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

Protocol Code: ULYCLLFBR
Tumour Group: Lymphoma
Contact Physician: Dr Laurie H. Sehn

ELIGIBILITY:
- First line therapy of chronic lymphocytic leukemia or small lymphocytic lymphoma
- Not medically fit to tolerate fludarabine-based therapy
- Symptomatic disease requiring systemic treatment
- A Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to https://cap.phsa.ca/).

EXCLUSIONS:
- 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, AST, 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, AST, ALT, bilirubin

PREMEDICATIONS:
Antiemetic protocol for moderately emetogenic chemotherapy (see protocol SCNAUSEA)

For riTUXimab Portion:

diphenhydramINE 50 mg PO prior to riTUXimab and then q 4 h during the IV infusion, if the infusion exceeds 4 h
acetaminophen 650-1000 mg PO prior to riTUXimab and then q 4 h during the IV infusion, if the infusion exceeds 4 h

SUPPORTIVE MEDICATIONS:
If HBsAg or HBcoreAb positive, start lamivUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.
TREATMENT:

Cycle 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>bendamustine</td>
<td>70 mg/m²* on days 1 and 2</td>
<td>IV in 250 to 500 mL NS over 1 hour (concentration range = 0.2 to 0.6 mg/mL)</td>
</tr>
<tr>
<td>riTUXimab</td>
<td>375 mg/m² on day 1 or 2 whenever possible, but not later than 72 h after day 1 of bendamustine</td>
<td>IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*** (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)</td>
</tr>
</tbody>
</table>

*May escalate dose to 90 mg/m² if tolerated.

Cycle 2, 3, 4, 5 and 6

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<td>500 mg/m² on day 1 or 2 whenever possible, but not later than 72 h after day 1 of bendamustine</td>
<td>IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*** (500-1000 mg prepared in 250 mL or 500 mL; 1000-1300 mg prepared in 250 mL [if overfill included] or 500 mL)</td>
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*May escalate dose to 90 mg/m² if tolerated.

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

** 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.

***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.

DOSE MODIFICATIONS:

1. Hematological, day 1 only

<table>
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<th>ANC (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>bendamustine</th>
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<tr>
<td>greater than or equal to 1 and greater than or equal to 75</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 1 or less than 75</td>
<td>Delay until recovery</td>
<td></td>
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</tbody>
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Warning: The information contained in these documents are a statement of consensus of BC Cancer Agency professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer Agency's terms of use available at www.bccancer.bc.ca/legal.htm
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:** 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 for six months afterwards. 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.

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 BCCA Hypersensitivity Guidelines.

5. **Rituximab Hypersensitivity:** Refer to BCCA 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 30-50 x 10^9/L. While there is no requirement to withhold riTUXimab based on lymphocyte count, clinicians may wish to pre-mEDIATE 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.

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.

Date activated: 1 Jan 2017

Date revised:

References: