

BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia (CLL) with Bendamustine and riTUXimab

Protocol Code

LYCLLFBR

Tumour Group

Lymphoma

Contact Physicians

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ELIGIBILITY:

Patients must:

- Have chronic lymphocytic leukemia or small lymphocytic lymphoma which has not been previously treated,
- Not be medically fit to tolerate fludarabine-based therapy, and
- Have symptomatic disease requiring systemic treatment

EXCLUSIONS:

Patients must not have:

- Hodgkin's lymphoma or diffuse large B-cell lymphoma

CAUTION:

- Creatinine clearance (CrCl) less than 40 mL/min
- AST or ALT greater than 2.5 x upper limit of normal and total bilirubin greater than 1.5 x upper limit of normal

TESTS:

- Baseline, then as indicated:
 - Required before first treatment: CBC & Diff, creatinine, ALT, total bilirubin
 - Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2: HBsAg, HBsAb, HBcoreAb
- Before Day 1 of each treatment cycle: CBC & Diff
- If clinically indicated: creatinine, ALT, total bilirubin, HBV viral load (see protocol [SCHBV](#))

PREMEDICATIONS:

Antiemetic protocol for moderately 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
- 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:**Cycle 1**

Drug	Dose	BC Cancer Administration Guideline
bendamustine	90 mg/m ² on Days 1 and 2	IV in 250 to 500 mL NS over 1 hour
riTUXimab	375 mg/m ² on Day 1 or 2 whenever possible, but not later than 72 h after Day 1 of bendamustine	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours**

Cycle 2, 3, 4, 5 and 6

Drug	Dose	BC Cancer Administration Guideline
bendamustine	90 mg/m ² on Days 1 and 2	IV in 250 to 500 mL NS over 1 hour
riTUXimab***,†	500 mg/m ² on Day 1 or 2 whenever possible, but not later than 72 h after Day 1 of bendamustine	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 of bendamustine	Subcutaneous over 7 minutes into abdominal wall‡ Observe for 15 minutes after administration

Repeat every 28 days. Maximum 6 cycles. Discontinue if definite progression at any time.

**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 riTUXimab hypersensitivity below.

***The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30-50 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.

†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).

DOSE MODIFICATIONS:

1. Hematological, Day 1 only

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	bendamustine
greater than or equal to 1.0	and	greater than or equal to 75	100%
less than 1.0	or	less than 75	Delay until recovery

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Thrombocytopenia:** Support with platelet transfusion may be required.
3. **Hepatitis B Reactivation:** See [SCHBV protocol](#) for more details.
4. **Bendamustine Infusion Reactions and Hypersensitivity:** Bendamustine can cause allergic type reactions during the IV infusion such as fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred rarely, particularly in the second and subsequent cycles of therapy. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. Consider pre-treatment with antihistamines, antipyretics and corticosteroids for patients experiencing Grade 1 or 2 infusion reactions; consider discontinuing treatment for patients experiencing Grade 3 or 4 infusion reactions. See BC Cancer Hypersensitivity Guidelines.
5. **Rituximab 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 the 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).
6. **Tumour Lysis Syndrome:** Tumor lysis syndrome has been associated with bendamustine, possibly leading to acute renal failure and death. Usual onset occurs during the first cycle. Maintain adequate volume status and monitor blood chemistry, including potassium and uric acid levels if indicated. Allopurinol has been used, but the concomitant use of bendamustine and allopurinol can cause increased risk of severe skin toxicity.
7. **Drug Interactions:** CYP1A2 inhibitors can potentially decrease plasma concentration of bendamustine. CYP1A2 inducers can potentially increase plasma concentration of bendamustine.
8. **Skin Reactions:** Rash, toxic skin reactions and bullous exanthema have been reported with bendamustine. They may be progressive and increase in severity with further treatment. Monitor closely. If skin reactions are severe or progressive, consider withholding or discontinuing bendamustine.
9. **Fatal Cytokine Release Syndrome** has been reported with riTUXimab. It usually occurs within 1-2 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 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 $30\text{--}50 \times 10^9/\text{L}$. 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.

10. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported with riTUXimab. If such a reaction occurs, riTUXimab should be discontinued.
11. **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.
12. **Medication Safety:** riTUXimab is formulated differently for IV versus subcutaneous administration. Use caution during prescribing, product selection, preparation and administration.
 - **The riTUXimab IV formulation** is supplied as **10 mg/mL solution** which must be diluted prior to administration.
 - **The riTUXimab subcutaneous formulation for CLL** is supplied as a fixed dose of **1600 mg/13.4 mL** ready-to-use solution which contains hyaluronidase to facilitate injection.
 - **The riTUXimab subcutaneous formulation for NHL** is supplied as a fixed dose of **1400 mg/11.7 mL** ready-to-use solution which contains hyaluronidase to facilitate injection.
13. **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. Alina Gerrie or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Eichhorst B, Fink A, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol* 2016;17:928–42.