BC Cancer Protocol Summary for Treatment of Burkitt Lymphoma and Leukemia (ALL-L3) with Cyclophosphamide, vinCRIStine, DOXOrubicin, Methotrexate, Leucovorin (CODOX-M) and riTUXimab

Protocol Code	*LYCODOXMR*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Kevin Song*

ELIGIBILITY:

Patients must have:
- Any stage of newly diagnosed Burkitt lymphoma (formerly small non-cleaved Burkitt-type),
- Burkitt leukemia (ALL-L3), or
- High-grade B-cell lymphoma with double hit cytogenetics

Note:
- This protocol is usually given before IVACR and is considered to be part A of the Magrath protocol.
- Risk categories defined as:
  - Low risk
    - Stage I, II or III and
    - Bulk less than 5 cm and
    - LDH normal and
    - Not stage IV
  - High risk
    - Stage IV or
    - Bulk greater than or equal to 5 cm or
    - LDH greater than normal
- riTUXimab must be used in combination with CODOX-M in order to be reimbursed by the BC Cancer.

EXCLUSIONS:
Patients must not have:
- Serum creatinine above 150 micromol/L or estimated creatinine clearance below 60 mL/min

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

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

- Pleural effusion, ascites, or full extremity edema
- AST, ALT, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

TESTS:
- **Baseline (required before first treatment):** CBC & Diff, creatinine, electrolytes panel, ALT, total bilirubin, alkaline phosphatase, GGT, uric acid, LDH, urine pH
- **Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2):** HIV, HBsAg, HBsAb, HBcAb, HCAb, CMV serology, HSV serology
- **Prior to Day 1 of each cycle:** CBC & Diff, creatinine, electrolytes panel, ALT, total bilirubin, alkaline phosphatase, GGT, uric acid, LDH

- **Daily q am during treatment (**required but results do not have to be available to proceed with treatment**):** CBC & Diff, creatinine, electrolytes panel
- **Prior to IT chemo**: Platelets, PTT, INR (on day 3 and after day 18 when IT chemo is given)
- **Twice weekly (Monday and Thursday):** ALT, total bilirubin
- **Day 8:** ALT, bilirubin, alkaline phosphatase, GGT
- **Day 10 pre-methotrexate**: creatinine, ALT, alkaline phosphatase, GGT, total bilirubin
- **Immediately pre-methotrexate and q6h:** urine pH
- **If clinically indicated starting on Day 11 (i.e. post methotrexate):** daily ALT, total bilirubin, alkaline phosphatase, LDH, GGT
- **At hour 48** (from start of methotrexate infusion) **or morning of day 12, then daily q am:** methotrexate levels (until less than 0.1 micromol/L; note date and time of withdrawal as well as start time of infusion on specimen.)

PREMEDICATIONS:
For Day 1 & 2 CODOX-M portion:
- **dexamethasone** 12 mg PO pre-chemotherapy on days 1 and 2
- **ondansetron** 8 mg PO pre-chemotherapy, then 8 mg PO every 12 hours on days 1 and 2
- may consider **aprepitant 125 mg** PO pre-chemotherapy on day 1 then 80 mg PO daily post-chemotherapy on days 2 and 3
- **prochlorperazine 10 mg** PO q6h prn on days 1 and 2 or
- **metoclopramide 10 mg** PO q6h prn on days 1 and 2
- **dimenhyDRINATE 50 mg** PO/IV q6h prn on days 1 and 2

For Day 8 riTUXimab portion:
- For intravenous infusion:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab IV and then* q4h during the IV infusion, *if the infusion exceeds 4h*
  acetaminophen 650-975 mg PO *prior to riTUXimab IV and then* q4h during the IV infusion, *if the infusion exceeds 4h*

- For subcutaneous injection:
  diphenhydrAMINE 50 mg PO *prior to riTUXimab subcutaneous*
  acetaminophen 650-975 mg PO *prior to riTUXimab subcutaneous*

