Regimen Monograph

A - Regimen Name

CISPRALT Regimen

CISplatin-Raltitrexed

Disease Site	Lung - Mesothelioma
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	First-line treatment of malignant mesothelioma. See NDFP eligibility form for detailed funding criteria.
Supplementary Public Funding	**raltitrexed** New Drug Funding Program (Raltitrexed - Advanced Malignant Pleural Mesothelioma (MPM)) (NDFP Website)

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B - Drug Regimen

raltitrexed (Round to nearest 0.5 mg)	3 mg /m²	IV	Day 1

CISplatin (Round to nearest 1 mg)	80 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Standard regimens for Cisplatin premedication and hydration should be followed. Refer to Cisplatin monograph

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E - Dose Modifications

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

Dosage with toxicity

Dosage in Myelosuppression ± Gastrointestinal Toxicity:

The doses of raltitrexed and cisplatin should be reduced based upon the worst hematologic and GI toxicity experienced in the previous cycle. Doses should not be re-escalated if reduced for toxicity.
Suggested dose levels for raltitrexed: 3, 2.25, 1.5 mg/m^2
Suggested dose levels for cisplatin: 80, 60, 40 mg/m^2

Toxicity Grade			*Action*[1]	*Raltitrexed*	*Cisplatin*
Grade 3 neutropenia / thrombocytopenia	**OR**	grade 2 GI toxicity	Hold [1]	↓ 1 dose level	↓1 dose level
Grade 3 neutropenia / thrombocytopenia	**AND**	grade 3 GI toxicity	Hold [1]	Discontinue	↓ 1 dose level
Grade 4 neutropenia / thrombocytopenia	**OR**	grade 3 GI toxicity	Hold [1]	↓ 2 dose levels	↓ 2 dose levels (If grade 3 GI only, ↓ 1 dose level if related to cisplatin)
		grade 4 GI toxicity	Hold [1]	Discontinue	↓ 2 dose levels
Grade 2 Neurotoxicity				No change	↓ 50%
Other ≥ grade 3 non-hematological	**AND**	1st occurrence	Hold [1]	↓ 1 dose level	↓ 1 dose level; discontinue if neurotoxicity
Grade 3 or 4 toxicity	**AND**	Recurrence after prior reduction	Discontinue	Discontinue	Discontinue
[1] Retreat only when GI toxicity resolved, platelets are ≥ 100 x 10^9/L, ANC ≥ 2 x 10^9/L, and WBC ≥ 4 x 10^9/L.; consider discontinuing if major organ toxicity.					

Hepatic Impairment

No adjustment required for Cisplatin.

Grade	*Initial Dose (baseline values)*	*During Treatment (worst in previous cycle)*
1	100%	No change
2	100%, watch carefully	Hold until ≤ grade 1
3	Extreme caution (no data)	Hold until ≤ grade 2
4	Do not treat (no data)	Discontinue

Renal Impairment

Renal impairment results in a significant reduction in raltitrexed clearance and doses must be

modified for renal impairment. Patients with renal impairment should be monitored carefully.

Creatinine Clearance (mL/min)	***Raltitrexed Dose as % of 3mg/m^2***	***Raltitrexed Dosing Interval***	***Cisplatin# (% of previous dose)***
>65	100%	q3w	100%
55-65	75%	q4w	100%
25-54	% equivalent to mL/min*	q4w	75% or 50%
10 - <25	DISCONTINUE	Not Applicable	
< 10			OMIT

*(e.g. if 30mL/min, give 30% of full dose.)
See Dosing section of CISPLATIN drug monograph.

Dosage in the Elderly

Geriatric patients may be at higher risk of developing nephrotoxicity, ototoxicity/neurotoxicity or hematologic adverse effects. Use with caution.

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F - Adverse Effects

Refer to raltitrexed, CISplatin 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**
• Nausea, vomiting (may be severe)	• Fatigue • Diarrhea (may be severe) • Nephrotoxicity (may be severe) • Hearing impairment • Myelosuppression +/- infection, bleeding (may	• Increased LFTs (may be severe) • Abdominal pain • Constipation • Rash • Mucositis	• Neuropathy • Arterial/venous thromboembolism • Arrhythmia • Hemolytic uremic syndrome • Hypersensitivity • Secondary

	be severe) • Anorexia	• Abnormal electrolytes	malignancy • Vasculitis

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G - Interactions

Refer to raltitrexed, CISplatin drug monograph(s) for additional details

- Nephrotoxic and ototoxic drugs may increase the risk of nephro and ototoxicity; avoid if possible or caution during or shortly after cisplatin therapy (for 1-2 weeks)
- Phenytoin levels may be altered by cisplatin. Monitor and adjust phenytoin dose as required.
- Avoid folinic or folic acid (or preparations containing these) as this may interfere with raltitrexed action

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H - Drug Administration and Special Precautions

Refer to raltitrexed, CISplatin drug monograph(s) for additional details

Administration

Raltitrexed:

- Mix in 50-250 mL (NS, D5W); infuse IV over 15 minutes.
- Do not admix with other drugs
- Reconstituted and diluted solutions do not need to be protected from light

CISplatin:

- Ensure good urinary output during chemotherapy visit. Patient should void at least once during chemotherapy visit. Use locally approved hydration regimens.
- Blood pressure should be taken before and after chemotherapy.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.

- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Contraindications

- Patients with known hypersensitivity to platinum containing compounds
- Patients who are myelosuppressed
- Patients with severe renal and/or hepatic impairment
- Patients with hearing impairment, unless the potential benefits outweigh the risk

Other warnings/precautions

- Caution is necessary in patients with poor general condition, prior radiotherapy, mild to moderate hepatic impairment and in elderly patients
- Raltitrexed results in asthenia and malaise; it may impair ability to drive and to operate machinery

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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 before each cycle. Interim counts should be done in first cycle and repeated if dose modifications necessary
- Mandatory renal function tests prior to each cycle (including electrolytes and magnesium) and urinalysis
- Baseline and regular liver functions tests
- Suggest weekly CBC for patients who develop signs of GI toxicity
- Audiogram; baseline and as clinically indicated
- Clinical toxicity assessment (including infection, diarrhea, neurologic, ototoxicity, fatigue, stomatitis, cutaneous 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	4-6 hours
Pharmacy Workload (average time per visit)	41.187 minutes
Nursing Workload (average time per visit)	46.667 minutes

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K - References

Cisplatin and raltitrexed drug monographs, Cancer Care Ontario.

Van Meerbeeck J Gaafar R,, Manegold C, et al. Randomized Phase III study of cisplatin with or without Raltitrexed in patients with MPM: An Intergroup study of the European Organization for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23:6881-9.

PEBC Advice Documents or Guidelines

- Endorsement of the 2018 ASCO Treatment of Malignant Pleural Mesothelioma Guideline

June 2019 added PEBC guideline link

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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.

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