BC Cancer Protocol Summary for Treatment of Newly Diagnosed or Relapsed/Refractory Natural Killer or T-Cell Lymphoma using Gemcitabine, Oxaliplatin and Pegaspargase

Protocol Code	*LYGEMOXPEG*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Kerry Savage* *Dr. Laurie Sehn*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:

Patients must have:
- Newly diagnosed or relapsed/refractory natural killer (NK) or T-cell lymphoma, when the LYSMILE protocol is considered too toxic, or
- NK/T-cell lymphoma that is not appropriate for other regimens

Patients should have:
- Adequate hematologic function (absolute neutrophil count greater than 1.5×10^9/L, platelet count greater than 100×10^9/L and hemoglobin greater than 90 g/L),
- Adequate renal function (serum creatinine less than or equal to 133 micromol/L and creatinine clearance greater than or equal to 50 mL/min), and
- Adequate hepatic function (total bilirubin less than or equal to 2 x ULN and AST/ALT less than or equal to 3 x ULN)

EXCLUSION:
- CNS involvement

TESTS:
- Baseline: CBC & Diff, creatinine, sodium, potassium, magnesium, calcium, phosphate, albumin, bilirubin (direct and indirect), ALT, alkaline phosphatase, GGT, LDH, triglycerides, lipase, random glucose, uric acid, INR, PT, PTT, fibrinogen
- Baseline: (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HBsAg, HBsAb, HBcore Ab, EBV DNA
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.

- Prior to each cycle: CBC & Diff, creatinine, sodium, potassium, magnesium, calcium, phosphate, albumin, bilirubin (direct and indirect), ALT, alkaline phosphatase, GGT, LDH, triglycerides, lipase, random glucose, uric acid, INR, PT, PTT, fibrinogen
- Prior to treatment on day 8: CBC & Diff
- If clinically indicated: EBV DNA, HBV viral load (see protocol SCHBV)
- At least every 2 or 3 cycles: physician review to evaluate for peripheral neuropathy and other toxicity.

For pegaspargase:

Before each dose:

- INR, PT, PTT, fibrinogen (refer to appendix)
- Every Monday and Thursday**:** ALT, alkaline phosphatase, GGT, bilirubin (direct and indirect), lipase, random glucose

SUPPORTIVE MEDICATIONS:

Venous thrombosis prophylaxis

- Pegaspargase may cause coagulation abnormalities. If Khorana score 2 or higher, physician to consider referral to VGH Thrombosis Clinic for consideration of thromboprophylaxis (see table after **References** to calculate Khorana score)

Premedications

Day 1:

- Antiemetic protocol for moderate emetogenic chemotherapy (see SCNAUSEA)
- Prior to pegaspargase
  - acetaminophen 650 mg PO
  - diphenhydrAMINE 25 to 50 mg PO or IV
  - hydrocortisone 100 mg IV

Day 8:

- Antiemetic protocol for non-emetogenic chemotherapy (see SCNAUSEA)

Antiviral

- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- valACYclovir 500 mg PO daily or acyclovir 200 mg PO three times daily throughout treatment and for 4 weeks after discontinuation

- Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.
- Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
gemcitabine†	1000 mg/m^2 on Day 1 and Day 8	IV in 250 mL NS over 30 minutes
oxaliplatin	130 mg/m^2 on Day 1	IV in 250 to 500mL D5W over 2 hours
pegaspargase	2500 units/m^2 on Day 1 (Use 1500 units/m^2 for older and less fit patients)	IV in 100 mL NS over 1 h or IM*. For IV: BP and vitals monitoring** before and at 15, and 30 minutes during administration and at the end (at 60 minutes); observe for 1 h after end of administration For IM: BP and vitals monitoring** and visual inspection of injection site before and after injection, and observe for 1 hour after injection

† Consider dose reduction to 75% for gemcitabine in patients greater than 70 years of age

* IV preferred over IM as it eliminates painful injections and has a faster time to peak levels

**Monitoring after each dose of pegaspargase is required as the risk of hypersensitivity reactions exists/increases with each exposure.

