BC Cancer Protocol Summary for Palliative Therapy of Metastatic Colorectal Cancer using Oxaliplatin and Raltitrexed in Patients Intolerant to Fluorouracil or Capecitabine

***Protocol Code**:* *GIAVRALOX*

***Tumour Group**:* *Gastrointestinal*

***Contact Physician**:* *GI Systemic Therapy*

ELIGIBILITY:
- Stage IV colorectal cancer patients with documented intolerance to fluorouracil or capecitabine
- Known or suspected DPD deficiency
- ECOG performance status less than or equal to 2

EXCLUSIONS:
- Inadequate renal function (if serum creatinine is abnormal or if it may not correlate well with the creatinine clearance due to factors such as age or weight loss, obtain creatinine clearance.)
- Clinically significant cardiac arrhythmias requiring drug therapy.
- Severe pre-existing peripheral neuropathy
- Avoid in patients with congenital long QT syndrome.

CAUTIONS:
- Adequate marrow reserve, renal and liver function

TESTS AND MONITORING:
- Baseline: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, albumin, sodium, potassium, magnesium, calcium, appropriate imaging study. Optional: CEA, CA 19-9.
- Prior to each cycle: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, albumin, sodium, potassium, magnesium, calcium.
- If clinically indicated: CEA, CA 19-9
- Baseline and routine ECGs for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.

PREMEDICATIONS:
- Antiemetic protocol for high-moderate emetogenic chemotherapy (see SCNAUSEA)
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

TREATMENT:
A Cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
raltitrexed	3 mg/m^2	IV in 100 mL NS over 15 minutes
oxaliplatin*	130 mg/m^2	IV in 250 to 500 mL of D5W over 2 hours. Flush lines pre infusion with D5W (oxaliplatin is NOT compatible with NS).

* Concurrent use of up to 500 mL D5W hydration at maximum rate of 250 mL/h with peripheral administration of oxaliplatin can be given.

- Repeat every 21 days (one cycle) until disease progression or unacceptable toxicity.
- Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

DOSAGE MODIFICATIONS (Sections A, B & C)

A. Dose Modifications for NEUROLOGIC Toxicity
B. Dose Modifications for HEMATOLOGIC Toxicity
C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with Oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

Table 1 - Dose Levels for NEUROLOGIC Toxicity (Section A)

Agent	Dose Level 0 (Starting Dose)	Neurotoxicity Dose Level –1N	Neurotoxicity Dose Level –2N	Neurotoxicity Dose Level –3N
oxaliplatin	130 mg/m^2	100 mg/m^2	65 mg/m^2	Discontinue Therapy

**If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (ie if hematologic toxicity mandates dose –2 reduction (85 mg/m^2) and neurologic toxicity mandates dose –2N reduction (65 mg/m^2), then 65 mg/m^2 is given.*

A. Dose Modifications for NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 – 7 days	greater than 7 days	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease one neurotoxicity dose level
Grade 3	↓1 neurotoxicity dose level	↓1 neurotoxicity dose level	Discontinue therapy
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Increase duration of infusion to 6 hours	N/A	N/A

Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias/dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Table 2 Dose Levels for NON-NEUROLOGIC TOXICITY (Sections B & C)

Agent	Dose Level 0 (Starting dose)	Dose Level -1	Dose Level -2	Dose Level -3
oxaliplatin	130 mg/m^2	100 mg/m^2	85 mg/m^2	Discontinue Therapy

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**oxaliplatin**	**raltitrexed**
▪ If ANC less than 1.5 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). ▪ If ANC remains less than 1.5 after 2 weeks, discontinue treatment.	1	greater than or equal to 1.5	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.5	Delay then maintain dose level	Delay then maintain dose level
	3	0.5 to less than 1.0	Delay then ↓ 1 dose level	Delay then decrease dose to 75%
	4	less than 0.5	Delay then ↓ 2 dose levels	Delay then decrease dose to 50%
	Grade	**Platelets (x10^9/L)**	**oxaliplatin**	**raltitrexed**
▪ If platelets less than 100 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 100 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). ▪ If platelets remain less than 100 after 2 weeks, discontinue treatment.	1	greater than or equal to 100	Maintain dose level	Maintain dose level
	2	50 to less than 100	Delay then maintain dose level	Delay then decrease dose to 75%
	3	25 to less than 50	Delay then ↓ 1 dose level	Delay then decrease dose to 50%
	4	less than 25	Delay then ↓ 2 dose levels	Delay then decrease dose to 50%

