

BCCA Protocol Summary for Treatment of Burkitt Lymphoma and Leukemia (ALL-L3) with Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Leucovorin (CODOX-M) and Rituximab

Protocol Code	<i>LYCODOXMR</i>
Tumour Group	<i>Leukemia/BMT</i>
Contact Physician	<i>Dr. Kevin Song</i>

ELIGIBILITY:

- All stages of newly diagnosed Burkitt lymphoma (formerly small non-cleaved Burkitt-type) and Burkitt leukemia (ALL-L3). This protocol is usually given before IVAC 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
- A "Class II Drug Registration Form" must be submitted at the time of initiation of treatment. Rituximab must be used in combination with CODOX-M in order to be reimbursed by the BCCA.

EXCLUSIONS:

1. Serum Creatinine above 150 micromol/L or estimated creatinine clearance below 60 mL/min

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

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

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

TESTS:

- **Baseline:** CBC & diff, platelets, creatinine, lytes, AST, ALT, bilirubin, alkaline phosphatase, LDH, urine pH, HIV, HBsAg, HBsAb, HBcAb, HCAb, CMV serology, HSV serology
- **Daily q am during treatment:** CBC & diff, platelets, creatinine, lytes
- **Daily q am starting day 13 (day of methotrexate = day 10):** methotrexate levels (until less than 0.05 micromol/L; note date and time of withdrawal on the specimen.)
- **Immediately pre-methotrexate and q6h:** urine pH
- **Before each treatment:** CBC & diff, platelets, creatinine, lytes, AST, ALT, bilirubin, alkaline phosphatase, LDH

PREMEDICATIONS:

For Day 1 & 2 CODOX-M portion:

- Ondansetron 8 mg PO/IV pre-chemotherapy, then every 8 hours on days 1 and 2.
- Dexamethasone 12 mg PO pre-chemotherapy on days 1 and 2.

For Day 8 rituximab portion:

- Diphenhydramine 50 mg PO prior to rituximab and then q4h during the IV infusion, if the infusion exceeds 4 h.
- Acetaminophen 650-1000 mg PO prior to rituximab and then q4h during the IV infusion, if the infusion exceeds 4 h (maximum total daily acetaminophen dose = 4 g PO in patients with normal liver function).

For Day 10 CODOX-M portion:

- Ondansetron 8 mg PO/IV pre-chemotherapy.
- Prochlorperazine 10 mg PO/IV after Methotrexate infusion completed, followed by 10 mg PO/IV q4h PRN.

TREATMENT:

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

Treatment should be administered as an inpatient.

Drug	Dose	BCCA Administration Guideline
Cyclophosphamide	800 mg/m ² on days 1, 2	IV in 500 mL NS over 30 min
Vincristine	1.4 mg/m ² (max 2 mg) on days 1, 8	IV in 50 mL NS over 15 min
Doxorubicin	50 mg/m ² on day 1	IV in 50 mL NS over 15 min
Rituximab**	375 mg/m ² on day 8	IV in 500 mL NS over 3-8 h* (may divide dose equally into two 250 mL NS infusion bags to maintain 1-4 mg/mL concentration range).
Methotrexate	3000 mg/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 0.05 micromol/L***.
Posthydration		IV 2/3:1/3 + 100 mEq sodium bicarbonate/L at 125 mL/h, until leucovorin rescue completed.
Cytarabine	50 mg IT on day 1	Via lumbar puncture or Ommaya ventricular reservoir; qs to 6 mL with <u>preservative-free</u> NS. Day 1 dose should only be given, if there are no blasts present in the peripheral blood and if platelets are greater than 50 x10 ⁹ /L.
Filgrastim	less than 60 kg: 300 mcg 61-96 kg: 480 mcg greater than 96 kg: 600 mcg	SC daily starting on day 13, until neutrophils greater than 1.

Low risk patients should have LYCODOX-M followed by LYIVAC then a second cycle of LYCODOX-M.

High risk patients should have LYCODOX-M followed by LYIVAC then high dose therapy with stem cell rescue for definitive treatment.

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.

** If the peripheral blood lymphocyte count is above $30 \times 10^9/L$

- First Cycle: Rituximab should be omitted.
- Subsequent Cycles: Rituximab may be introduced with careful monitoring and individualized slow infusion (discuss with Dr. Kevin Song **or a member of the Leukemia/BMT tumour group at (604) 875-4863**

***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 0.05 micromol/L:

Methotrexate Level (micromol/L= 10^{-6} mol/L)	Leucovorin Dose
less than 0.05	None
0.05 – 0.9	25 mg PO/IV q6h
1 – 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.

Alkalinizing Regimen and Prehydration:

- IV 2/3:1/3 + 100 mEq sodium bicarbonate/L at 125 mL/hr x 4 hrs pre-methotrexate.
- Oral sodium bicarbonate 3250 mg PO q4h until methotrexate level is less than 0.05 micromol/L (start on 0800h of day planned for methotrexate).
- Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than 7 before starting methotrexate.

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 $100 \times 10^9/L$) 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/m² IV q6h, until creatinine returns to normal and methotrexate level is less than 0.05 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:** Doxorubicin only:

Bilirubin (mmol/L)	Dose Modification
2-35	100%
36-85	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.

Methotrexate only: If either AST, ALT or bilirubin is greater than twice normal, consider omitting.

- 6. 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:** All patients should be tested for HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100mg/day orally for the entire duration of the chemotherapy and for six months afterwards. The 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:** 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 BCCA Hypersensitivity Guidelines.
6. **Fatal Cytokine Release Syndrome (0.04-0.07%)** may occur within 24 hours of initiating rituximab infusion. It usually occurs within 1-2 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.
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.

Supportive Care:

All patients should be hospitalized for LYCODOX-M (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 $1 \times 10^9/L$.

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 $10 \times 10^9/L$. All blood products should be irradiated before administration to prevent graft versus host disease.
3. **Cytomegalovirus (CMV):** Patients who are serologically negative for CMV should receive CMV negative blood products, when being transfused (red cells or platelets).
4. **Antibiotics:**
 - a. Antibacterial: Fever (greater than $38^{\circ}C$) 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 $0.5 \times 10^9/L$ 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: Amphotericin B 10 mg/m^2 intravenously daily will be given prophylactically to all patients starting on day 12 and continued until neutrophil recovery. The dose should be increased to 0.5 mg/kg/day , if strong suspicion of fungal infection develops.
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 daily (or Acyclovir 5 mg/kg IV q12h) at least from day 12 to the day of recovery from mucositis.

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.

Date activated: 1 Dec 2006

Date(s) revised: 1 Jul 2011 (rituximab infusion rate clarified)

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.
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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.