Regimen Monograph

A - Regimen Name

PRAL Regimen

Pralatrexate

Disease Site
Hematologic
Lymphoma - T-cell

Intent
Palliative

Regimen Category
Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
Treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) in patients with good performance status, who have undergone previous systemic treatment, none of which include romidepsin.

Supplementary Public Funding
PRALAtrexate
New Drug Funding Program (Pralatrexate - Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)) (NDFP Website) (Alternative dosing schedules are eligible for funding, as long as the schedule does not exceed the maximum funded single dose and/or schedule as outlined in the NDFP form's 'Funded Dose' section.)

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B - Drug Regimen

Standard Schedule:

PRALAtrexate†	30 mg /m²	IV	Days 1, 8, 15, 22, 29, 36

†Consider the use of leucovorin to reduce the risk of mucositis.

Alternate Schedule (Columbia regimen):

Cycle 1:

PRALAtrexate	10 mg /m²	IV	Day 1
leucovorin**	15 mg	PO	BID; Days 3 to 6
PRALAtrexate	20* mg /m²	IV	Day 8
leucovorin**	15 mg	PO	BID; Days 10 to 13
PRALAtrexate	30* mg /m²	IV	Day 15
leucovorin**	15 mg	PO	BID; Days 17 to 20

Cycle 2 and onwards:

PRALAtrexate	30 mg /m²	IV	Days 1, 8, 15
leucovorin**	15 mg	PO	BID; Days 3-6, 10-13, 17-20

* may escalate from previous dose if mucositis ≤ grade 1
** to reduce risk of mucositis

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C - Cycle Frequency

Standard Schedule:

REPEAT EVERY **49 DAYS** (once weekly for 6 out of 7 weeks)

Until disease progression or unacceptable toxicity

Alternate Schedule:

REPEAT EVERY **28 DAYS** (once weekly for 3 out of 4 weeks)

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care

- Folic acid 1 to 1.25 mg PO daily: start 10 days prior to first pralatrexate dose; continue during treatment and for 30 days after last pralatrexate dose.
- Vitamin B_{12} 1 mg IM: administer within 10 weeks prior to first pralatrexate dose and every 8 to 10 weeks thereafter (after first dose, subsequent B_{12} doses may be administered on the same day as pralatrexate)

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Prior to administering any pralatrexate dose:

- Mucositis should be ≤ grade 1.
- Absolute neutrophil count (ANC) should be ≥ 1×10^9/L.
- Platelet count should be ≥ 100×10^9/L for first dose and ≥ 50×10^9/L for all subsequent doses.

Dosage with toxicity

Do not make up omitted doses at the end of a cycle.

Dose Levels

Dose Levels for Dose Reduction:

Dose Level	Pralatrexate dose (mg/m^2)	Dose in Severe Renal Impairment (mg/m^2)
0	30	15
-1	20	10
-2	Discontinue	

Dose Levels for Dose Escalation (Alternate Schedule):

Dose Level	Pralatrexate dose (mg/m^2)	Dose in Severe Renal Impairment (mg/m^2)
0	10	Not applicable
1	20	10
2	30	15

Non-Hematologic toxicities:

Table 1 - Alternate Schedule (Cycle 1)

Mucositis Toxicity	Pralatrexate dose		
	Day 1	Day 8	Day 15
Grade 0 to 1	10 mg/m^2	↑ 1 dose level	↑ 1 dose level
Grade 2 to 4	Hold until recovery to Grade 0, then restart at 10 mg/m^2	Hold until recovery to Grade ≤ 1, then restart at same dose level	Hold until recovery to Grade ≤ 1, then restart at same dose level

Table 2 - Standard Schedule (All cycles) and Alternate Schedule (Cycle 2 onward)

Toxicity on Day of Treatment	Grade	Action†
Mucositis	2	Hold until recovery to ≤ grade 1; restart at same dose
	2 recurrence or grade 3	Hold until recovery to ≤ grade 1; restart at 1 dose level ↓
	4	Discontinue
All other non-Hematologic toxicities	3	Hold until recovery to ≤ grade 2; restart at 1 dose level ↓
	4	Discontinue

† Do not re-escalate dose after a reduction due to toxicity. Mucositis appears to occur mainly in cycle 1 and incidence declines in subsequent cycles. With the alternate schedule, may consider dose re-escalation after several weeks for patients in whom a dose ≤ 30 mg/m^2 is determined to be safe.

