BC Cancer Protocol Summary for Treatment of Lymphoma with Dose-Adjusted Etoposide, DOXOrubicin, vinCRIStine, Cyclophosphamide, predniSONE and riTUXimab with Intrathecal Methotrexate

Protocol Code	*LYEPOCHR*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Laurie Sehn* *Dr. Kerry Savage*

ELIGIBILITY:

One of the following lymphomas:

- Patients with an aggressive B-cell lymphoma and the presence of a dual translocation of *MYC* and *BCL2* (i.e., double-hit lymphoma). Histologies may include DLBCL, transformed lymphoma, unclassifiable lymphoma, and intermediate grade lymphoma, not otherwise specified (NOS).
- Patients with Burkitt lymphoma, who are not candidates for CODOXM/IVACR (such as those over the age of 65 years, or with significant co-morbidities)
- Primary mediastinal B-cell lymphoma

Ensure patient has central line

EXCLUSIONS:

- Cardiac dysfunction that would preclude the use of an anthracycline.

TESTS:

- Baseline (required before first treatment): CBC and diff, platelets, BUN, creatinine, bilirubin. ALT, LDH, uric acid
- 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,
- Baseline (optional, results do not have to be available to proceed with first treatment): HCAb, HIV
- Day 1 of each cycle: CBC and diff, platelets, (and serum bilirubin if elevated at baseline; serum bilirubin does not need to be requested before each treatment, after it has returned to normal), urinalysis for microscopic hematuria (optional)
- Days 2 and 5 of each cycle (or days of intrathecal treatment): CBC and diff, platelets, PTT, INR
- For patients on cyclophosphamide doses greater than 2000 mg: Daily urine dipstick for blood starting on day cyclophosphamide is given. If positive at any time, notify doctor and send urine sample for urinalysis and verification and accurate determination of hematuria.
- CBC and diff, platelets starting Day 4 and then twice-weekly (i.e., Monday and Thursday) continuously during cycle. NB: twice-weekly CBC & diff, platelets are used to determine the nadir information which is required for dosing in the subsequent cycle and for the ANC recovery post nadir which is required to determine the duration of the filgrastim treatment in the current cycle.

- **Proceed with methotrexate intrathecal injection if, within 48 hours:**
  - PTT less than or equal to the upper limit of normal
  - INR less than 1.5
  - Platelets greater than or equal to 50 x 10^9/L (For platelets less than 50x10^9/L, physicians may consider platelet transfusion prior to proceeding with treatment.)
- Filgrastim (G-CSF) Usage Form - cycle 1
- VICTORY Program Enrolment Form for filgrastim – cycle 1
- Reassess all sites of disease after cycles 4 and 6 to determine response

PREMEDICATIONS:
For etoposide, prednisone, vinCRIStine, cyclophosphamide, DOXOrubicin portion (i.e., EPOCH portion)
- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

For riTUXimab portion
- diphenhydrAMINE 50 mg PO prior to **riTUXimab** and then q4h during the IV infusion, if infusion exceeds 4 h
- acetaminophen 650-975 mg PO prior to **riTUXimab** and then q4h during the IV infusion, if infusion exceeds 4 h
- predniSONE as ordered for the LYEPOCHR

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
- cotrimoxazole 1 DS tab PO 3 times each week (Monday, Wednesday and Friday)
- pantoprazole 40 mg PO daily (or equivalent)
- docusate and senna (sennosides 8.6 mg) 2 tablets PO twice daily prn constipation

Prevention of Tumor Lysis Syndrome (TLS) - Cycle 1 only:
Prophylaxis suggested for high-risk patients:
- High tumour burden,
- Elevated uric acid level
- Lymphocyte count greater than 25 x 10^9/L, or
- CrCl less than 70 mL/min

