BC Cancer Protocol Summary for Treatment of Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL) with Pralatrexate

Protocol Code: *LYPRA*

Tumour Group: *Lymphoma*

Contact Physician: *Dr. Kerry Savage*

ELIGIBILITY:

- Relapsed or refractory peripheral T-cell lymphoma (PTCL)* with at least one prior treatment
- ECOG 0-2
- Adequate marrow reserve (ANC greater than 1 x 10^9/L, platelets greater than or equal to 100 x 10^9/L)
- Adequate renal function creatinine clearance greater than or equal to 30 mL/min
- Adequate liver function (bilirubin less than or equal to 26 micromol/L, ALT less than or equal to 2.5 x ULN)
- Patients are eligible to either romidepsin (ULYROMI) or pralatrexate (LYPRA)

* including patients transformed from mycosis fungoides

EXCLUSIONS:

- Mycosis fungoides (exception: transformed)
- Sezary syndrome
- History of brain metastases or CNS disease
- Congestive heart failure class III or IV
- Use with caution in patients with a prior allogeneic transplant

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH
- Before each treatment: CBC & differential, platelets
- Prior to each cycle: CBC and differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH

PREMEDICATIONS:

- **Vitamin supplementation mandatory** prior to first dose of pralatrexate to reduce risk of mucositis:
  - folic acid 1 to 1.25 mg PO once daily starting at least 10 days prior and continue until 30 days after last dose
  - vitamin B12 1000 mcg IM within 10 weeks prior and continue every 8 to 10 weeks during therapy

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:

To minimize mucositis, pralatrexate is recommended to be given once weekly for 3 weeks out of every 4 weeks in a dose escalation strategy for cycle 1 (per Columbia protocol)[2]. Subsequent cycles are maintained at the same dosing frequency and level once target dose level is attained. Leucovorin is given for 4 days starting 2 days after each pralatrexate dose to further reduce the risk of mucositis.

CYCLE 1:

Drug	Dose				BC Cancer Administration guideline
	Day 1	Day 8	Day 15	Day 22	
pralatrexate	10 mg/m^2	20 mg/m^2	30 mg/m^2	None	IV push over 3 to 5 minutes
leucovorin	15 mg BID Days 3 to 6	15 mg BID Days 10 to 13	15 mg BID Days 17 to 20		PO

CYCLE 2 onwards:

Drug	Dose				BC Cancer Administration guideline
	Day 1	Day 8	Day 15	Day 22	
pralatrexate	30 mg/m^2	30 mg/m^2	30 mg/m^2	None	IV push over 3 to 5 minutes
leucovorin	15 mg BID Days 3-6	15 mg BID Days 10-13	15 mg BID Days 17-20		PO

1 cycle = 28 days
Treat until progression

DOSE MODIFICATIONS:

Doses may be omitted or reduced based on patient tolerance. Omitted doses should not be made up at the end of the cycle. Once a dose reduction for toxicity occurs, do not re-escalate.

1. Hematological on Day 1, 8, 15

Blood count	Duration of Toxicity	Action	Pralatrexate Dose upon Restart	Pralatrexate Dose upon restart with severe renal impairment
ANC greater than or equal to 1.0 x 10^9/L AND platelets greater than or equal to 50 x 10^9/L†	N/A	100% dose	--	--
ANC less than 1.0 x 10^9/L*	1 week	Omit dose	Continue prior dose	Continue prior dose
	2 weeks or recurrence*	Omit dose	20 mg/m^2	10 mg/m^2
	3 weeks or 2nd recurrence	Discontinue	--	--
Platelets less than 50 x 10^9/L	1 week	Omit dose	Continue prior dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2	10 mg/m^2
	3 weeks	Discontinue	--	--

†Note: For first dose (cycle 1 day 1), platelet count must be greater than or equal to 100 x 10^9/L

*May consider the use of filgrastim but will not be a benefit of PharmaCare.

