

BCCA Protocol Summary for Treatment of Advanced Indolent Lymphoma using Cyclophosphamide, Vincristine, Prednisone and Rituximab (CVP-R)

Protocol Code LYCVPR

Tumour Group Lymphoma

Contact Physician Dr. Richard Klasa

ELIGIBILITY:

- Indolent lymphoma (Follicular lymphoma, grade 1,2 or 3, Lymphoplasmacytic lymphoma, Marginal zone lymphoma or lymphoma not otherwise classifiable, grade 1)
 - advanced stage at diagnosis
 - at relapse if patient not refractory (previous response greater than 6 months)
- Small lymphocytic lymphoma/chronic lymphocytic leukemia, at relapse (note: small lymphocytic lymphoma is a variant of CLL, see LYFLUDR)
- A “Class II Drug Registration Form” must be submitted at the time of initiation of treatment

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

PREMEDICATIONS:

For CVP 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 650-1000 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 LYCVPR protocol

TREATMENT:

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

Drug	Dose	BCCA Administration Guideline
Vincristine	1.4 mg/m ² on day 1 (no maximum dose)	IV in 50 mL NS over 15 mins
Cyclophosphamide	1000 mg/m ² on day 1	IV in 100 to 250 mL* NS over 20 min to 1 hour *Use 250 mL for dose greater than 1000 mg.
Prednisone	100 mg starting on day 1	PO daily in am with food x 5 consecutive days
Rituximab**	375 mg/m ² on day 1 or 2 whenever possible but not later than 72 h after CVP	IV in 250 to 500 mL NS over 1 hour 30 min to 8 hours* (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)

*Start the Rituximab (first dose) 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 of 250 mL bag (or 100 mL of 500 mL bag) of the dose over 30 minutes then infuse the remaining 200 mL of 250 mL bag (or 400 mL of 500 mL bag) (4/5) over 1 hour (total infusion time = 1 hour 30 min). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

Repeat every 21 or 28 days (see dose modifications) for 8 cycles. For further use, CAP approval is required.

** 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. Joseph Connors or tumour group delegate at (604) 877-6000 or 1-800-663-3333).

DOSE MODIFICATIONS:

1. Hematological:

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose Modification
less than 1.2	or	less than 100	delay x 1 week

2. Neurotoxicity: Vincristine only

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

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation:** Vincristine causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
3. **Hypersensitivity:** 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. 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).
4. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1-2 hours of initiating the first Rituximab 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.
5. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, Rituximab should be discontinued.
6. **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 an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
7. **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.

Call Dr. Richard Klasa or tumour group chair at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 13 August 2004 (as ULYCVPR)

Date revised: 1 Jan 2012 (Relapsed patient added to Eligibility)

REFERENCES:

1. Marcus R, Imrie K, et al. An international, multi-centre, randomized, open-label phase III trial comparing rituximab added to CVP chemotherapy to CVP chemotherapy alone in untreated stage III/IV follicular non-Hodgkin's lymphoma. *Blood* 2003; 102; 28a (abstract 87)

2. Byrd JC, Peterson BL, et al. Randomized phase II 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 9712. *Blood* 2003; 101:6-14. (re: shortened rituximab infusion duration)