

BC Cancer Protocol Summary for Treatment of Non-Hodgkin Lymphoma with Bendamustine and ritUXimab

Protocol Code

LYBENDR

Tumour Group

Lymphoma

Contact Physician

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ELIGIBILITY:

- Patients with previously untreated indolent non-Hodgkin lymphoma (follicular, marginal zone, lymphoplasmacytic) and mantle cell lymphoma
- Patients with relapsed/refractory indolent non-Hodgkin lymphoma (follicular, marginal zone, lymphoplasmacytic) or mantle cell lymphoma
- For relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma, use ULYCLLBENDR protocol
- Advanced stage symptomatic disease requiring therapy

EXCLUSIONS:

- Hodgkin's lymphoma, diffuse large B-cell lymphoma
- 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, platelets, creatinine, ALT, 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, HBcoreAb
- Before day 1 of each treatment cycle: CBC & diff, platelets
- If clinically indicated: creatinine, ALT, bilirubin

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:

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:

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*
	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) on day 1 or 2 whenever possible but not later than 72 h after day 1 of bendamustine	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 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.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.

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

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:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Thrombocytopenia:** Support with platelet transfusion may be required.
- 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.
- 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.
- 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).
- 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. Allopurinol has been used, but the concomitant use of bendamustine and allopurinol can cause increased risk of severe skin toxicity.
- Drug Interactions:** CYP1A2 inhibitors can potentially decrease plasma concentration of bendamustine. CYP1A2 inducers can potentially increase plasma concentration of bendamustine.
- 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.
- 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. 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.
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 or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Rummel MJ, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the STIL (study group indolent lymphomas, Germany). *Blood*. 2010;116(21):abstr 856.
2. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. *Cancer* 2010; 116:106-14.
3. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-10.