For Day 10 CODOX-M portion:
- **ondansetron** 8 mg PO/IV pre-chemotherapy
- **prochlorperazine** 10 mg PO after methotrexate infusion completed, followed by 10 mg PO q6h PRN

SUPPORTIVE MEDICATIONS:
- furosemide 20 mg IV Q4H PRN Days 1-4 if output is less than 400 mL during a 4 hour period while patient is on IV
- Hyperhydration with NS with potassium chloride and magnesium sulfate from 0600h on Day 1 until 48 hours after last dose of cyclophosphamide
- furosemide 20 mg IV after completion of each dose of cyclophosphamide
- Prophylactic Antimicrobials (start day 12)
  - fluconazole 400 mg PO DAILY
  - If HSV seropositive: valACYclovir 500 mg PO BID **OR** acyclovir 5 mg/kg IV q12h
- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per BC Cancer Protocol Summary for Hepatitis B Virus Reactivation (SCHBV).
- filgrastim (G-CSF) as per preprinted order; start on Day 13 and continue until ANC is greater than 1

TREATMENT:
START TREATMENT WITHIN 48 HOURS OF DIAGNOSIS, EVEN IF STAGING IS INCOMPLETE.

Treatment should be administered as an inpatient.

Drug	Dose	BC Cancer Administration Guideline
cyclophosphamide	800 mg/m^2 on Days 1, 2	IV in 100-250 mL NS over 30 to 60 minutes
vinCRIStine	1.4 mg/m^2 (max 2 mg) on Days 1, 8	IV in 50 mL NS over 15 minutes
DOXOrubicin	50 mg/m^2 on Day 1	IV push
riTUXimab**†	375 mg/m^2 on Day 8	IV in 250 to 500 mL NS over 3 to 8 h* (may divide dose equally into two 250 mL NS infusion bags to maintain 1 to 4 mg/mL concentration range).
	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) on Day 8	subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
methotrexate	3 g/m^2 on Day 10	IV in 1000 mL NS over 4 h, if urine pH greater than 7
leucovorin	25 mg q6H (start on day 11)	Starting exactly 24 h after start of methotrexate infusion; IV for 4 doses, then PO until methotrexate level less than 0.1 micromol/L***.
cytarabine	50 mg IT¥ on Day 3 and after Day 18	Via lumbar puncture or Ommaya ventricular reservoir; qs to 6 mL with preservative-free NS. Dose should only be given if there are no blasts present in the peripheral blood, if platelets are greater than or equal to 50 x10^9/L, INR less than 1.5, and PTT less than or equal to upper limit of normal. Note: For platelets less than 50x10^9/L, physicians may consider platelet transfusion prior to proceeding with treatment.
filgrastim	less than 75 kg: 300 mcg 76 to 110 kg: 480 mcg greater than 110 kg: 600 mcg	subcutaneous daily starting on day 13, until neutrophils greater than 1.

Note: One staff physician signature is required. Orders written by other providers MUST be cosigned.

Low risk patients should have LYCODOXMR followed by LYIVACR (one full Magrath protocol) then a second cycle of LYCODOXMR. Recommended minimum of 21 days between each cycle.

High risk patients should have LYCODOXMR followed by LYIVACR then a second cycle of LYCODOXMR followed by LYIVACR (two full Magrath protocol). Recommended minimum of 21 days between each cycle.

A total of 8 doses of IT chemotherapy should be given for all patients during their complete treatment course which will include further cycles of chemotherapy and possible stem cell transplant.

*Start the initial infusion at 50 mg/h and, after 60 min, 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) (1/5 of total volume) of the dose over 30 minutes then infuse the remaining 200 mL (or 400 mL) (4/5) over 60 minutes (total infusion time = 90 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 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.

