# BC Cancer Protocol Summary for the Treatment of Relapsed or Refractory Advanced Stage Aggressive B-Cell Non-Hodgkin's Lymphoma with Ifosfamide, CARBOplatin, Etoposide and riTUXimab

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| ***Protocol Code*** | *LYRICE* |
| ***Tumour Group*** | *Lymphoma* |
| ***Contact Physician*** | *Dr. Laurie Sehn* |

## ELIGIBILITY:

Patients must:

- Be greater than or equal to 18 years of age,
- Have aggressive histology lymphoma in the WHO classification including
    - diffuse large B-cell lymphoma
    - mediastinal large B-cell lymphoma
    - T-cell rich B-cell lymphoma
    - intravascular large B-cell lymphoma, and
- Have relapsed disease

Patients should have:

- ECOG Performance Status 0,1,2 or 3, and
- Adequate renal, hepatic, and bone marrow function

## TESTS:

- Baseline (required before first treatment): CBC & Diff, total bilirubin, ALT, alkaline phosphatase, LDH, creatinine, calcium
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2): Hepatitis B and C serology (HBsAg, HBsAb, HBcoreAb, HepCAb), HIV, pregnancy test for women of childbearing age
- Prior to each cycle: CBC & Diff, total bilirubin, LDH, creatinine
- Prior to each ifosfamide treatment on Days 1, 2, and 3: urine dipstick for blood. – if positive at any time, notify doctor, send urine sample for urinalysis for verification and accurate measurement of hematuria
- If clinically indicated: HBV viral load, ALT (see protocol SCHBV)

## PREMEDICATIONS:

- Antiemetic protocol for highly 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:

| Drug | Dose¥ | BC Cancer Administration Guideline |
|---|---|---|
| Ifosfamide§ | 1667 mg/m$^2$/day<br>(total dose per cycle = 5000 mg/m$^2$) | IV in 500 mL NS over 2 hours on Days 1,2,3 |
| mesna (IV)§ | 1667 mg/m$^2$/day<br>(total dose per cycle = 5000 mg/m$^2$) | IV in 500 mL NS over 2 hours on Days 1,2,3 |
| mesna (PO) | 2000 mg | PO 2 h and 4 h after completion of ifosfamide infusion on Days 1,2,3 |
| CARBOplatin | AUC 5 x (GFR¶ + 25)<br>(maximum dose 800 mg) | IV in 100 to 250 mL NS over 1 hour on Day 1 |
| etoposide | 100 mg/m2/day<br>(total dose per cycle = 300 mg/m$^2$) | IV in 250 to 1000 mL NS over 45 min to 1 hour 30 min on Days 1,2,3<br>(Use non-DEHP equipment with 0.2 micron in-line filter) |
| riTUXimab**† | 375 mg/m$^2$ | IV in 250 to 500 mL NS over 1 hour 30 minutes-8 hours* Day 1 (or Day 2 or Day 3) |
| | **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‡<br>Observe for 15 minutes after administration |

§ Ifosfamide and Mesna infused concurrently via Y- site connector placed immediately before injection site

¥ Consider dose reduction to 75% for ifosfamide, IV mesna, CARBOplatin and etoposide in patients greater than 70 years of age.

¶The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR. When a nuclear renogram is available, this clearance would take precedence. Maximum CARBOplatin dose is 800 mg.

Note: The same method of estimation should be used throughout the treatment course (i.e., if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

*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 $10^9$ /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.

†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 3 weeks for up to 6 cycles.

**DOSE MODIFICATIONS:**

1. **Hematological**

| ANC (X $10^9$/L) | DOSE MODIFICATION |
|---|---|
| greater than or equal to 0.8 | 100% |
| less than 0.8 | 100% plus Filgrastim* 5mcg / kg subcutaneous daily x 5-10 days, starting on Day 7 |

The patient should be treated with filgrastim (G-CSF) in doses sufficient to allow full dose treatment on schedule. *Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate filgrastim (G-CSF) is*

*required. (See Pharmacare guidelines and submit special authority request to Pharmacare for filgrastim coverage)*

**Filgrastim* 300 mcg: up to 75 kg

480 mcg: 76 kg to 110 kg

600 mcg: greater than 110 kg

| **Platelet Count (PLT) (x $10^9$/L)** | **DOSE MODIFICATION** |
|---|---|
| Greater than or equal to 75 | 100% |
| less than 75<br>(on treatment day) | Hold treatment until PLT greater than or equal to 75 x$10^9$/L and then administer at 100% dosing |

Consider RBC transfusion support in individuals that have an expected hemoglobin nadir below 70 to 80 g/L and platelet transfusions to keep platelets greater than 20 x $10^9$/L.

2. **Renal dysfunction:** Check renal function prior to each cycle and adjust dose of CARBOplatin accordingly. Discontinue protocol if CrCl less than 60 mL/min.

## 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. **Extravasation**: etoposide causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Hypersensitivity**: Hypersensitivity reactions including anaphylaxis have been reported with etoposide. Monitor etoposide infusion for 15 minutes for signs of hypotension. 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). See BC Cancer Hypersensitivity Guidelines.

5. **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 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.
6. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
7. **Urotoxicity:** Ifosfamide can cause hemorrhagic cystitis, hematuria and nephrotoxicity. No dose modifications for ifosfamide is required for transient or persistent hematuria. Administration with MESNA and ample hydration is required for gross hematuria. Avoid concurrent nephrotoxic drugs.
8. **CNS toxicity:** Ifosfamide can cause encephalopathy (manifest as confusion, lethargy, seizures or coma). Avoid CNS depressant medications. If drowsiness develops while receiving ifosfamide, discontinue all sedating medications and continue ifosfamide. If patient is confused, not arousable or comatose, discontinue ifosfamide. If ifosfamide is the cause of CNS depression, then it should not be given again. If the CNS changes are not due to ifosfamide, then ifosfamide can be re-instituted providing the previous medications contributing to CNS toxicity are not given again with it. If a seizure occurs on ifosfamide, then that cycle should be discontinued. Further cycles may be given if the patient is on anticonvulsants.
9. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
10. **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.
11. **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.

12. **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 Sehn or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**