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

Protocol Code	*LYSMILE*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Kerry Savage*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:
- Newly diagnosed or relapsed / refractory natural killer (NK) or T-cell lymphoma

EXCLUSIONS:
- Pleural effusion, ascites or full extremity edema
- Creatinine clearance less than 60 mL/min or serum creatinine greater than 132 micromol/L
- ANC less than 1.0 x 10^9/L, Platelets less than 100 x 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 & diff, 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
- **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 and 48 hours afterwards:
- INR, PT, PTT, fibrinogen (refer to appendix)
- If Fibrinogen < 1g/L, give 10 units of cryoprecipitate.
- **Fresh frozen plasma NOT RECOMMENDED** because it contains asparagine and counteract benefit of pegaspargase.

Every Monday and Thursday: GGT, ALT, alkaline phosphatase, bilirubin (direct and indirect), amylase, lipase, random glucose

SUPPORTIVE MEDICATIONS:

Venous thrombosis prophylaxis

- If Khorana score 2 or higher, consider referral to VGH Thrombosis Clinic for consideration of thromboprophylaxis (see table on page 7 to calculate Khorana score)

Premedications

- ondansetron 8 mg PO/IV daily pre-chemo on Days 1 to 4
- prochlorperazine 10 mg PO after methotrexate infusion completed and then 10 mg PO q4h PRN
- For etoposide reaction: hydrocortisone 100 mg IV and diphenhydrAMINE 50 mg IV as needed
- 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 po q4h PRN

Antimicrobial Prophylaxis

- ciprofloxacin 500 mg PO BID starting on Day 1 and continue until ANC greater than 1 x 10^9/L
- cotrimoxazole 1 DS tablet PO three times a week starting when methotrexate level is less than 0.1 micromol/L and continue for the duration of treatment. Stop 48 hours prior to next cycle. Continue for 6 weeks after treatment ends.
- fluconazole 400 mg PO daily starting on Day 6 and continue until ANC greater than 1 x 10^9/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 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:

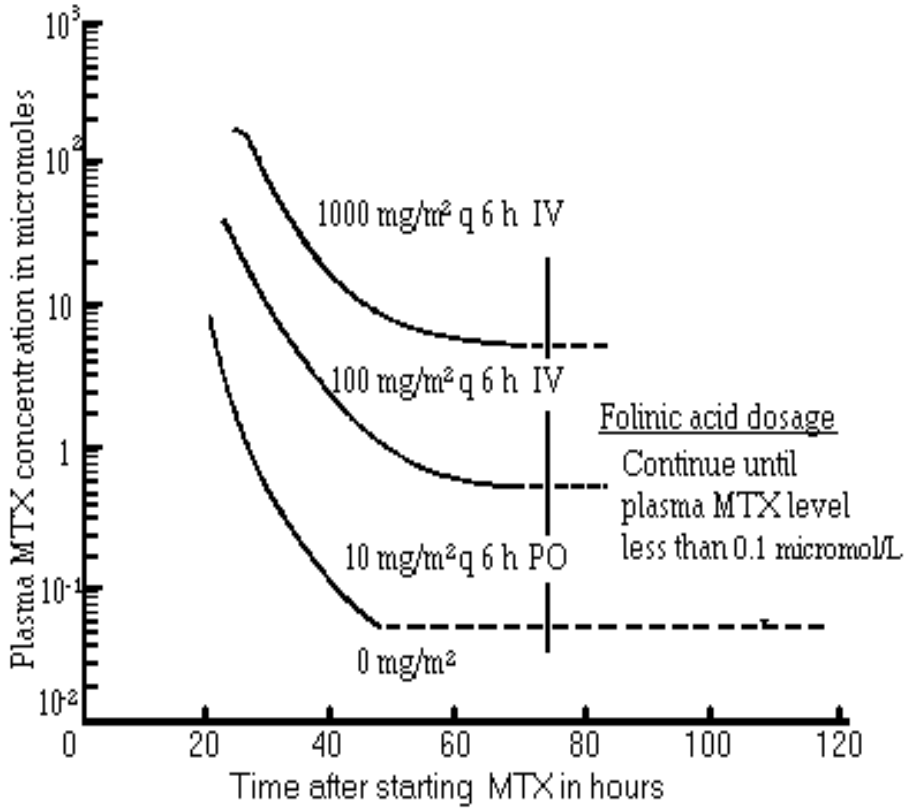
Drug	Dose	BC Cancer Administration Guideline
methotrexate*	2 g/m^2 on Day 1	IV in 1000 mL NS over 6 hours
leucovorin (folinic acid)	25 mg q6h Starting exactly 24 hours after start of methotrexate infusion	IV in 50 mL NS over 15 minutes for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L
dexamethasone	40 mg/d on Days 2 to 4	PO
etoposide	100 mg/m^2/d on Days 2 to 4	IV in 250 to 1000 mL NS over 45 min to 1 h 30 min (use non-DEHP equipment with 0.2 micron in-line filter)
mesna	1500 mg/m^2/d on Days 2 to 4, starting 1 h before ifosfamide	IV in 1000 mL NS over 22 h
ifosfamide	1500 mg/m^2/d on Days 2 to 4	IV in 500 mL NS over 20 h
mesna	750 mg/m^2 on Day 5, starting end of Day 4 mesna infusion	IV in 500 mL NS over 12 h
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 110 kg Starting on Day 6 DAILY until ANC greater than 1 x 10^9/L, starting at least 24 h after end of chemotherapy	SC
pegaspargase	1500 to 2500 units/m2 on Day 8*	IV in 100 mL NS over 1 h or IM±. BP and vitals during administration; observe for 1 h after end of administration