2. Mucositis

For Cycle 1: During dose escalation phase

Week	Pralatrexate dose	Grade 0-1 of mucosal inflammation	Grade 2 or greater of mucosal inflammation	Dose upon recovery to Grade 0-1
1	10 mg/m^2	Escalate dose on week 2	Hold until grade 0	10 mg/m^2
2	20 mg/m^2	Escalate dose on week 3	Reduce to 10 mg/m^2	10 mg/m^2
3	30 mg/m^2	Remain at 30 mg/m^2	Reduce to 20 mg/m^2	20 mg/m^2
4	---	---	---	---

Cycle 2 onwards

Mucositis Toxicity± on day of treatment	Action	Dose upon recovery to Grade 0-1	Dose upon recovery to Grade 0-1 in patients with severe renal impairment
Grade 0-1	Continue current dose	—	—
Grade 2 (Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated)	Omit	Continue prior dose	Continue prior dose
Grade 2 recurrence	Omit	20mg/m^2	10 mg/m^2
Grade 3 (Severe pain, interfering with oral intake)	Omit	20mg/m^2	10 mg/m^2
Grade 4 (Life threatening consequences; urgent intervention indicated)	Discontinue	--	--

±Mucositis tends to be predominately a cycle 1 event and declines in subsequent cycles. May consider re-escalation of dose after several weeks if previous dose reduction was due to mucositis toxicity only

3. Renal dosing

Renal impairment[¥]	Pralatrexate Dose
Mild to moderate (CrCl[¥] greater than or equal to 30 mL/min)	30 mg/m^2
Severe (CrCl 15-29 mL/min)	15 mg/m^2
End stage renal disease including dialysis (CrCl less than 15 mL/min)	Avoid

[¥] Creatinine clearance calculated using the Cockcroft-Gault Formula:

$$\text{GFR} = \frac{\text{N x (140 - age in years) x weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

N=1.23 for males and 1.04 for females

4. Other Treatment-related Toxicities[₸]

Toxicity Grade on Day 1 of Treatment	Action	Dose upon recovery to Grade 0-1	Dose upon recovery to Grade 0-1 in patients with severe renal impairment
Grade 0-2	Continue dose	--	--
Grade 3	Omit	20 mg/m^2/week	10mg/m^2/week
Grade 4	Discontinue	--	--

[₸]Renal and hepatic toxicity grade criteria:

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	Greater than ULN* – 1.5 x ULN	Greater than 1.5 – 3 x ULN	Greater than 3 – 6 x ULN	Greater than 6 x ULN
Bilirubin	Greater than ULN – 1.5 x ULN	Greater than 1.5 – 3 x ULN	Greater than 3 – 10 x ULN	Greater than 10 x ULN
ALT	Greater than 3 x ULN	Greater than 3.0-5 x ULN	Greater than 5-20 x ULN	Greater than 20 x ULN
alkaline phosphatase	Greater than ULN – 2.5 x ULN	Greater than 2.5 - 5 x ULN	Greater than 5 – 20 x ULN	Greater than 20 x ULN

*ULN=upper limit of normal

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PRECAUTIONS:

1. **Mucositis** including inflammation of the gastrointestinal, respiratory, and genitourinary tracts is common and fatalities have been reported. Monitor for mucosal inflammation weekly and omit or reduce dose if greater than or equal to grade 2 is observed. Appropriate prescription of leucovorin, folic acid and vitamin B12 is essential to reduce the risk of mucositis.
2. **Severe dermatologic reactions:** skin exfoliation, ulceration and toxic epidermal necrolysis (TEN) have been reported with pralatrexate. Fatalities have occurred after the first dose of pralatrexate, even when a reduced dose was administered. Patients with extensive skin involvement may be at greater risk of developing severe skin reactions with onset occurring usually early in the course of therapy. It may be progressive and increase in severity with further treatment. Monitor closely and hold or permanently discontinue pralatrexate for severe reactions.
3. **NSAIDS**: Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pralatrexate
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Thrombocytopenia**: Hold vitamin B12 IM injections until platelets greater than 50 x 10^9/L
6. **Hepatic toxicity**: Persistent liver function test abnormalities may indicate hepatic toxicity and require dose modification or discontinuation.

Contact Dr. Kerry Savage or tumour group delegate at (604) 877-6000 with any problems or questions regarding this treatment program.

REFERENCES:

1. O'Connor O, Pro B, Pinter-Brown L et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 2011:29(9):1182-9.
2. O'Connor O, Amengual J, Colbourn D. et al. Pralatrexate: a comprehensive update on pharmacology clinical activity and strategies to optimize use. Leukemia Lymphoma 2017:58(11):2548-557.
3. Servier Canada Inc. FOLOTYN® product monograph. Laval, Quebec;19 October 2018.