BC Cancer Protocol Summary for Treatment of Lymphoma with Dexamethasone, Cytarabine, Platinum and riTUXimab

Protocol Code	*LYDHAPR*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Diego Villa*

ELIGIBILITY:
Patients must have:
- Aggressive histology lymphoma in the WHO classification including
  - diffuse large B-cell lymphoma
  - mediastinal large B-cell lymphoma
  - T-cell rich B-cell lymphoma
  - intravascular large B-cell lymphoma, and
- Relapsed disease, or
- Relapsed/refractory mantle cell lymphoma

Patients should have:
- ECOG Performance Status 0,1,2 or 3
- Adequate renal, hepatic, and bone marrow function

EXCLUSIONS:
- Creatinine clearance (CrCl) less than 45 mL/min

TESTS:
- Baseline: CBC & Diff, creatinine, ALT, total bilirubin
  - Recommended but optional: alkaline phosphatase, sodium, potassium, magnesium, calcium
- Baseline (required but results do not have to be available to proceed with first treatment, results must be checked before proceeding with cycle 2): HBsAg, HBsAb, HBcoreAb
- Before each cycle: CBC & Diff, creatinine, ALT, total bilirubin
  - If clinically indicated: alkaline phosphatase, sodium, potassium, magnesium, calcium, HBV viral load (see protocol SCHBV)
- Before treatment on Day 8 (if CISplatin is given on Day 1 and 8): CBC & Diff, creatinine

PREMEDICATIONS:
- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA).

For 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 to 975mg 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 to 975 mg PO *prior to riTUXimab subcutaneous*

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- dexamethasone 0.1% ophthalmic drops 2 drops in each eye every 6 hours, starting immediately before first dose of cytarabine and continuing until 48 hours after the last dose of cytarabine

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	40 mg on Days 1 to 4	PO *(Note: The anti-emetic premedication is separate from the dexamethasone given as part of the protocol; both should be prescribed separately.)*
CISplatin¥	75 mg/m^2 on Day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour
cytarabine¶	2000 mg/m^2 on Day 2 and 3	IV in 100 mL NS over 2 hours
rituximab**†	375 mg/m^2 on Day 1 or 2 whenever possible but not later than 72 h after DHAP	IV in 250 to 500 mL NS over 1 hour 30 minutes to 8 hours*
	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 1 or 2 whenever possible but not later than 72 h after DHAP	Subcutaneous over 5 minutes into abdominal wall‡ Observe for 15 minutes after administration

¥ Alternatively CARBOplatin may be used instead of CISplatin. See Renal Dysfunction under Dose Modifications. Note: it is acceptable for physicians to substitute CARBOplatin for CISplatin for reasons other than reduced GFR (for example, concerns around ototoxicity with CISplatin).

¶ Complete high dose cytarabine cerebellar toxicity nursing assessment form prior to each cytarabine dose (**see Appendix I**)

*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. IV first dose should also be given to patients previously treated more than 6 months ago.

‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible. If restarting more than 6 months from prior subcutaneous rituximab, give first dose by IV infusion (using the IV formulation).

Repeat every 21 days. Maximum prior to high dose chemotherapy and stem cell transplant, 3 cycles; otherwise 6 cycles. Discontinue if definite progression at any time.

DOSE MODIFICATIONS:

1. **Hematological on Day 1**

ANC ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose (all drugs)**
greater than or equal to 1.0	and	greater than or equal to 75	100%
greater than or equal to 1.0	and	less than 75	Delay 1 week*
			If platelets greater than or equal to 75 give 100% dose of all drugs If platelets less than 75 but greater than 50, proceed at 100% and support with platelet transfusions
less than 1.0	and	greater than or equal to 75	Delay 1 week*
			If ANC greater than or equal to 1 give 100% If ANC less than 1 but greater than or equal to 0.5, proceed at 100% and start filgrastim**
less than 1.0	and	less than 75	Delay 1 week*
			If ANC greater than or equal to 0.5 and platelets greater than or equal to 50, proceed with 100% and start filgrastim with platelet transfusions If ANC less than 0.5 and/or platelets less than 50, defer and check counts every 7 days. When both ANC greater than or equal to 0.5 and platelets greater than or equal to 50, resume as above

*if counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e. at 4 weeks) despite counts
** filgrastim should be given prophylactically for all future cycles.

Hematological on Day 8 (if CISplatin split dose given)

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (CISplatin)
greater than or equal to 1.0	and	greater than or equal to 75	100%
greater than or equal to 0.5 and less than 1.0	and	greater than or equal to 75	100% and start filgrastim * OR Reduce to 75% of current cycle's day 1 dose
greater than or equal to 0.5 and less than 1.0	and	less than 75 and greater than or equal to 50	Reduce to 75% of current cycle's day 1 dose
less than 0.5	or	less than 50	Omit and start filgrastim**

* if counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e. at 4 weeks) despite counts

** filgrastim should be given prophylactically for all future cycles.

2. **Renal Dysfunction**

Delay for one week if ***serum*** creatinine greater than 3 x ULN where ULN = local upper limit of normal range. If serum creatinine less than 3 x ULN adjust CISplatin dose as follows

Creatinine Clearance (ml/min)	CISplatin dose
greater than or equal to 60	75 mg/m^2 on Day 1
45 to 59	37.5 mg/m^2 on Days 1 and 8 or go to CARBOplatin¥ option
less than 45	***Delay***

¥ Alternatively CARBOplatin can be used instead of CISplatin per physician discretion for reasons other than reduced GFR (for example, concerns around ototoxicity).

