

BCCA Protocol Summary for Treatment of Lymphoma with Doxorubicin, Cyclophosphamide, Vincristine, Prednisone and Rituximab (CHOP-R)

Protocol Code LYCHOP-R

Tumour Group Lymphoma

Contact Physician Dr. Joseph Connors

ELIGIBILITY:

- All stages of newly diagnosed diffuse large B-cell lymphoma
- mantle cell lymphoma, advanced stage at diagnosis
- A “Class II Drug Registration Form” must be submitted at the time of initiation of treatment. Rituximab must be used in combination with CHOP in order to be reimbursed by BCCA.

EXCLUSIONS:

- Congestive cardiac failure requiring current treatment (LYCHOP-R may be used but doxorubicin should be omitted, see cardiotoxicity below)

TESTS:

- Baseline (required before first treatment): CBC and diff, platelets, bilirubin
- Baseline (required, but results do not have to be available to proceed with first treatment): LDH, HBsAg, HBcoreAb
- Before each treatment: CBC and diff, platelets, (and bilirubin if elevated at baseline)
- Reassess all sites of disease after cycles 4 and 6 to determine duration of treatment

PREMEDICATIONS:

For CHOP portion

Ondansetron 8 mg PO pre-chemotherapy
 Dexamethasone 12 mg PO pre-chemotherapy

For Rituximab portion

Diphenhydramine 50 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h
 Acetaminophen 650 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h
 Prednisone as ordered for the LYCHOP-R protocol

TREATMENT:

Note that the rituximab is given once with each dose of CHOP, not weekly as is used when rituximab is used as single agent.

Drug	Dose	BCCA Administration Guideline
Doxorubicin	50 mg/m ² on day 1	IV push
Vincristine	1.4 mg/m ² * on day 1 (*no cap on dose)	IV push (dilute Vincristine to 20 mL with NS in a 30 mL syringe)
Cyclophosphamide	750 mg/m ² on day 1	IV in 100-250* mL NS over 20-60 minutes (*use 250 mL for doses greater than 1000 mg)

Drug	Dose	BCCA Administration Guideline
Prednisone	45 mg/m ² **on days 1-5 (**round off dose to nearest 25mg)	PO in am with food (the Prednisone dose for that day should be taken on the morning of the Rituximab infusion)
Rituximab	375 mg/m ² on day 1 or 2 whenever possible but not later than 72 h after CHOP	IV in 250 mL NS over 90 minutes-8 hours* (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)

*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) 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.

Repeat every 21 days or when the neutrophil and platelet counts have recovered sufficiently to allow 100% dosing, if that is determined sooner than every 21 days.

Limited stage: CHOP-R x 3 cycles, followed by radiation therapy

Advanced stage: CHOP-R x 6-8 cycles (2 cycles post maximum response, minimum 6 cycles)

Discontinue if no response after 2 cycles.

CNS Prophylaxis:

Patients with paranasal sinus involvement with large cell lymphoma who have a complete response at the completion of their chemotherapy should receive intrathecal methotrexate 12 mg alternating with intrathecal cytarabine 50 mg twice weekly x 6 doses (3 doses of each over 3 weeks) starting in week 18. (See protocol LYIT for details)

DOSE MODIFICATIONS:

1. Elderly Patients (age greater than 75 years):

Cycle 1 doses of cyclophosphamide and doxorubicin should be administered at 75% doses. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full 100% doses, but using the baseline experience with the 75% doses to guide these decisions.

2. Hematological: doxorubicin, cyclophosphamide and etoposide, if used, see below:

ANC (x10 ⁹ /L)	Dose Modification
≥ 0.8	100%
< 0.8	100% plus filgrastim 300 mcg daily x 5 days, starting 7 days after each IV chemotherapy

The patient should be treated with Filgrastim (G-CSF) in doses sufficient to allow full dose treatment on a 21 day schedule, using the above dose modifications. Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate Filgrastim (G-CSF) is required. (See Pharmacare guidelines)

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 20 x 10⁹/L.

3. Neurotoxicity: vincristine only:

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

4. **Hepatotoxicity:** doxorubicin only:

Bilirubin (mmol/L)	Dose Modification
2-35	100%
35-85	50%
Greater than 85	Omit doxorubicin. ADD cyclophosphamide 350 mg/m ² to the dose already planned.

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs. Serum bilirubin does not need to be requested before each treatment.

5. **Cardiotoxicity:** doxorubicin only:

When doxorubicin cannot be used due to proven cardiac dysfunction, it can be replaced by Etoposide 50 mg/m² IV on day 1 (Use non-PVC Equipment), 100 mg/m² PO on day 2 and 3.

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 lifelong dose of 450 mg/m² to be exceeded. (BCCA Cancer Drug Manual)
3. **Extravasation:** Doxorubicin and vincristine cause pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
4. **Hypersensitivity:** If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to BCCA 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. Patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion completed. 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 BCCA Hypersensitivity 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/day orally, for the entire duration of chemotherapy and for six months afterwards. 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 a hepatologist and consideration given to halting chemotherapy.

Call Dr. Joseph Connors or tumour group delegate @ (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 05 Mar 2001

Date revised: 01 Nov 2006 (clarified vital signs monitoring)

References:

1. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;328:1002-6.
2. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, et al. Hydroxyldaunomycin (Adriamycin) combination therapy in malignant lymphoma. *Cancer* 1976;38:484-93.
3. Coiffier B, Lepage E, Herbrecht R, Tilly H, et al. Mabthera (rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma (DLCL): interim results of a randomized GELA trial. *Blood* 2000;96(11):223a (abstract #950).
4. Byrd JC, Peterson BL, Morrison VA, Park K, 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 2712. *Blood* 2003; 101:6-14. (re: shortened rituximab infusion)