

BC Cancer Protocol Summary for Treatment of Refractory or Relapsing Extranodal Natural Killer or T-Cell Lymphoma Using Pegaspargase, Methotrexate and Dexamethasone

Protocol Code	<i>LYASPMEDEx</i>
Tumour Group	<i>Lymphoma</i>
Contact Physician	<i>Dr. Kerry Savage</i>

ELIGIBILITY:

- Relapsed/refractory NK/T-cell lymphoma, nasal-type when the SMILE protocol is considered too toxic

EXCLUSIONS:

- Creatinine clearance less than 60 mL/min or serum creatinine greater than 132 micromol/L
- ANC less than $1.0 \times 10^9/L$, Platelets less than $100 \times 10^9/L$
- AST or ALT greater than 5 x ULN
- Bilirubin greater than 34 micromol/L

TESTS:

- Baseline and prior to each cycle:
- CBC and differential, platelets, creatinine, electrolytes panel, phosphate, albumin, bilirubin (direct and indirect), ALT, alkaline phosphatase, GGT, LDH, urine pH, triglycerides, amylase, lipase, random glucose, uric acid
- EBV DNA load
- Hepatitis B serology (HBsAg, anti-HBsAg, anti-HBcore Ab) if not previously done
- Daily: CBC and diff, platelets, creatinine, electrolytes panel

For methotrexate:

- Urine pH immediately before treatment and every 6 hours during treatment
- If clinically indicated, post methotrexate: daily ALT, bilirubin, alkaline phosphatase, LDH, GGT
- **At hour 48** (from start of methotrexate infusion), **or morning of day 3, then daily q am:** methotrexate levels (until less than 0.1 micromol/L; note date and time of withdrawal as well as start time of infusion on specimen.)

For pegaspargase:

Before each dose:

- INR, PT, PTT, fibrinogen, antithrombin (refer to appendix)
- Every Monday and Thursday: ALT, alkaline phosphatase, GGT, bilirubin (direct and indirect), amylase, 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

- ondansetron 8 mg PO/IV daily pre-chemo on **Day 1**
- prochlorperazine 10 mg PO after methotrexate infusion completed and then 10 mg PO q6h PRN
- Prior to pegaspargase: acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO or IV and hydrocortisone 100 mg IV
- For delayed emesis on or after Day 5:
 - dexamethasone 4 mg PO BID x 3 days
 - prochlorperazine 10 mg q6h PRN

Antimicrobial Prophylaxis

- cotrimoxazole 1 DS tablet PO three times a week. Discontinue cotrimoxazole 48 hours before beginning chemotherapy and resume when the plasma methotrexate is, or is projected to be less than 0.1 micromol/L

Antiviral .

- 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
- valacyclovir 500 mg PO daily or acyclovir 200mg PO three times daily throughout treatment and for 4 weeks after discontinuation

Diuresis

- furosemide 20 mg PO if daily fluid intake greater than output by 500 to 800 mL

Start Alkalinizing Regimen and Prehydration 4 to 12 hours prior to methotrexate:

- Discontinue all other IV hydration before starting alkalinizing regimen.
- IV D5W with potassium chloride 20 mEq/L and sodium bicarbonate 150 mEq/L at 125 mL/h for at least 4 hours prior to methotrexate until urine pH is greater than 7. Hydration may be temporarily held during methotrexate infusion (per physician/nursing discretion). Continue hydration post-methotrexate infusion until methotrexate level is less than 0.1 micromol/L.
- Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than 7 before starting methotrexate.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
methotrexate ^y	3 g/m ² on Day 1	IV in 1000 mL NS over 6 hours
leucovorin (folinic acid)	25 mg q6h Starting exactly 24 hours after start of methotrexate infusion	IV in 50 mL NS over 15 minutes for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L
dexamethasone	40 mg/d on Days 1 to 4	PO
pegaspargase	2500 units/m ² on Day 2 (use 1500 units/m ² of pegaspargase for older and less fit patients)	IV in 100 mL NS over 1 h or IM*. For IV: BP and vitals monitoring** before, 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

Drug	Dose	BC Cancer Administration Guideline
filgrastim	5 mcg/kg rounded to nearest prefilled syringe: 300 mcg: up to 75 kg 480 mcg: greater than 75 kg 600 mcg: greater than 110kg Starting on Day 6 DAILY until ANC greater than $1.0 \times 10^9/L$, starting at least 24 h after end of chemotherapy	SC

