BC Cancer Protocol Summary for Palliative Chemotherapy for Metastatic Colorectal Cancer using Raltitrexed in Patients with Previous Fluorouracil Toxicity

Protocol Code	*GIRALT*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

INDICATIONS:
Raltitrexed has a favorable toxicity profile with equivalent efficacy compared with 5-fluorouracil (5-FU)/ leucovorin in the management of patients with advanced colorectal cancer not eligible for combination chemotherapy. It is recommended as an alternative for patients in the following situations:

- Patients unable to tolerate fluorouracil or capecitabine despite dose reductions as described in their respective protocols. Poor tolerance is defined as Grade 2 or worse gastrointestinal or hematologic toxicity or other serious toxicity, such as cardiac, that requires discontinuation of fluorouracil-based treatment.
- Patients in late relapse (greater than 6 months) after adjuvant treatment where the fluorouracil-based treatment was poorly tolerated.

ELIGIBILITY:

- Metastatic or unresectable colorectal adenocarcinoma
- ECOG 0-2
- Previous toxicity with fluorouracil
- For more than 6 cycles, a “Compassionate Access Program” request must be completed and approval given.
- Should only be used under the supervision of a BC Cancer or CON medical oncologist

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

TESTS:

- Baseline: CBC & diff, platelets; bilirubin, ALT, LDH, alkaline phosphatase; ECG; creatinine, appropriate tumour markers and imaging study
- Prior to each treatment: CBC & diff, platelets; creatinine, bilirubin, ALT, LDH, alkaline phosphatase; calculate creatinine clearance for age greater than 65 years at first cycle and repeat with each cycle if increase in creatinine during treatment

PREMEDICATIONS:

- Antiemetic protocol for low moderate emetogenic chemotherapy (see SCNAUSEA).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
raltitrexed	3 mg/m²	IV in 100 mL NS over 15 minutes

Repeat every 21 days until disease progression, unacceptable toxicity or 6 cycles or as long as there is evidence of a favorable response.

DOSE MODIFICATIONS:

1. **Hematology –** on treatment day

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to 1.49	or	75 to 99	75%
0.5 to 0.9	or	50 to 74	Delay until counts recover, then resume at 75%
less than 0.5	or	less than 50	Delay until counts recover, then resume at 50%

2. **Non-Hematologic Toxicities**

Grade	Stomatitis	Diarrhea	Dose
1	Painless ulcers, erythema or mild soreness	Increase of 2-3 stools/day or mild increase in loose water colostomy output	100%
2	Painful erythema, edema, or ulcers but can eat	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Omit until toxicity resolved then resume at 75%
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Omit until toxicity resolved then resume at 50%
4	As above but mucosal necrosis, and/or requires parenteral support	Increase of 10 or more stools/day or grossly bloody diarrhea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral IV support; dehydration	Discontinue further use.

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

Creatinine Clearance	Dose	Dosing Interval
greater than 65 mL/min	Full	q3w
55-65 mL/min	75%	q4w
25-55 mL/min	% equivalent to creatinine clearance, e.g., if 30 mL/min give 30% of full dose	q4w
less than 25 mL/min	No therapy	N/A

For patients greater than 65 years old, calculate creatinine clearance at the first cycle and repeat with each cycle if increase in serum creatinine during treatment.

Cockcroft/Gault formula:

$$CrCl = \frac{N\ (140\text{-}age) \times weight\ (kg)}{serum\ creatinine\ (micromol/L)}$$

Where N = 1.04 for females, and 1.23 for males

4. **Hepatic dysfunction:** Transient elevation of liver transaminase is noted with raltitrexed. For Grade 2 or 3 hepatic impairment, no dose modification is needed, but the liver enzymes should be monitored carefully. Not recommended in severe hepatic impairment.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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 with NSAIDS and warfarin but no clinical evidence of a significant interaction has been found.
3. **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
4. **Cardiac rhythm or function abnormalities:** tachycardias, atrial fibrillation and congestive heart failure have been reported with raltitrexed.

Call the GI Systemic Therapy physician at your regional cancer centre or Dr. Sanjay Rao at (250) 712-3900 or 1-888-563-7773 with any problems or questions regarding this treatment program.

REFERENCES:

1. Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). Br J Cancer 1998; 77: 15-21.

2. Cunningham D, Zalcberg JR, Rath U, et al. 'Tomudex' (ZD1694): results 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.