Suggested prophylactic treatment:
- Monitor electrolytes (including potassium, calcium, and phosphate), creatinine and uric acid
- Ensure adequate hydration. Intravenous fluids should be given as indicated based on overall risk of tumour lysis syndrome. Suggest hospitalization for high-risk patients for cycle 1 with aggressive hydration (2-3 L/m^2/24 h) to achieve urine output greater than 100 mL/h.
- allopurinol 300 mg PO daily (to decrease urate formation)
- If phosphate becomes elevated, add AMPHOJEL (aluminum hydroxide) 15-30 mL PO q4h
- rasburicase (FASTURTEC) can be considered on a case by case basis

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
etoposide	**Cycle 1 to Cycle 6,** on Day 1 to Day 4 inclusive: 50 mg/m^2/day (total dose per cycle = 200 mg/m^2)	IV in the same 500-1000 mL non-DEHP NS infusion bag by continuous infusion over 24 h daily; for a total of 96 hours per cycle (use non-DEHP equipment with 0.2 micron in-line filter) - 500 mL non-DEHP NS for etoposide less than or equal to 125 mg - 1000 mL non-DEHP NS for etoposide greater than 125 mg
DOXOrubicin	**Cycle 1 to Cycle 6,** on Day 1 to Day 4 inclusive: 10 mg/m^2/day (total dose per cycle = 40 mg/m^2)	
vinCRIStine	**Cycle 1 to Cycle 6:** on Day 1 to Day 4 inclusive: 0.4 mg/m^2*/day (*no cap on dose) (total dose per cycle = 1.6 mg/m^2)	
cyclophosphamide	**Cycle 1 to Cycle 6:** on Day 5 (or Day 1): 750 mg/m^2	IV in 100 to 250 mL NS over 1 hour (*use 250 mL for doses greater than 1000 mg)
predniSONE	**Cycle 1 to Cycle 6:** on Day 1 to Day 5 inclusive: Total daily dose = 120 mg/m^2 i.e., 60 mg/m^2 BID (round off dose to nearest 25 mg) Note: may reduce predniSONE dose per physician discretion based on patient tolerance	PO with food (On day of riTUXimab, ensure morning predniSONE taken prior to riTUXimab infusion)

Drug	Dose	BC Cancer Administration Guideline
riTUXimab**†	**Cycle 1 to Cycle 6:** on Day 1 (or Day 5)	
	375 mg/m^2	IV in 250 to 500 mL NS over 1 hour 30 min*
	If patient received IV riTUXimab in the past with no severe reactions requiring early termination, or if patient received subcutaneous riTUXimab in the past, riTUXimab doses can be given by subcutaneous administration†	
	1400 mg (fixed dose in 11.7 mL)	subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
methotrexate***	**Prophylaxis** **Cycle 3 to 6:** on Day 2 and Day 5: 12 mg (total 8 treatments) Note: Physician may start intrathecal chemotherapy with Cycle 1 if high risk of CNS disease Physician may change the days of intrathecal chemotherapy Ensure a minimum of 48 hours between doses **Treatment of Meningeal Lymphoma********	Intrathecal qs to 6 mL with **preservative-free NS**
filgrastim	**Cycle 1 to Cycle 6:** Starting on Day 6 DAILY until ANC recovery (5.0 x 10^9/L past the nadir) 300 mcg: up to 75 kg 480 mcg: 76kg to 110 kg 600 mcg: greater than 110kg	subcutaneously

*Start the (first dose of riTUXimab) 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 infusion-related reactions 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. If patient tolerated IV riTUXimab (no severe reactions requiring early termination) i.e., in active treatment or maintenance treatment or if patient tolerated subcutaneous riTUXimab previously i.e., active treatment or maintenance treatment the patient can receive all subsequent treatment using subcutaneous riTUXimab.

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

***Concurrent use of co-trimoxazole and methotrexate may result in an increased risk of methotrexate toxicity. The tumour group believes this drug interaction is not clinically significant with IT methotrexate 12 mg.

