week 2 Day 1, etc), for a total of 8 doses.

DOSE MODIFICATIONS:

1. **Hematologic:** There is no dose reduction for hematologic blood counts. Treatment may be delayed for Grade 3 to 4 toxicity to allow recovery. Consider RBC transfusion support in individuals that have an expected hemoglobin nadir below 70 to 80g/L and platelet transfusions to keep platelets greater than 20 x 10^9/L (see Precautions). G-CSF (filgrastim) may be considered in special situations, such as patients with severe neutropenic fever or where it is desirable to resolve neutropenia as soon as possible (see Pharmacare guidelines and submit Special Authority request to Pharmacare for filgrastim coverage as it is not a BC Cancer benefit drug).

2. **Renal Dysfunction: cladribine**

For any patient with a creatinine above normal and for all patients above the age of 60 years, a creatinine clearance should be measured or calculated using the following formula:

Estimated creatinine clearance (in mL/minute) =

For men: [1.23 x (140-age)(weight in kg)] ÷ creatinine in micromol/L
For women: [1.04 x (140-age)(weight in kg)] ÷ creatinine in micromol/L

Creatinine clearance (mL/minute)	Actual cladribine Dose and Schedule (note change in number of days)
Greater than or equal to 70	0.15 mg/kg/day x **5 consecutive days**
30 to less than 70	0.15 mg/kg/day x **3 consecutive days**
Less than 30	DO NOT USE

PRECAUTIONS:

1. **Hypersensitivity:** 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.
2. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 2 hours of initiating the first infusion. Initially, it is characterized 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 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.

3. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
4. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
5. **Need for irradiated blood products:** Potentially life-threatening transfusion-related graft-versus-host disease has been described in patients actively receiving cladribine. The Canadian Blood Service recommends that patients on cladribine should receive irradiated blood products, effectively eliminating this risk.
6. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
7. **Severe neurotoxicity:** has been reported with high doses of cladribine or overdose (4 to 9 times the doses used with this protocol), including irreversible neurologic toxicity, Guillain-Barré and Brown-Séquard syndromes.
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.

Contact the LY Systemic Therapy physician at your regional cancer centre or the LY Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Chihara D, Arons E, Stetler-Stevenson M, et al. Randomized Phase II Study of First-Line Cladribine With Concurrent or Delayed Rituximab in Patients With Hairy Cell Leukemia. J Clin Oncol. 2020 May 10;38(14):1527-1538.
2. Chihara D, Arons E, Stetler-Stevenson M, et al. Long term follow-up of a phase II study of cladribine with concurrent rituximab with hairy cell leukemia variant. Blood Adv. 2021 Dec 14;5(23):4807-4816.
3. Kreitman R, Wang H, Delgado Colon D, et al. Phase 2 trial of cladribine plus immediate rituximab for 1st-line treatment of hairy cell leukemia – long term follow-up of original and additional patient cohorts. Blood; 146, Supp.1, 2025 Nov 3:3609.

Appendix. Dose Bands

riTUXimab DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)
From:	**To:**	
Less than 364		**Pharmacy prepares specific dose**
364	442.49	**400**
442.5	480.49	**460**
480.5	554.49	**500**
554.5	665.49	**600**
665.5	776.49	**700**
776.5	887.49	**800**
887.5	999.49	**900**
999.5	1099.49	**1000**
1099.5	1199.49	**1100**
1199.5	1299.49	**1200**
1299.5	1399.49	**1300**
1399.5	1499.49	**1400**
1499.5	1599.49	**1500**
More than 1599.49		**Pharmacy prepares specific dose**