***Methotrexate must be given in a hospital, where rapid reporting of methotrexate levels is available. Leucovorin dose modifications commence 48 hours following the start of methotrexate infusion, based on that morning's methotrexate level. Methotrexate levels are repeated q am and leucovorin dose is adjusted according to the following scheme and continued until methotrexate level less than 0.1 micromol/L:

Methotrexate Level (micromol/L=10^{-6} mol/L)	**Leucovorin Dose**
less than 0.1	None
0.1 to 0.9	25 mg PO/IV q6h
1.0 to 8.0	100 mg/m^2 IV q6h
greater than 8.0	1000 mg/m^2 IV q6h

Patients must have creatinine clearance greater than 60 mL/min, as well as vigorous IV hydration and urine alkalinization to maintain urine pH above 7.

START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE:
▪ Discontinue all other IV hydration before starting alkalinizing regimen.
▪ IV D5W with potassium chloride 20 mEq/L and sodium bicarbonate 150 mEq/L at 125 mL/h for at least 4 hours prior to methotrexate until urine pH is greater than 7. Hydration may be temporarily held during methotrexate infusion (per physician/nursing discretion). Continue hydration post-methotrexate infusion until methotrexate level is less than 0.1 micromol/L.
• Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than 7 before starting methotrexate.

¥ Note: Anticoagulants should be held prior to and on day of IT treatment.

Prophylactic low molecular weight heparin

- none night prior and resume the day after the procedure

Therapeutic low molecular weight heparin

- Once daily therapeutic low molecular weight heparin should be held 36 hours prior to the procedure and resumed the day after the procedure
- In patients at high risk of thrombosis (e.g., acute thrombosis, less than 30 days from diagnosis of VTE), MD may consider changing to BID dosing and giving half the therapeutic dose of low molecular weight heparin at 24 hours prior to the procedure, and resuming the day after the procedure

DOSE MODIFICATIONS:

1. Hematologic Toxicity: Cyclophosphamide and DOXOrubicin ONLY:
For the first cycle of CODOX-M no adjustments are necessary for an abnormal hematology profile. The second cycle of CODOX-M should be given after hematological recovery (ANC greater than 1, platelets greater than $100x10^9$/L) from the last chemotherapy cycle given.

2. Renal dysfunction: If GFR or creatinine clearance (CrCl) less than 60 mL/min, reversible causes of renal dysfunction should be treated and the patient reassessed for suitability for this treatment once renal function improves.
Use the ***same*** renal function measure throughout the treatment course, i.e. if estimated GFR was used initially, subsequent dosing should be based on GFR and ***not*** CrCl

Methotrexate Only

GFR or Creatinine Clearance	Dose Modification
greater than 100 mL/minute	100%
85 to 99.9 mL/minute	85%
60 to 84.9 mL/minute	62%
less than 60 mL/minute	Hold

If serum creatinine obtained after starting methotrexate is increased to greater than 50 % above baseline increase leucovorin to 100 mg/m^2 IV q6h, until creatinine returns to normal and methotrexate level is less than 0.1 micromol/L.

3. Mucositis: Mucositis greater than or equal to grade 3 (painful erythema, edema or ulcers and cannot eat), reduce methotrexate to 80% or prolong routine rescue for 2 more days (unless abnormal methotrexate levels).

4. Neurotoxicity: vinCRIStine only:

Toxicity	Dose Modification
Dysesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

5. Hepatotoxicity: For DOXOrubicin:

Total bilirubin (micromol/L)	Dose Modification
2 to 35	100%
36 to 85	50%
Greater than 85	Omit DOXOrubicin and no substitution is required

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs.

6. Hepatic dysfunction: At high doses, methotrexate can cause elevation of bilirubin and other liver enzymes. Even though these abnormalities are generally reversible, delaying treatment until liver enzymes significantly improve or return to near normal values before starting the next cycle is recommended. The table below may be used as a guide to dose reductions but more conservative dosing is strongly recommended for higher doses of methotrexate (8 g/m^2) at physician discretion.