¥ Intrathecal methotrexate is not needed in the majority of patients with primary mediastinal B cell lymphoma

******Treatment of leptomeningeal Lymphoma**

If the CSF is cytologically positive for malignant cells at the start of therapy, the CSF should be treated with methotrexate and/or cytarabine as soon as possible. Suggested treatment as follows:

Induction- intrathecal methotrexate (12 mg by lumbar route) alternating with cytarabine (50 mg by lumbar route). Administer induction treatment twice a week for 2 weeks past negative cytology with a minimum of 4 weeks treatment.

Consolidation- Following induction, change frequency to weekly x 6, alternating methotrexate and cytarabine.

Maintenance- Following consolidation, change frequency to monthly x 4 (with either methotrexate or cytarabine).

Due to unforeseeable events, the above therapy may be modified as clinically indicated. In some cases it may be necessary to administer radiation to the head and/or spine. Patients who fail to clear or relapse in the CSF should be considered for alternate therapies and/or radiation. Substitution with liposomal cytarabine can be considered, but schedule should be determined in consultation with a BC Cancer pharmacist. Note: liposomal cytarabine is accessed via the Health Canada Special Access Programme (SAP) on a patient-specific basis.

Repeat protocol every 21 days for 6 cycles

Discontinue if no response after 2 cycles

DOSE MODIFICATIONS:

Hematological:

a) On treatment day: Day 1

ANC (x10^9/L)	Dose Modification
greater than or equal to 1.0	100%
less than 1.0	filgrastim 5 mcg/kg x 1 day then treat the following day if ANC is greater than 1.0

Platelets (x10^9/L)	Dose Modification
greater than or equal to 75	100%
less than 75	delay until platelets are greater than 75

Patients with bone marrow involvement should be treated irrespective of the ANC and platelet counts based on physician discretion.

Dose levels are adjusted based on nadir ANC and platelet count of last cycle:

Nadir ANC (x 10^9/L)		Nadir Platelet (x 10^9/L)	Dose Level
greater than or equal to 0.5	and	greater than or equal to 25	Increase by one dose level above last cycle*
less than 0.5 on one or two measurements	and	greater than or equal to 25	Maintain same dose level as last cycle
less than 0.5 on 3 or more measurements	or	less than 25	Decrease by one dose level below last cycle**

*Dose adjustments ABOVE level 1 apply to etoposide, DOXOrubicin and cyclophosphamide

**Dose adjustments BELOW level 1 apply to cyclophosphamide only

Note: Rarely, patients may develop prolonged neutropenia (ANC less than 0.5) for over seven days or life-threatening infections associated with organ failure or prolonged morbidity. In these cases, clinicians should use their clinical judgement regarding dose reduction. No need to reduce doses for:

- non-life threatening infections
- non-life threatening neutropenia or thrombocytopenia in patients with bone marrow compromise due to marrow involvement by lymphoma

Etoposide Dose Level							
– 2	**–1**	**1***	**2**	**3**	**4**	**5**	**6**
50 mg/m^2	50 mg/m^2	50 mg/m^2	60 mg/m^2	72 mg/m^2	86 mg/m^2	104 mg/m^2	124 mg/m^2

*starting dose level

DOXOrubicin Dose Level*							
– 2	**–1**	**1***	**2**	**3**	**4**	**5**	**6**
10 mg/m^2	10 mg/m^2	10 mg/m^2	12 mg/m^2	14 mg/m^2	17 mg/m^2	21 mg/m^2	25 mg/m^2

*starting dose level

Cyclophosphamide Dose Level*							
– 2	**–1**	**1***	**2**	**3†**	**4†**	**5†**	**6†**
480 mg/m^2	600 mg/m^2	750 mg/m^2	900 mg/m^2	1080 mg/m^2	1296 mg/m^2	1555 mg/m^2	1866 mg/m^2

*starting dose level

†Mesna is recommended when cyclophosphamide dose exceeds 2000 mg to prevent hemorrhagic cystitis. This may start at cyclophosphamide dose level 3 or higher. See Table 1 for mesna dose.

