ELIGIBILITY:
- Patients with relapsed aggressive B-cell non-Hodgkin’s lymphomas with good performance status who have been off treatment with riTUXimab for more than 3 months and who are being treated with curative intent (note: patients whose disease responds to LYGDPR may be candidates for high dose chemo-radiotherapy and heme stem cell transplant)

EXCLUSIONS:
- Creatinine clearance (CrCl) less than 45 mL/min
- CNS involvement

TESTS:
- Baseline, then as indicated:
  - Required before first treatment: CBC & diff, platelets, creatinine, bilirubin, AST, ALT
  - 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
  - Recommended but optional: bilirubin, alkaline phosphatase, magnesium, calcium
- Before day 1 of each treatment cycle: CBC & diff, platelets, creatinine
- If CISplatin dose is given day 1 and 8: before day 8 of each treatment cycle: creatinine
- NOTE: Day 8 CBC & diff, platelets are not required and there are no dose modifications due to CBC & diff, platelets on day 8
- Before each treatment cycle: Use calculated creatinine clearance and serum creatinine to determine CISplatin dose, see dose modifications below.

PREMEDICATIONS:
Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA).
(The dexamethasone dose is not adjusted when used with aprepitant as per the ASCO Guidelines for Antiemetics in Oncology: Update 2006)

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 650-975mg 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>gemcitabine</td>
<td>1000 mg/m² day 1 &amp; 8</td>
<td>IV in 250 mL NS over 30 min¶</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>40 mg/d days 1 to 4</td>
<td>Oral daily in am with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(Note: The anti-emetic premedication is separate from the Dexamethasone given as part of the protocol; both should be prescribed separately.)</em></td>
</tr>
<tr>
<td>CISplatin</td>
<td>75 mg/m² day 1</td>
<td>Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour</td>
</tr>
<tr>
<td>rTUXimab**†</td>
<td>375 mg/m² on day 1 or 2 whenever possible but not later than 72 h after GDP</td>
<td>IV in 250 mL NS over 1 hour 30 minutes to 8 hours*</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(doses between 500 to 1000 mg can be prepared in either 250 mL or 500 mL NS)</em></td>
</tr>
</tbody>
</table>

If first IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by SC administration

1400 mg (fixed dose in 11.7 mL) on day 1 or 2 whenever possible but not later than 72 h after GDP | SC over 5 minutes into abdominal wall‡  
Observe for 15 minutes after administration

¶ gemcitabine may be given during prehydration for CISplatin

*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 rTUXimab based on lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to rTUXimab infusion or omit the rTUXimab 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 rTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.
Estimate calculated creatinine clearance (CrCl) with following formula:

\[
\text{CrCl (mL/min)} = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}
\]

(N=1.04 for females, N=1.23 for males)

Borderline cases (CrCl 60 to 70 mL/min): perform nuclear renogram for GFR, if available

Repeat every 21 days. Maximum prior to high dose chemotherapy and stem cell transplant, 3 cycles; otherwise 6 cycles. Discontinue if definite progression at any time.

**DOSE MODIFICATIONS:**

1. **Hematological, day 1 only**

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (all drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1 and greater than or equal to 50</td>
<td>less than 50</td>
<td>100%</td>
</tr>
<tr>
<td>less than 1 or less than 50</td>
<td></td>
<td>Delay 1 week</td>
</tr>
</tbody>
</table>

2. **Renal Dysfunction**

   Delay for one week if *serum* creatinine greater than 3 x ULN where ULN = local upper limit of normal range. If serum creatinine less than 3 x ULN adjust CISplatin dose as follows

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>CISplatin dose</th>
<th>Gemcitabine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>75 mg/m^2 on Day 1</td>
<td>100%</td>
</tr>
<tr>
<td>45 to 59</td>
<td>37.5 mg/m^2 on Days 1 and 8</td>
<td>100%</td>
</tr>
<tr>
<td>less than 45</td>
<td>Delay</td>
<td>Delay/Omit*</td>
</tr>
</tbody>
</table>

*Delay if day 1; if day 8, omit if *serum* creatinine greater than 3 x ULN where ULN = local upper limit of normal range.

**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. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
4. **Pulmonary Toxicity:** Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
5. **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.

6. **Hypersensitivity**: riTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. For 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.

7. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 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 \( \times 10^9 \) /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.

8. **Rare Severe Mucocutaneous Reactions**: (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.

9. **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.

10. **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.

11. **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.

References:

N/A