BC Cancer Protocol Summary for Treatment of Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia with Fludarabine and riTUXimab

Protocol Code	*LYCLLFLUDR*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Laurie H. Sehn* *Dr. Alina Gerrie*

ELIGIBILITY:
- Chronic lymphocytic leukaemia/small lymphocytic lymphoma or prolymphocytic leukemia
  - at time of initial need for systemic treatment if not eligible for LYFCR
  - at relapse if patient not refractory (previous response greater than 6 months)

TESTS:
- Baseline (required before first treatment): CBC & diff, platelets, serum creatinine, bilirubin, ALT
- Baseline (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 each treatment: CBC & diff, platelets, serum creatinine

PREMEDICATIONS:
- No premedication is required for fludarabine.

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:

CYCLE 1:

Drug	Dose	BC Cancer Administration Guideline
fludarabine¶	40 mg/m^2/day x 5 consecutive days (Day 1 to 5) (round dose to nearest 10 mg)	PO Do not chew, break or crush the tablets.
riTUXimab**†	375 mg/m^2 on day 1 NOTE: riTUXimab and PO fludarabine to start on the same day.	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours*

CYCLE 2 and subsequent treatments:

Drug	Dose	BC Cancer Administration Guideline
fludarabine¶	40 mg/m^2/day x 5 consecutive days (Day 1 to 5) (round dose to nearest 10 mg)	PO Do not chew, break or crush the tablets.
riTUXimab**†	500 mg/m^2 on day 1 NOTE: riTUXimab, and PO fludarabine to start on the same day.	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	
	1600 mg (fixed dose in 13.4 mL) on day 1 NOTE: riTUXimab and PO fludarabine to start on the same day.	Subcutaneous over 7 minutes into abdominal wall‡ Observe for 15 minutes after administration

¶ If PO fludarabine is not practical, substitute IV fludarabine according to the following schedule:

Drug	Dose	BC Cancer Administration Guideline
fludarabine	25 mg/m^2/day x 5 consecutive working weekdays (day 1 to 5) (may skip Sat/Sun/holidays) NOTE: riTUXimab to be given within 72 h of IV fludarabine.	IV in 100 mL NS over 30 min

*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 minutes). 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 the 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 for 6 cycles. For further cycles, "Compassionate Access Program (CAP)" approval is required.

DOSE MODIFICATIONS:

1. **Hematologic**:

ANC (x 10^9/L)*		**Platelets (x 10^9/L)***	**fludarabine and riTUXimab**
less than 1.2	OR	less than 100	Delay until count recovery

*No dose reduction if decreased counts are due to disease.

2. **Renal Dysfunction**: For any patient with a serum creatinine above normal and for all patients above the age of 60 years, a creatinine clearance should be measured or calculated using the following formula to determine the initial dose of fludarabine.

Estimated creatinine clearance (in mL/minute) =

For men: [1.23 x (140-age in y)(weight in kg)] ÷ serum creatinine in micromol/L
For women: [1.04 x (140-age in y)(weight in kg)] ÷ serum creatinine in micromol/L

Creatinine Clearance (mL/min)	**Dose**	**fludarabine Actual Dose and Schedule (Note change in number of days)**	
		PO	**IV**
greater than or equal to 70	100%	40 mg/m^2/day x **5 days**	25 mg/m^2/day x **5 days**
30 to less than 70	50%	32 mg/m^2/day x **3 days**	20 mg/m^2/day x **3 days**
less than 30	DO NOT USE		

After the first cycle of fludarabine it is not necessary to re-calculate the creatinine clearance or to re-adjust the fludarabine dose unless the serum creatinine is above the normal range. If this occurs, use the above calculation and dose modification table.

If a reduced dose of fludarabine was used for initial treatment and well tolerated it may be appropriate for the dose to be increased in subsequent cycles regardless of renal function. This decision must be individualized by the treating oncologist and cannot be reduced to a formula.

PRECAUTIONS:

1. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Need for irradiated blood products**: potentially life-threatening transfusion-related graft-versus-host-disease has been described in patients actively receiving fludarabine. The Canadian Blood Service recommends that patients on fludarabine should receive irradiated blood products, effectively eliminating this risk.
3. **Hepatitis B.** The immunosuppression associated with fludarabine may increase the risk of re-activation of hepatitis B. Although the risk of this is probably small, fludarabine should be avoided in patients with known prior hepatitis B (HBsAg positive or anti-hepatitis B antibody positive) unless the clinical situation justifies this increased risk and this has been explained to the patient.
4. **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.
5. **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).
6. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 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 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.
7. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
8. **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.
9. **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 or 1600mg/13.4mL ready-to-use solution which contains hyaluronidase to facilitate injection.
10. **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, Dr. Alina Gerrie or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. Cheson B, et al. Fludarabine. J Clin Oncol 1991;9:175-88.
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5. Byrd JC, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.
6. O'Brien SM, Kantarjian H, Thomas DA, et al: Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19(8):2165-70.