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	AUC 5 on Day 1 Dose= AUC x (GFR+25) (maximum 800 mg)	IV in 250 mL NS over 30 minutes

Estimate calculated creatinine clearance (CrCl) with following formula:

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

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

Borderline cases (CrCl 60 to 70 mL/min): perform nuclear renogram for GFR, if available.

The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR;. When a nuclear renogram is available, this clearance would take precedence. Maximum CARBOplatin dose is 800 mg.

Note: The same method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

Consider re-calculation of CARBOplatin dose if serum creatinine changes ± 20% from baseline.

Prehydration is not required if CARBOplatin is given.

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. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
4. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
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. 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). See BC Cancer Hypersensitivity Guidelines.
6. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1 to 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. The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count is greater than 30 to 50 x 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.

7. **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.
8. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, riTUXimab should be discontinued.
9. **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.
10. **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.
11. **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.

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

References:

1. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014; 32:3490-97.
2. Gisselbrecht C, Glass B, Mournier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010; 28 (27): 4184-4190.
3. Kanat O, Ozet A, Ataergin S, et al. Modified outpatient dexamethasone, cytarabine and cisplatin regimen may lead to high response rates and low toxicity in lymphoma. Med Princ Pract 2010; 19(5): 344-7.
4. Olivieri A, Brunori M, Capelli D, et al. Salvage therapy with an outpatient DHAP schedule followed by PBSC transplantation in 79 lymphoma patients: an intention to mobilize and transplant analysis. Eur J Hematol 2004; 72(1): 10-17.

APPENDIX I: High Dose Cytarabine Cerebellar Toxicity Nursing Assessment Form

High Dose Cytarabine: Cerebellar Toxicity Nursing Assessment

BC CANCER Provincial Health Services Authority — Vancouver Coastal Health — Providence Health Care How you want to be treated.

One of the potential side effects of **high dose cytarabine** (greater than 1.5 g/m²) is **cerebellar toxicity.**

Nurses must complete coordination assessments and obtain patient's signature **PRIOR to each dose** of cytarabine to assess for cerebellar toxicity.

If changes in signature or **abnormal assessments** are noted, **HOLD** dose and notify provider.

See last page for assessment guidelines.

Date	Patient Signature	Coordination Assessments		Nurse signature
		Finger/nose	**Hand flip**	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	

High Dose Cytarabine Cerebellar Toxicity Assessment
Approved by nursing (BC Cancer, VCH BMT, PHC) 1 Apr 2023 Page **1** of **3**

Date	Patient Signature	Coordination Assessments		Nurse signature
		Finger/nose	Hand flip	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	
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		Satisfactory ☐ Needs further assessment ☐	Satisfactory ☐ Needs further assessment ☐	

High Dose Cytarabine Cerebellar Toxicity Assessment
Approved by nursing (BC Cancer, VCH BMT, PHC) 1 Apr 2023

Page 2 of 3

Signature Screening Assessment

A non-toxic signature will be clear and exhibit regular size writing. Please ensure patients are using a clipboard or other hard surface to write on. Patients should be in an upright position when signing.

NOTE: A failed signature will be very large, very shaky and non-comparable to patient's original.

Satisfactory: Not Satisfactory:

Coordination Assessments

Finger/nose[1] - the nurse holds their index finger approximately 2 feet away from the patient's face. The patient must then touch the nurse's index finger and then their nose. The nurse will move their finger and the patient will repeat the motion several times with the nurse's finger in a different location. Visual aids should be in place for this assessment where required by the patient.

A failed test will result in the patient not connecting - the finger will miss off to the side.

Hand Flipping[1] - ask the patient to place their hand in the opposite hand and quickly flip it front to back. **Dysdiadochokinesia** is the medical term for an impaired ability to perform rapid, alternating movements. A typical response is quick back and forth flipping. A cerebellar toxic effect will result in slow, incomplete flipping

If the patient is unable to participate in these assessments, additional cerebellar assessments can be found within your organization's designated reference materials. Cerebellar toxicity assessment prior to high-dose cytarabine administration is required.

1. (May 26, 2018). Cerebellar examination. Medistudents. Retrieved March 1, 2023, from https://www.medistudents.com/osce-skills/cerebellar-examination. Content including images used with gratitude and permission

Cerebellar examination. Medistudents. Retrieved March 1, 20023, from: https://www.medistudents.com/osce-skills/cerebellar-examination.