Repeat every 21 days for 4 to 6 cycles (4 cycles for limited stage, 6 cycles for advanced stage)

DOSE MODIFICATIONS:

1. **Hematological:** Consider RBC transfusion support in individuals that have an expected hemoglobin nadir below 70 to 80 g/L and platelet transfusions to keep platelets greater than 10 x 10^9/L

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (all drugs)
greater than 1.0	and	greater than or equal to 75	100%
less than or equal to 1.0	and	less than 75	Delay 1 week
			Start filgrastim 5 mcg/kg SC daily until ANC recovery (1.0 x 10^9/L past the nadir)** 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 If platelets less than 50, give 75% dose of all drugs

** filgrastim 300 mcg: up to 75 kg
480 mcg: 76 kg to 110 kg
600 mcg: greater than 110 kg

Filgrastim should be given prophylactically for all future cycles. Submit a special authority request to Pharmacare for filgrastim coverage if curative intent.

2. **Oxaliplatin NEUROLOGIC Toxicity**

Neurotoxicity Definitions

Grade 1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for rechallenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

Dose Modifications for Oxaliplatin NEUROLOGIC Toxicity

	Starting Dose	**Dose Level –1**	**Dose Level -2***
oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2

Toxicity Grade	**Duration of Toxicity**		**Persistent (present at start of next cycle)**
	1 – 7 days	**greater than 7 days**	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	Discontinue*
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal **(see precautions)**	Maintain dose level	N/A	N/A

3. **Pegaspargase-related toxicities:**

Fibrinogen level (g/L)	Action
Greater than or equal to 0.5	Continue pegaspargase
Less than 0.5 and no signs of bleeding	4g fibrinogen concentrate followed by pegaspargase
Less than 0.5 and signs of non-CNS hemorrhage	4g fibrinogen concentrate. HOLD pegaspargase and resume once greater than or equal to 0.5 g/L
Less than 0.5 and signs of CNS hemorrhage	4g fibrinogen concentrate. DISCONTINUE pegaspargase.

Fresh frozen plasma NOT RECOMMENDED because it contains asparagine and counteracts benefit of pegaspargase.

See appendix for additional dose modifications for pegaspargase

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see below)

   For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication:

   45 minutes prior to oxaliplatin:
   - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

   30 minutes prior to oxaliplatin:
   - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications. The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

2. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	**Pharyngo-laryngeal Dysesthesia**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.

4. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
5. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
6. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
7. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
8. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
9. **Hepatitis B Reactivation:** See SCHBV protocol for more details.

Call Dr. Kerry Savage, 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. Wang J, Wang H, Wang Y et al. Analysis of the efficacy and safety of a combined gemcitabine, oxaliplatin and pegaspargase regimen for NK/T-cell lymphoma. Oncotarget 2016; 7(23): 35412-35422
2. Yan G, Huang H, Wang X et al. P-Gemox Regimen (Pegaspargase, Gemcitabine, oxaliplatin) for Extranodal Natural Killer Cell Lymphoma: 10 Years' Real-World Clinical Experience from China. Blood 2018
3. Li X, Cui Y, Sun Z et al. DDGP versus SMILE in newly diagnosed Advanced Natural Killer/T-cell Lymphoma: A Randomized Controlled, Multicenter, Open-label Study in China. Clinical Cancer Research 2016; 22(21): 5223-28.
4. Bade N, Lu C, Patzke C et al. Optimizing pegylated asparaginase use: An institutional guideline for dosing, monitoring, and management. J Oncol Pharm Practice 2020; 26(1): 74-92.