Methotrexate only:

Total bilirubin (micromol/L)		*AST or ALT(units/L)*	*Dose Modification*
2 to 49			100%
50 to 85	OR	3 x ULN	75%
Greater than 85			Omit

7. Cardiotoxicity: DOXOrubicin only: omit DOXOrubicin and do not replace.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Third space fluids**: Patients with clinically or radiologically detectable third space fluid (e.g., pleural effusion, ascites, full extremity pitting edema) should NOT be given high dose methotrexate.
3. **Renal elimination**: Patients with elevated serum creatinine or calculated creatinine clearance below 60 mL/min should NOT receive high dose methotrexate. Avoid concomitant use of drugs that may inhibit renal elimination of methotrexate such as non-steroidal anti-inflammatory drugs (NSAIDs), salicylates and sulfa drugs.
4. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
5. **Hypersensitivity**: riTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. Directly observe patient during treatment and monitor pulse, respiratory rate and blood pressure every 15 minutes until a stable infusion rate is reached, then hourly until 15 minutes after conclusion of the infusion. 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). Please also refer to the BC Cancer Hypersensitivity Guidelines.
6. **Fatal Cytokine Release Syndrome** (0.04 to 0.07%) may occur within 24 hours of initiating riTUXimab infusion. It usually occurs within 1 to 2 hours of initiating the first infusion. Initially, it is characterized 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 with riTUXimab. 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. **Possible interactions with proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole)** have been reported, resulting in elevated methotrexate levels and increased risk of methotrexate toxicity. Consider discontinuing proton pump inhibitors 1 day prior to methotrexate administration. If their use is required, closely monitor methotrexate levels and monitor for signs of methotrexate toxicity.
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:** be 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.

Supportive Care:
All patients should be hospitalized for LYCODOXMR. Consideration should be made to transfer the patient under the care of the Leukemia/BMT program of British Columbia. They may be discharged when they have recovered from the acute symptomatic side effects of treatment, are eating well, are off antibiotics and their granulocyte count is greater than 1 x 10^9/L.

1. **Venous Access**: All patients should have a triple lumen HICKMAN®-type central catheter for blood sampling and administration of medications and blood products.
2. **Blood Products**: Packed red blood cells should be given sufficiently often to keep the hemoglobin above 80 g/L. Platelet transfusions should be given to keep the platelet count above 10 x10^9/L.
   Antibiotics:
   a. Antibacterial: Fever (greater than 38^{o}C) will be thoroughly evaluated at any time it occurs and treated with antibiotics regardless of granulocyte count, if the treating oncologist judges that infection may be present. Fever while the granulocyte count is below 0.5 x 10^9/L ***must*** be treated with broad spectrum intravenous antibiotics which provide wide coverage of gram negative ***and*** gram positive bacteria. Several of the medications which patients on this protocol may be receiving have the potential to cause renal dysfunction, including furosemide, acyclovir, amphotericin B, aminoglycosides, and vancomycin. This potential should be remembered when anti-bacterial agents are chosen. Thus, use of aminoglycosides or vancomycin should be usually reserved for situations when no less nephrotoxic agent can be employed.
   b. Antifungal: Fluconazole 400 mg PO daily will be given prophylactically to all patients starting on day 12 and continued until neutrophil recovery or recovery of mucositis, whichever is later.
3. **Herpes Virus Prophylaxis**: All patients with a positive herpes simplex virus (HSV) serologic titre or a history of previous cold sores should receive valACYclovir 500 mg PO BID (or acyclovir 5 mg/kg IV q12h) at least from day 12 and continued until neutrophil recovery or recovery from mucositis, whichever is later.

Call Dr. Kevin Song or a member of the Leukemia/BMT tumour group at (604) 875-4863 with any problems or questions regarding this treatment program.

References:

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4. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106(7):1569-80.
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6. Dodd KC et al. Periprocedural antithrombotic management for lumbar puncture: Association of British Neurologists clinical guideline. Practical Neurology 2018:18 (6): 436-466