

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

**Protocol Code**

LYGDPR

**Tumour Group**

Lymphoma

**Contact Physician**

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## ELIGIBILITY:

- Greater than or equal to 18 years of age
- 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
- Relapsed disease
- ECOG Performance Status 0,1,2 or 3
- No major impairment of renal, hepatic, or bone marrow function

## EXCLUSIONS:

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

## TESTS:

- Baseline, then as indicated:
  - Required before first treatment: CBC & diff, platelets, creatinine, bilirubin, ALT
  - Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2: HBsAg, HBcoreAb
  - Recommended but optional: bilirubin, alkaline phosphatase, magnesium, calcium
- Before each treatment:
  - Day 1: CBC & diff, platelets, creatinine
  - Day 8: CBC & diff, platelets  
Creatinine (if cisplatin dose is given day 1 and 8)
- Before each treatment cycle: Use calculated creatinine clearance and serum creatinine to determine CISplatin dose, see dose modifications below.

## PREMEDICATIONS:

For cisplatin use antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA).

For CARBOplatin use antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA protocol)

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 650-975mg 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 650-975 mg PO prior to riTUXimab subcutaneous

**SUPPORTIVE MEDICATIONS:**

If HBsAg or HBcoreAb positive, start lamivudine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive

**TREATMENT:**

Drug	Dose <sup>‡</sup>	BC Cancer Administration Guideline
gemcitabine	1000 mg/m <sup>2</sup> day 1 & 8	IV in 250 mL NS over 30 min¶¶
dexamethasone	40 mg/d days 1 to 4	Oral daily in am with food <i>(Note: The anti-emetic premedication is separate from the Dexamethasone given as part of the protocol; both should be prescribed separately.)</i>
CISplatin*	75 mg/m <sup>2</sup> 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
riTUXimab**†	375 mg/m <sup>2</sup> on day 1 or 2 whenever possible but not later than 72 h after GDP	IV in 250 to 500 mL NS over 1 hour 30 minutes to 8 hours*
	<b>If IV infusion tolerated (no severe reactions requiring early termination), subsequent doses can be given by subcutaneous administration</b>	
	1400 mg (fixed dose in 11.7 mL) on day 1 or 2 whenever possible but not later than 72 h after GDP)	Subcutaneous over 5 minutes into abdominal wall‡  Observe for 15 minutes after administration

<sup>‡</sup>Consider dose reduction to 75% for gemcitabine and cisplatin or carboplatin in patients greater than 70 years of age

¶¶ gemcitabine may be given during prehydration for CISplatin

\* 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).

\*Start the (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 (or 100 mL) of the dose over 30 minutes then infuse the remaining 200 mL (or 400 mL) (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.

\*\*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<sup>9</sup> /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. ‡During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.

Estimate calculated 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)

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

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 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /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

ANC (x10 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /L)	Dose (all drugs)
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% gemcitabine (and cisplatin) and start filgrastim * OR Reduce gemcitabine (and cisplatin) 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 gemcitabine (and cisplatin) to 75% of current cycle's day 1 dose
less than 0.5	or	less than 50	Omit gemcitabine (and cisplatin) 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	Gemcitabine dose
greater than or equal to 60	75 mg/m <sup>2</sup> on Day 1	100%
45 to 59	37.5 mg/m <sup>2</sup> on Days 1 and 8 or go to CARBOplatin <sup>‡</sup> option	100%
less than 45	<b>Delay</b>	<b>Delay/Omit*</b>

**\*Delay if day 1; if day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.**

<sup>‡</sup> 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 only Dose= AUC x (GFR+25) (maximum 800 mg)	IV in 250 mL NS over 30 minutes

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  $\pm$  20% from baseline.

Prehydration is not needed if carboplatin is given

#### PRECAUTIONS:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Thrombocytopenia:** Support with platelet transfusion may be required.
- 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.
- Pulmonary Toxicity:** Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
- 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 during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. 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.
- 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.
- 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  $50 \times 10^9$  /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.

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. Laurie Sehn 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 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. *JCO* 2014; 32(31):3490-96.
2. Gopal et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. *Leuk Lymphoma*. 2010; 51(8):1523-9.
3. Moccia et al. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. *Leuk Lymphoma*. 2017; 58(2):324-332.