Khorana score for estimating venous thromboembolism risk in patients with cancer

Risk Factor	Points
Site of primary tumor	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
All other sites	0
Prechemotherapy platelet count greater than 350 $x10^9$/L	1
Hemoglobin less than 100g/L or use of ESAs	1
Prechemotherapy WBC greater than $11x10^9$/L	1
BMI greater than 35kg/m^2	1

Table adapted from UptoDate

ESA: erythropoiesis-stimulating agents

BMI: Body mass index= $\frac{\text{weight (kg)}}{\text{height } (m^2)}$

APPENDIX: PEGASPARGASE TOXICITY MONITORING GUIDE

Toxicity	Grade 2	Grade 3	Grade 4
Hypersensitivity (e.g, urticaria, wheezing, laryngospasm, hypotension)	For urticaria **WITHOUT** bronchospasm, hypotension, edema or need for parenteral intervention, stop infusion and follow SCDRUGRX. **CONTINUE** pegaspargase if safe to do so.	For wheezing or other **SYMPTOMATIC** bronchospasm with or without urticaria, indicated parenteral intervention, angioedema or hypotension, **DISCONTINUE** pegaspargase	For life-threatening consequences or indicated urgent intervention, **DISCONTINUE** pegaspargase
Pancreatitis	For **ASYMPTOMATIC** amylase or lipase elevation **> 3x ULN** (chemical pancreatitis) or only radiological abnormalities, **CONTINUE** pegaspargase observe closely for rising amylase or lipase levels	For amylase or lipase elevation > 3x ULN until enzyme levels stabilise or are declining, **HOLD** pegaspargase For **SYMPTOMATIC** pancreatitis, **PERMANENTLY DISCONTINUE** pegaspargase	**PERMANENTLY DISCONTINUE** all pegaspargase for clinical pancreatitis (vomiting, severe abdominal pain) with amylase or lipase elevation > 3x ULN for more than 3 days and /or development of pancreatic pseudocyst
Hypertriglyceridemia	If triglyceride <11.3mmol/L**, CONTINUE** pegaspargase but follow closely for evolving pancreatitis	For triglyceride > 11.3mmol/L, **HOLD** pegaspargase ; follow closely for pancreatitis. After triglyceride level returns to normal range, **RESUME** pegaspargase at prior dose level.	
Hyperglycemia	For uncomplicated hyperglycemia, **CONTINUE** pegaspargase	For hyperglycemia requiring insulin therapy, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase at prior dose level.	For hyperglycemia with life-threatening consequences or indicated urgent intervention, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase and do not make up for missed doses
Hepatic transaminasemia	For ALT or AST > 3 to 5 x ULN, **CONTINUE** pegaspargase	For ALT or AST > 5 to 20 x ULN, **DELAY NEXT** pegaspargase dose until < Grade 2 and **give 75% dose**	For ALT or AST > 20 x ULN, **DISCONTINUE** pegaspargase if toxicity reduction to < Grade 2 takes more than 1 wk
Hyperbilirubinemia	If direct bilirubin < 51 micromol/L, **CONTINUE** pegaspargase	If direct bilirubin $\geq$ 51 to 85 umol/L, **HOLD** pegaspargase and **RESUME** when direct bilirubin is < 34 micromol/L.	If direct bilirubin is > 85 micromol/L, **DISCONTINUE** ALL pegaspargase and do not make up for missed doses
Non-CNS thrombosis	For abnormal lab findings **WITHOUT** clinical correlates, **CONTINUE** pegaspargase	**HOLD** pegaspargase until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed. **DO NOT HOLD** pegaspargase for abnormal laboratory findings **WITHOUT** clinical correlate	**HOLD** pegaspargase until acute toxicity and clinical signs resolved and anticoagulant therapy stable or completed
Non-CNS hemorrhage	For bleeding in conjunction with hypofibrinogenemia, **HOLD** pegaspargase until bleeding $\leq$ Grade 1; **DO NOT HOLD** pegaspargase for abnormal laboratory findings **WITHOUT** a clinical correlate	**HOLD** pegaspargase until bleeding $\leq$ Grade 1, acute toxicity and clinical signs resolved and coagulant replacement therapy stable or completed	
CNS thrombosis	For abnormal lab findings **WITHOUT** a clinical correlate, **CONTINUE** pegaspargase	**DISCONTINUE** all pegaspargase; if CNS symptoms and signs fully resolved and significant pegaspargase dose remains to be given, may resume at lower dose and/or longer intervals between doses	**PERMANENTLY DISCONTINUE** all pegaspargase
CNS hemorrhage	DISCONTINUE pegaspargase ; DO NOT withhold pegaspargase for abnormal lab findings WITHOUT a clinical correlate		