

BC Cancer Protocol Summary for Treatment of Burkitt Lymphoma and Leukemia (ALL-L3) with Ifosfamide, Mesna, Etoposide, Cytarabine (IVAC) and riTUXimab

Protocol Code

LYIVACR

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 after CODOXMR and is considered to be part B of the Magrath protocol.
- riTUXimab must be used in combination with IVAC in order to be reimbursed by BC Cancer

TESTS:

- **Baseline (required before first treatment):** CBC & diff, platelets, creatinine, sodium, potassium, ALT, bilirubin, alkaline phosphatase, GGT, uric acid, LDH, urine pH, urine dipstick for blood
- **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, HBcoreAb, HCAb, CMV serology, HSV serology
- **Prior to each cycle:** CBC & diff, platelets, creatinine, sodium, potassium, ALT, bilirubin, alkaline phosphatase, GGT, uric acid, LDH, urine dipstick for blood
- **Daily q am during treatment (required but results do not have to be available to proceed with treatment):** CBC & diff, platelets, creatinine, sodium, potassium
- **Every Monday and Thursday during treatment:** ALT
- **Daily q am until 48 hours after completion of ifosfamide:** urine dipstick for blood. If positive at any time, notify doctor and send urine sample for urinalysis for verification and accurate determination of hematuria
- **PTT, INR, Platelets** prior to IT MTX (on Day 6 and after Day 18)

PREMEDICATIONS:

For Day 1 to 5 IVAC portion:

- ondansetron 8 mg PO/IV pre-chemotherapy, then every 12 hours until day 5
- dexamethasone 12 mg PO pre-chemotherapy daily until day 5

For Day 4 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:

- dimenhyDRINATE 50mg IV q 6 h prn

- Prophylactic Antimicrobials (start day 7)
 - fluconazole 400 mg PO DAILY
 - If HSV seropositive: valACYclovir 500 mg PO BID **OR** acyclovir 5 mg/kg IV q12h.
- 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.
- filgrastim (G-CSF) as per preprinted order; start on Day 7 and continue until ANC is greater than $1.0 \times 10^9/L$

HYDRATION:

At least 4 hours before starting chemotherapy, start IV hydration with D5W ½ NS with potassium chloride and magnesium sulfate/L at 125 mL/h (3000 mL/day).

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
cytarabine	2000 mg/m ² IV q12h on days 1 and 2.	IV in 100 mL NS over 2 h
ifosfamide	1500 mg/m ² IV on days 1,2,3,4,5.	IV in 500 mL NS over 2 h
MESNA	375 mg/m ² IV qid on days 1 to 5	IV in 100 mL D5W over 15 min
etoposide	60 mg/m ² IV on days 1,2,3,4,5	IV in 250 to 500 mL NS over 45 min, using non-DEHP bag and tubing with 0.2 micron in-line filter.
riTUXimab**†	375 mg/m ² IV on day 4	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 4	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration
methotrexate	12 mg IT* on day 6 and after day 18	Dose should only be given if there are no blasts present in the peripheral blood, platelets are greater than or equal to $50 \times 10^9/L$, INR less than 1.5, and PTT less than or equal to upper limit of normal Note: For platelets less than $50 \times 10^9/L$, 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 7, until neutrophils greater than 1.

Low risk patients should have LYCODOXMR given prior to LYIVACR, followed by 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.

*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 10⁹ /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.

‡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: For the first cycle of LYIVAC no adjustments are necessary for an abnormal hematology profile, if it is being given as initial treatment or salvage. If LYIVAC is being given after a cycle of CODOX-M, it should be given after hematological recovery (ANC greater than 1, platelets greater than 100 x 10⁹/L) from CODOX-M.

2. Renal dysfunction: If creatinine clearance 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. Methotrexate, given by any route, should be given with special caution if the creatinine clearance is less than 30 mL/minute with all subsequent doses determined based on hematologic and mucosal tolerance for the first dose given.

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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. The patients should also be monitored with frequent liver function tests and hepatitis B virus DNA every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with a hepatologist and consideration given to halting chemotherapy.
3. **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 BC Cancer Hypersensitivity Guidelines.
4. **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 50×10^9 /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.
5. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported with rituximab. If such a reaction occurs, rituximab should be discontinued.
6. **Cerebellar Toxicity:** The incidence of cerebellar toxicity is about 10% in patients treated with high doses of cytarabine. Cerebellar dysfunction is characterized by dysarthria, dysdiadochokinesia, dysmetria, and ataxia. In many patients, cerebral dysfunction is seen concomitantly. Cerebral dysfunction manifests as somnolence, confusion, cognitive dysfunction, memory loss, psychosis or seizures. Seizures, if they occur, are usually self-limited and do not recur once therapy is stopped. In most patients, neurologic dysfunction resolves in 5 to 10 days, but in some patients toxicity may be irreversible or fatal. There is a high (~60%) incidence of recurrent cerebellar toxicity in patients who have already experienced toxicity. It is not conclusively known, if cytarabine therapy should be discontinued if neurological toxicity develops. Risks for developing cerebellar toxicity include: patient older than 60 years of age, impaired renal function and total dose received. Cerebellar toxicity typically will occur in the final 2 to 3 doses. Renal insufficiency i.e., creatinine clearance less than 60 mL/min is a known risk factor for neurotoxicity for patients receiving high dose cytarabine. Methods used to decrease the risk of neurotoxicity in these patients include: decreasing the dose

(from 3 g/m² to 2 g/m²), utilizing a once-daily rather than twice-daily schedule, shortening the course, and modifying the dose based on the calculated daily creatinine clearance.

7. **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. Methylene blue may be given for ifosfamide-induced encephalopathy (see BC Cancer Drug Manual).
8. **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.
9. **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.

SUPPORTIVE CARE:

All patients should be hospitalized for LYIVAC (R). 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 10⁹/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 x 10⁹/L.
3. **Antibiotics:**
 - a. **Antibacterial:** Fever (greater than 38°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 10⁹/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 antibacterial agents are chosen. Thus, the use of aminoglycosides or vancomycin should usually be 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 7 and continued until neutrophil recovery or recovery of mucositis, whichever is later.
6. **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) starting on day 7 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:

1. Lacasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. *Leuk Lymphoma*. 2004;45:761-767.
2. Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol*. 1996;14:925-934.
3. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol*. 2002;13:1264-1274.
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.
5. Taplitz RA, Kennedy EB, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018; 36:3043-3054.