

BCCA Protocol Summary for the Treatment of Relapsed or Refractory Advanced Stage Aggressive B-Cell Non-Hodgkin’s Lymphoma with Ifosfamide, Carboplatin, Etoposide and Rituximab

Protocol Code

ULYRICE

Tumour Group

Lymphoma

Contact Physician

Dr. Joseph Connors

ELIGIBILITY:

- greater than or equal to 18 years of age
- Aggressive histology lymphoma in the WHO classification including
 - o diffuse large B-cell lymphoma
 - o mediastinal large B-cell lymphoma
 - o T-cell rich B-cell lymphoma
 - o intravascular large B-cell lymphoma
- Relapsed
- ECOG Performance Status 0,1,2 or 3
- No major impairment of renal, hepatic, or bone marrow function

NOTE: A BCCA “Compassionate Access Program” or “Undesignated Indication” request with appropriate clinical information for each patient must be approved prior to treatment.

TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, total bilirubin, alkaline phosphatase, LDH, creatinine, calcium
- Baseline (required, but results do not have to be available to proceed with first treatment): Hepatitis B and C serology (HBsAg, anti-HBsAg, anti-HBcore Ab, anti-HepC), HIV, pregnancy test for women of childbearing age
- Before each treatment: CBC & diff, platelets, total bilirubin, LDH, creatinine

PREMEDICATIONS:

Agent(s)	Dose	Route	Schedule
Ondansetron	8 mg	PO	15 min pre-chemotherapy daily
Dexamethasone	12 mg	PO	15 min pre-chemotherapy daily
Diphenhydramine	50 mg	PO	Prior to rituximab and then q 4h during rituximab infusion
Acetaminophen	650-1000 mg	PO	Prior to rituximab and then q 4h during rituximab infusion

TREATMENT:

Drug	Dose	BCCA Administration Guideline
Ifosfamide	1667 mg/m ² /day (total dose per cycle = 5000 mg/m ²)	IV infusion over 2 hours on days 1,2,3
Mesna (IV)	1667 mg/m ² /day (total dose per cycle = 5000 mg/m ²)	IV infusion over 2 hours on days 1,2,3 (with ifosfamide)
Mesna (PO)	2000 mg	PO 2 h and 4 h after completion of ifosfamide infusion on days 1,2,3
Carboplatin	5 x (25 + CrCl*) (maximum dose 800 mg)	IV infusion day 1 over 1 hour
Etoposide	100 mg/m ²	IV infusion day 1,2,3 over 30 minutes
Rituximab**	375 mg/m ²	IV in 250-500 mL NS over 90 minutes-8 hours*** day 1 (or day 2 or day 3) (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)

*Carboplatin dosed via the Calvert formula with an AUC of 5, **maximum dose 800 mg**
Estimate Creatinine Clearance (CrCl) with following formula:

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

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

**If the peripheral blood lymphocyte count is above 30 x 10⁹/L, the Rituximab should be omitted from that cycle.

***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 3 weeks x 4 cycles.

DOSE MODIFICATIONS:

1. Hematological

ANC (X 10 ⁹ /L)	DOSE MODIFICATION
greater than or equal to 0.8	100%
less than 0.8	100% plus Filgrastim 300 mcg daily x 5-10 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 schedule.

Platelet Count (PLT) (x 10 ⁹ /L)	DOSE MODIFICATION
= 75	100%
less than 75 (on treatment day)	Hold treatment until PLT greater than or equal to 75 x10 ⁹ /L and then administer at 100% dosing

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 10 x 10⁹/L.

- 2. Renal dysfunction:** Calculate creatinine clearance prior to each cycle and adjust dose of carboplatin accordingly. Discontinue protocol if CrCl less than 60 mL/min.
- 3. Hematuria:** Instruct patient to dipstick urine for blood prior to chemo – daily and with each void at home. Patient to call physician immediately if positive for blood. Patient to call physician immediately if they become drowsy. Chemo Room RN to ensure patient has been taught to do urine dipstick for blood. Chemo Room RN to ensure patient has tested urine for blood prior to each dose. See SCMESNA.

PRECAUTIONS:

- 1. Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- 2. Thrombocytopenia:** Support with platelet transfusion may be required.
- 3. Extravasation:** Etoposide causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
- 4. Hypersensitivity:** Hypersensitivity reactions including anaphylaxis have been reported with etoposide. Monitor etoposide infusion for 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. For the 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). 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. **Urotoxicity:** Ifosfamide can cause hemorrhagic cystitis and nephrotoxicity. Administration with MESNA and ample hydration is required. Avoid concurrent nephrotoxic drugs.
8. **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.
9. **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.
10. **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. Joseph Connors or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 01 Aug 2006

Date last revised: 01 June 2009 (revised acetaminophen dose)