ELIGIBILITY:
- greater than or equal to 18 years of age
- 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
- Relapsed
- ECOG Performance Status 0,1,2 or 3
- No major impairment of renal, hepatic, or bone marrow function

TESTS:
- Baseline (required before first treatment): CBC & diff, platelets, 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, anti-HBsAg, anti-HBcore Ab, anti-HepC), HIV, pregnancy test for women of childbearing age
- Prior to each cycle: CBC & diff, platelets, total bilirubin, LDH, creatinine

PREMEDICATIONS:

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>ondansetron</td>
<td>8 mg</td>
<td>PO</td>
<td>15 min pre-chemotherapy daily</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>12 mg</td>
<td>PO</td>
<td>15 min pre-chemotherapy daily</td>
</tr>
</tbody>
</table>
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 SC
  acetaminophen 650-975 mg PO prior to rituximab SC

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

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide§</td>
<td>1667 mg/m2/day (total dose per cycle = 5000 mg/m2)</td>
<td>IV in 500 mL D5W over 2 hours on days 1,2,3</td>
</tr>
<tr>
<td>mesna (IV)§</td>
<td>1667 mg/m2/day (total dose per cycle = 5000 mg/m2)</td>
<td>IV in 500 mL D5W over 2 hours on days 1,2,3</td>
</tr>
<tr>
<td>mesna (PO)</td>
<td>2000 mg</td>
<td>PO 2 h and 4 h after completion of ifosfamide infusion on days 1,2,3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>5 x (25 + CrCl¶) (maximum dose 800 mg)</td>
<td>IV in 250 mL NS over 1 hour on day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m2/day (total dose per cycle = 300 mg/m2)</td>
<td>IV infusion day 1,2,3 over 45 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Use non-DEHP equipment with in-line filter)</td>
</tr>
<tr>
<td>rituximab**†</td>
<td>375 mg/m2</td>
<td>IV in 250 to 500 mL NS over 1 hour 30 minutes-8 hours* day 1 (or day 2 or day 3) (doses between 500 to 1000 mg can be prepared in either 250 mL or 500 mL NS)</td>
</tr>
<tr>
<td></td>
<td>If first IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by SC administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1400 mg (fixed dose in 11.7 mL)</td>
<td>SC over 5 minutes into abdominal wall‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observe for 15 minutes after administration</td>
</tr>
</tbody>
</table>

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

¶ Maximum dose 800 mg

† Ifosfamide and mesna administered concurrently via Y-site connector placed immediately before injection site
CARBOplatin dosed via the Calvert formula with AUC of 5, **maximum dose 800 mg**

Estimate Creatinine Clearance (CrCl) with following formula:

\[
CrCl \text{ (mL/min)} = N \times (140 - \text{age in years}) \times \text{wt (kg)} \\
\text{serum creatinine (micromol/L)} \\
(N = 1.04 \text{ for females, } N = 1.23 \text{ for males})
\]

*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 \times 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.

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

Repeat every 3 weeks x 4 cycles.

**DOSE MODIFICATIONS:**

1. **Hematological**

<table>
<thead>
<tr>
<th>ANC ((X \times 10^9/\text{L}))</th>
<th><strong>DOSE MODIFICATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 0.8</td>
<td>100%</td>
</tr>
<tr>
<td>less than 0.8</td>
<td>100% plus Filgrastim 300 mcg daily x 5-10 days, starting 7 days after each IV chemotherapy</td>
</tr>
</tbody>
</table>
The patient should be treated with filgrastim (G-CSF) in doses sufficient to allow full
dose treatment on schedule.

<table>
<thead>
<tr>
<th>Platelet Count (PLT) (x 10^9/L)</th>
<th>DOSE MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 75</td>
<td>100%</td>
</tr>
<tr>
<td>less than 75 (on treatment day)</td>
<td>Hold treatment until PLT greater than or equal to 75 x10^9/L and then administer at 100% dosing</td>
</tr>
</tbody>
</table>

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater
than 10 x 10^9/L.

2. **Renal dysfunction**: Calculate creatinine clearance prior to each cycle and adjust
dose of carboplatin accordingly. Discontinue protocol if CrCl less than 60 mL/min.

3. **Hematuria**: Instruct patient to dipstick urine for blood prior to chemo – daily and with
each void at home. Patient to call physician immediately if positive for blood. Patient
to call physician immediately if they become drowsy. Chemo Room RN to ensure
patient has been taught to do urine dipstick for blood. Chemo Room RN to ensure
patient has tested urine for blood prior to each dose. See SCMESNA.

**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 and nephrotoxicity. Administration with MESNA and ample hydration is required. 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**: 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.

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.