Note: Individual drug doses may be reduced per physician discretion (rather than according to dose level)

Table 1: Mesna dose at various dose levels of LYEPOCHR when cyclophosphamide dose exceeds 2000 mg

Cyclophosphamide Dose level	Drug	Dose	BC Cancer Administration Guideline
3	mesna*	216 mg/m^2	IV in 100 mL NS over 15 min
	cyclophosphamide	1080 mg/m^2	IV in 250 mL NS over 1 hour
	mesna*	432 mg/m^2 216 mg/m^2	Hours 4 and 8: PO in carbonated beverage OR IV in 100 mL NS over 15 minutes
4	mesna*	259 mg/m^2	IV in 100 mL NS over 15 min
	cyclophosphamide	1296 mg/m^2	IV in 250 mL NS over 1 hour
	mesna*	518 mg/m^2 259 mg/m^2	Hours 4 and 8: PO in carbonated beverage OR IV in 100 mL NS over 15 minutes
5	mesna*	311 mg/m^2	IV in 100 mL NS over 15 min
	cyclophosphamide	1555 mg/m^2	IV in 250 mL NS over 1 hour
	mesna*	622 mg/m^2 311 mg/m^2	Hours 4 and 8: PO in carbonated beverage OR IV in 100 mL NS over 15 minutes
6	mesna*	373 mg/m^2	IV in 100 mL NS over 15 min
	cyclophosphamide	1866 mg/m^2	IV in 250 mL NS over 1 hour
	mesna*	746 mg/m^2 373 mg/m^2	Hours 4 and 8: PO in carbonated beverage OR IV in 100 mL NS over 15 minutes

***** If cyclophosphamide dose is reduced, mesna should also be reduced according (i.e. if cyclophosphamide is reduced to 75%, mesna should also be reduced to 75%)

Patients must drink at least 3 Litres of fluids a day to ensure adequate hydration on day of cyclophosphamide and continue for 24-72 hours following treatment. If unable to drink 3 Litres per day, give the following hydration:

HYDRATION:
Hours 1:15 to 13:15: IV D5W-1/2 NS at 125 mL/h
May discontinue IV at hour 13:15 if no hematuria and patient is able to maintain oral hydration.

Elderly Patients (age greater than 75 years):
As per clinical judgment, a suggested approach is to administer Cycle 1 with 75% dosing of cyclophosphamide and DOXOrubicin. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full doses.

Ileus: vinCRIStine only
Note: constipation commonly occurs and stool softeners should be used

Clinical ileus	Dose of vinCRIStine
Less than 8 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting greater than 2 days	75%
8-12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting greater than 2 days	50%
Greater than 12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting greater than 2 days	Hold on next cycle. Restart at 50% dose on subsequent cycle.

Neurotoxicity: vinCRIStine only:

Toxicity	Dose of vinCRIStine
Dysesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	omit

Hepatic toxicity: vinCRIStine only

Bilirubin on Day 1	Dose of vinCRIStine
1.5-3.0 x ULN	75%
Greater than 3.0 x ULN	50%

Cardiotoxicity: DOXOrubicin only: see PRECAUTIONS

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m^2 of DOXOrubicin. (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
3. **Extravasation**: DOXOrubicin and vinCRIStine cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Infusion-related reactions**: If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to BC Cancer Infusion-Related Reactions 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 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 Infusion-Related Reactions 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.
6. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
7. **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 100 mg PO daily 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.

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. **Hematuria:** Cyclophosphamide may cause hemorrhagic cystitis at high doses. Adequate hydration (at least 3 Litres of fluid a day) and the use of mesna is recommended when cyclophosphamide dose exceeds 2000 mg which may occur at cyclophosphamide dose level 3 or higher. Refer to Table 1 for mesna dosing. Daily urine dipstick for blood. If positive at any time, notify doctor and send urine sample for urinalysis and verification and accurate determination of hematuria.

Call Dr. Laurie Sehn, Dr Kerry Savage or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

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