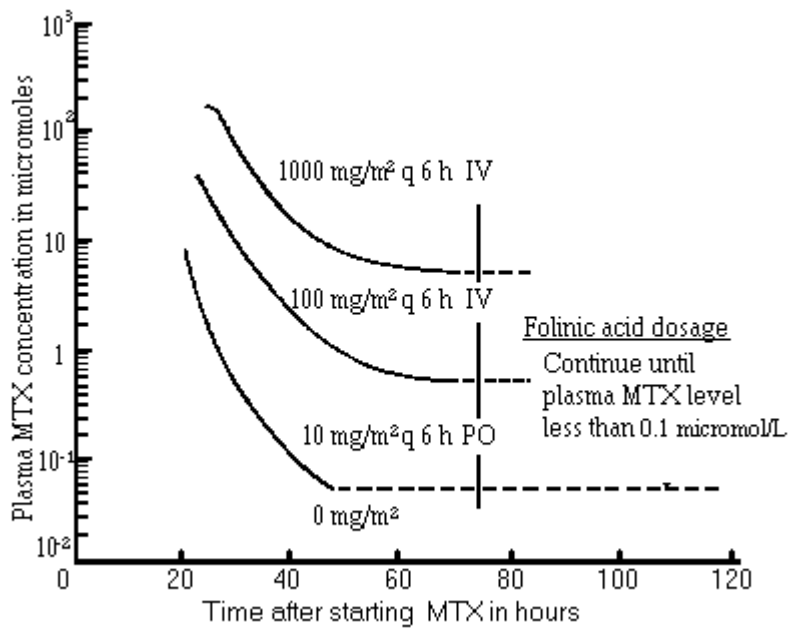
Note: One staff Physician signature is required. Orders written by other providers MUST be cosigned.

* 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 (total 3 cycles)

‡Methotrexate must be given in a hospital where rapid reporting of methotrexate levels is available. Plasma methotrexate levels are performed routinely each morning after starting the methotrexate infusion. At 24 hours, leucovorin rescue begins according to the protocol. A dose of leucovorin 25 mg q6h is used initially. The plasma methotrexate concentration done on day 3 is used to plot the initial slope of the curve on the Bleyer diagram below and should be used to increase the dose of leucovorin, if necessary. Leucovorin is continued until the plasma methotrexate is, or is projected to be less than 0.1 micromol/L



Reference: Bleyer WA. The clinical pharmacology of Methotrexate: new applications of an old drug. Cancer 1978;41:36-51.

Note: New laboratory method has a higher limit of detection and inaccuracies have been reported with methotrexate levels below 0.1 micromol/L .

Drug	Dosing regimen	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20
methotrexate	3 g/m ² /d IV in 1000 mL NS over 6 h	X																			
leucovorin	25 mg IV in 50 mL NS over 15 minutes every 6 h for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L* Starting exactly 24 hours after start of methotrexate infusion		X*	X*	X*	X*															
dexamethasone	40 mg PO 30 minutes before chemo	X	X	X	X																
pegaspargase	1500 or 2500 units/m ² IV or IM		X																		
filgrastim	5mcg/kg/d SC until ANC greater than 1 x 10 ⁹ /L** start D6, at least 24 h after chemo						X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**

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 $10 \times 10^9/L$.

Platelets ($\times 10^9/L$)	Dose (all drugs)
greater than or equal to 75	100%
less than 75 (on treatment day)	Hold treatment until platelet greater than or equal to $75 \times 10^9/L$ and then administer at 100% dosing

2. **Hepatic dysfunction:** At high doses, methotrexate can cause elevation of bilirubin and other liver enzymes. Even though these abnormalities are generally reversible, delaying treatment until liver enzymes significantly improve or return to near normal values before starting the next cycle is recommended. The table below may be used as a guide to dose reductions but more conservative dosing is strongly recommended for higher doses of methotrexate (8 g/m^2) at physician discretion.

Methotrexate only:

Bilirubin (micromol/L)		AST or ALT(units/L)	Dose Modification
2 to 49			100%
50 to 85	OR	3 x ULN	75%
Greater than 85			Omit

3. **Third space fluids** (ascites, pleural effusions): Omit methotrexate.
4. **Mucositis:** Grade 3 or 4 (painful erythema, edema, ulcers and cannot eat), reduce methotrexate to 80% or prolong routine rescue by 2 more days (unless patient has abnormal methotrexate levels)

5. 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:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
- Renal elimination:** Avoid concomitant use of drugs that may inhibit renal elimination of methotrexate such as non-steroidal anti-inflammatory drugs (NSAIDs), salicylates, and sulfa drugs.
- Possible interactions with proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole)** have been reported, resulting in elevated methotrexate levels and increased risk of methotrexate toxicity. Consider discontinuing proton pump inhibitors 1 day prior to methotrexate administration. If their use is required, closely monitor methotrexate levels and monitor for signs of methotrexate toxicity.
- Possible interaction with penicillins (e.g., amoxicillin, piperacillin, ticarcillin).** Penicillins compete with methotrexate for excretion sites in the renal tubules resulting in increased serum methotrexate and toxicity. Primarily a concern with high-dose methotrexate and thus the combination should be avoided if possible.
- 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 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.

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

References:

1. Jaccard A, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. *Blood* 2011;17(6):1834-9.
2. 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 $350 \times 10^9/L$	1
Hemoglobin less than 100g/L or use of ESAs	1
Prechemotherapy WBC greater than $11 \times 10^9/L$	1
BMI greater than 35kg/m^2	1

Table adapted from UptoDate

ESA: erythropoiesis-stimulating agents

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

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, CONTINUE pegaspargase	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	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 ≥ 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 ≤ Grade 1 ; DO NOT HOLD pegaspargase for abnormal laboratory findings WITHOUT a clinical correlate	HOLD pegaspargase until bleeding ≤ 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		