Hematologic Toxicities:

Toxicity on Day of Treatment	Duration of toxicity	Action*†
Platelet < 50 x 10^9/L	1 week	Hold; restart at same dose
	2 weeks	Hold; restart at 1 dose level ↓
	3 weeks	Discontinue
ANC 0.5-1 x 10^9/L and no fever	1 week	Hold; restart at same dose
ANC 0.5-1 x 10^9/L with fever or ANC < 0.5 x 10^9/L	1 week	Hold, give G-CSF support; restart at same dose
	2 weeks or recurrence	Hold, give G-CSF support; restart at 1 dose level ↓
	3 weeks or 2nd recurrence	Discontinue
*Administer subsequent doses only when platelet count ≥ 50×10^9/L and ANC ≥ 1×10^9/L on day of treatment. † Do not re-escalate dose after a reduction due to toxicity.		

Hepatic Impairment

The safety, efficacy and pharmacokinetics of pralatrexate have not been evaluated in patients with hepatic impairment. Patients with total bilirubin > ULN, AST or ALT > 2.5 x ULN or AST or ALT > 5 x ULN if documented hepatic lymphoma involvement were excluded from clinical trials.

Renal Impairment

Renal Impairment	Pralatrexate Dose (% of Usual Dose)
Mild to moderate (CrCl ≥ 30 mL/min)	No dosage adjustment necessary
Severe (CrCl 15-29 mL/min)	50%*
End-stage renal disease (ESRD), including dialysis	Avoid (unless the potential benefit outweighs risks**)

* Except 10 mg/m^2 starting dose in alternate schedule

**Serious reactions, including fatal cases of TEN and severe mucositis have been reported in patients with end-stage renal disease undergoing dialysis

Dosage in the Elderly

No overall differences in efficacy and safety were observed in patients ≥65 years compared with patients <65 years. No dose adjustment required; however, close monitoring for toxicity is recommended.

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F - Adverse Effects

Refer to pralatrexate drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Mucositis (may be severe) • Infection	• Myelosuppression (may be severe) • Nausea, vomiting • Fatigue • Anemia • Constipation • Fever, chills • Edema • Cough, dyspnea • Epistaxis	• Diarrhea • Rash, pruritus (may be severe) • Anorexia, weight loss • Abnormal electrolyte(s) • Musculoskeletal pain • ↑ LFTs • Abdominal pain • Night sweats • Tachycardia	• Cardiotoxicity • Infusion related reaction • Tumor lysis syndrome • Renal failure • Pneumonitis

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G - Interactions

Refer to pralatrexate drug monograph(s) for additional details

- No formal drug interactions with pralatrexate have been conducted.
- Use with caution and monitor for signs of systemic toxicity due to increased drug exposure with drugs that undergo substantial renal excretion (e.g. probenecid, NSAIDs, trimethoprim/sulfamethoxazole).

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H - Drug Administration and Special Precautions

Refer to pralatrexate drug monograph(s) for additional details

Administration

- Pralatrexate is for intravenous use only.
- Administered undiluted as an intravenous push over 3-5 minutes into the line of a free-flowing 0.9% sodium chloride Injection.
- Refrigerate at 2-8°C; protect from light.

Contraindications

- Patients with known hypersensitive to pralatrexate, any ingredient in the formulation or component of the container.

Other Warning/Precautions

- Patients should be cautioned not to drive cars, use machines or perform hazardous tasks if they experience fatigue.

Pregnancy/Lactation

- Pralatrexate is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **8 weeks** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects: Unknown. Semen preservation prior to initiation of pralatrexate therapy could be considered.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and weekly before each dose
- Liver function tests; Prior to the first and fourth doses in each cycle and as clinically indicated (before each cycle for alternate schedule)
- Renal function tests; Prior to the first and fourth doses in each cycle and as clinically indicated (before each cycle for alternate schedule)
- Mucosal inflammation; Baseline and weekly
- Clinical toxicity assessment for signs of infection, electrolyte imbalances, TLS, cardiac, dermatologic, GI, pulmonary, and musculoskeletal effects.; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	15.15 minutes
Nursing Workload (average time per visit)	35.00 minutes

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K - References

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood. 2012 May 3;119(18):4115-22. doi: 10.1182/blood-2011-11-390211

O'Connor OA, Amengual J, Colbourn D, et al. Pralatrexate: a comprehensive update on pharmacology, clinical activity and strategies to optimize use. Leuk Lymphoma. 2017 Nov;58(11):2548-57. doi: 10.1080/10428194.2017.1306642

O'Connor OA, 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. doi: 10.1200/JCO.2010.29.9024

Pralatrexate drug monograph, Ontario Health (Cancer Care Ontario).

Shustov AR, Shinohara MM, Dakhil SR, et al. Management of mucositis with the use of leucovorin as adjunct to pralatrexate in treatment of peripheral T-cell lymphomas (PTCL)- results from a prospective multicenter phase 2 clinical trial. Blood 2018;132(Supplement 1):2910.

September 2023 Updated the "Administrative Information" section with pharmacy and nursing workload.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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