*lower dose of pegaspargase for older and less fit patients

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

Repeat every 28 days (for 2 cycles, up to 6 cycles maximum)

*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 iv 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

Drug	Dosing regimen	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20
methotrexate	2 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																
etoposide	100 mg/m^2/d IV over 2 h (use non-DEHP equipment with in-line filter)		X	X	X																
mesna	1500 mg/m^2/d IV in 1000 mL NS over 22 h start 1 h before ifosfamide		X	X	X																
ifosfamide	1500 mg/m^2/d IV in 500 mL NS over 20 h		X	X	X																
mesna	750 mg/m^2/d IV in 500 mL NS over 12 h start after end of mesna Day 4 dose					X															
filgrastim	5 mcg/kg daily 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**
pegaspargase	1500 – 2500 units/m2 IV in 100 mL NS over 1 h or IM on Day 8								X												

NOTE: One staff Physician signature is required. Orders written by other providers MUST be co-signed.

DOSE MODIFICATIONS:

1. **Hematological:** Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 10 x 10^9/L.

Platelets (x10^9/L)	Dose (all drugs)
greater than or equal to 75	100%
less than 75 (on treatment day)	Hold treatment until platelets greater than or equal to 75 x10^9/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 (8g/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. **Etoposide hypotensive reaction:** Stop etoposide infusion. Lie patient flat and run NS IV. Give diphenhydrAMINE 25 to 50 mg IV and hydrocortisone 100 mg IV. Resume etoposide infusion in 20 to 30 minutes once patient is stable. For subsequent doses of etoposide, pre-medicate with diphenhydrAMINE 25 to 50 mg IV and hydrocortisone 100 mg IV.
6. **Pegaspargase-related toxicities:** see appendix.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **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.

3. **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.
4. **Extravasation**: etoposide causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Etoposide hypersensitivity**: Monitor infusion of etoposide for the first 15 minutes for signs of hypotension. Refer to BC Cancer SCDRUGRX protocol.
6. **Urotoxicity:** Ifosfamide can cause hemorrhagic cystitis and nephrotoxicity. Administration with MESNA and ample hydration is required (also see SCMESNA protocol). Avoid concurrent nephrotoxic drugs.
7. **Venous access**: ensure good venous access prior to starting ifosfamide so that mesna can be given at completion of ifosfamide.
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 rousable 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 started on lamivudine 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 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.

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. Yamaguchi M, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-6.
2. Kwong YL, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood 2012;120(15):2973-80.
3. Yamaguchi M, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008; 99:1016–20.
4. SMILE protocol for NK/T-cell lymphoma chemotherapy order form. National Cancer Centre Singapore, SingHealth. September 2013.
5. Qi et al. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. Leuk Lymphoma 2016; 57(11):2575-83.

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

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, **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		