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Diarrhea**	**oxaliplatin**	**raltitrexed**
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Delay until toxicity resolved then maintain dose level	Delay until toxicity resolved then resume at 75%
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Delay until toxicity resolved then maintain dose level	Delay until toxicity resolved then resume at 50%
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Discontinue as raltitrexed is discontinued	Discontinue further use
	Grade	**Stomatitis**	**oxaliplatin**	**raltitrexed**
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Delay until toxicity resolved then maintain dose level	Delay until toxicity resolved then resume at 75%
	3	Painful erythema, edema, ulcers, and cannot eat	Delay until toxicity resolved then maintain dose level	Delay until toxicity resolved then resume at 50%
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Discontinue as raltitrexed is discontinued	Discontinue further use

***If treatment with raltitrexed is delayed or discontinued, then oxaliplatin is also delayed or discontinued.**
Once a dose reduction has been made, all subsequent doses should be given at the reduced dose level.

Renal dysfunction: For patients with abnormal serum creatinine before treatment or on any subsequent cycle of treatment, check creatinine clearance and modify dose as follow.

Creatinine Clearance mL/min (CrCl)	raltitrexed only	dosing interval
greater than 65	100%	q3w
55 to 65	75%	q4w
25 to 54	% equivalent to CrCl eg. If 30 mL/min give 30% of full dose	q4w
less than 25	Discontinue	N/A

***If treatment with raltitrexed is delayed or discontinued, then oxaliplatin is also delayed or discontinued.**

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{N\,(140 - \text{age})\ \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

Hepatic dysfunction: Transient elevation of liver transaminase is noted with raltitrexed. For Grade 2 hepatic impairment, no dose modification is needed, but the liver enzymes should be monitored carefully. Treatment in patients with suspected drug-related rises in liver enzymes should be deferred until they decrease to Grade 2. Not recommended in severe hepatic impairment.

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see table below) For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity pre-medication:

   45 minutes prior to oxaliplatin:

   - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

   30 minutes prior to oxaliplatin:

   - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

2. **Pharyngolaryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	**Pharyngo-laryngeal Dysesthesia**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
6. **Drug Interactions:** Leucovorin (folinic acid), folic acid or vitamins containing these agents must not be used immediately prior to or during administration of raltitrexed, since they may interfere with its action. There is also a theoretical potential for interaction between raltitrexed and NSAIDS or warfarin but no clinical evidence of a significant interaction has been found.
7. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
8. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.

9. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
10. **Elderly patients**: Raltitrexed should be used with **caution in elderly** patients with special care taken to ensure adequate hydration in the event of stomatitis or diarrhea.
11. **Cardiac rhythm or functional abnormalities**: Tachycardias, atrial fibrillation and congestive heart failure have been reported with raltitrexed.
12. Vascular pain in the affected limb with venous access may be experienced by patients receiving peripheral oxaliplatin. Concurrent hydration in some cases has been shown to decrease associated discomfort.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Gravalos C, Salut A, Garcia-Giron C, et al. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. Clin Transl Oncol 2012;14:606-12.
2. Laudani A, Gebbia V, LEONARDI V, et al. Activity and toxicity of oxaliplatin plus raltitrexed in 5-fluorouracil refractory metastatic colorectal adeno-carcinoma. Anticancer Res 2004;24:1139-42.
3. Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). Br J Cancer 1998;77:15-21.
4. Cunningham D, Zalcberg JR, Rath U, et al. 'Tomudex' (ZD1694): Rresults of a randomized trial in advanced colorectal cancer demonstrate efficacy and reduced mucositis and leucopenia. The 'Tomudex' Colorectal Cancer Study Group. Eur J Cancer 1995;31A:1945-54.
5. Tomudex (raltitrexed) Product Monograph. Hospira Healthcare Corp. April 23, 2008
6. Van Ravensteijn S, van Merrienboer B, van Asten S, *et al.* Oxaliplatin infusion-related venous pain: prevention by simultaneous intravenous fluids. *BMJ Supportive & Palliative Care* 2021;11:226-229.