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

***Protocol Code**:*	*GIAVRALIR*
***Tumour Group**:*	*Gastrointestinal*
***Contact Physician**:*	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Stage IV colorectal cancer patients with documented intolerance to fluorouracil or capecitabine, or known or suspected DPD deficiency

Patients should have:

- ECOG performance status less than or equal to 2
- Adequate marrow reserve, renal and liver function

EXCLUSIONS:

Patients must not have:

- Clinically significant cardiac arrhythmias requiring drug therapy

CAUTIONS:

- Greater than 3 loose stools per day in patients without colostomy or ileostomy
- Patients with baseline hyperbilirubinemia (greater than 26 micromol/L) not explained by degree of liver metastases

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium
- Baseline if clinically indicated: CEA, CA19-9, GGT, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG

PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see Precautions)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.

TREATMENT:

A Cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
raltitrexed	3 mg/m^2	IV in 100 mL NS over 15 minutes
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 min. (irinotecan is compatible with NS).

- Repeat every 21 days (one cycle) until disease progression or unacceptable toxicity.
- All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with explicit instructions for the management of diarrhea.

DOSAGE MODIFICATIONS

Dose Levels Toxicities

Agent	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2

1. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x 10^9/L)	irinotecan	raltitrexed
▪ If ANC less than 1.5 on Day 1 of cycle, hold irinotecan treatment. Treatment with raltitrexed alone could be continued. If ANC less than 1.0 on Day 1, hold both irinotecan and raltitrexed. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.5 (irinotecan) or 1.0 (raltitrexed) 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 (irinotecan) or 1.0 (raltitrexed) 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 until counts recover and then maintain dose level	Decrease dose to 75%
	3	0.5 to less than 1.0	Delay until Delay until counts recover and then reduce 1 dose level	Delay until Delay until counts recover and then resume at 75%
	4	Less than 0.5	Delay until counts recover and then reduce 2 dose levels	Delay until counts recover and then resume at 50%

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Platelets (x 10^9/L)	irinotecan	raltitrexed
▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 75 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 75 after 2 weeks, discontinue treatment.	1	Greater than or equal to 100	Maintain dose level	Maintain dose level
		75 to less than 100		Decrease dose to 75%
	2	50 to less than 75	Delay until counts recover and then maintain dose level	Delay until counts recover and then resume dose at 75%
	3	25 to less than 50	Delay until counts recover and then resume at dose level -1N	Delay until counts recover and then resume dose at 50%
	4	10 to less than 25	Delay until counts recover and then resume at dose level -1N	Delay until counts recover and then resume dose at 50%
		Less than 10	Delay until counts recover and then resume at dose level -2N	

2. Dose Modifications for NON-HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Diarrhea	irinotecan	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% dose
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Delay until toxicity resolved then reduce 1 dose level	Delay until toxicity resolved then resume at 50% dose
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Delay until toxicity resolved then reduce 2 dose levels	Discontinue further use

Once a dose reduction has been made, all subsequent doses should be given at the reduced dose level.

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Stomatitis**	**irinotecan**	**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	Maintain dose level	Omit until toxicity resolved then resume at 75%
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	Omit until toxicity resolved then resume at 50%
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Maintain dose level	Discontinue further use

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 follows.

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 e.g., If 30 mL/min give 30% of full dose	q4w
Less than 25	Discontinue	N/A

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. **Diarrhea** may be life threatening and requires prompt, aggressive treatment.
   - Early diarrhea or abdominal cramps occurring within the first 24 hours is treated with atropine 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
   - Late diarrhea has an onset of 5 to 11 days post-treatment, a duration of 3 to 7 days and must be treated promptly with loperamide (eg, IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
     - 4 mg stat
     - then 2 mg every 2 hours until diarrhea-free for 12 hours
     - may take 4 mg every 4 hours at night
   - The use of drinks such as Gatorade or Powerade to replace fluid & body salts is recommended.
   - Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.
2. **Other cholinergic symptoms** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Gilbert's Disease** increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Disease using direct/indirect serum bilirubin is recommended.
5. **Hepatic dysfunction**: Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or ALT greater than 3x the upper limit of normal if no liver metastases, or ALT greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17 to 35 micromol/L.
6. **Pulmonary toxicity**: Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely. Supportive care is required.
7. **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.
   Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. Carbamazepine, Phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.
8. **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.
9. **Cardiac rhythm or functional 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 the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Chiara S, Nobile MT, Tomasello L, Acquati M, Taveggia P, Murolo C, Percivale P, Rosso R. Phase II trial of irinotecan and raltitrexed in chemotherapy-naive advanced colorectal cancer. Anticancer Res. 2005 Mar-Apr;25(2B):1391-1396.
2. Feliu J, Salud A, Escudero P, López-Gómez L, Pericay C, Castañón C, de Tejada MR, Rodríguez-García JM, Martínez MP, Martín MS, Sánchez JJ, Barón MG; Oncopaz Cooperative Group and Associated Hospitals. Irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study. Br J Cancer. 2004 Apr 19;90(8):1502-1507.
3. Aparicio J, Vicent JM, Maestu I, Bosch C, Galán A, Busquier I, Llorca C, Garcerá S, Campos JM, López-Tendero P, Balcells M. First-line treatment with irinotecan and raltitrexed in metastatic colorectal cancer. Mature results of a multicenter phase II study. Oncology. 2005;68(1):58-63. Epub 2005 Mar 8.
4. Carnaghi C, Rimassa L, Garassino I, Zucali PA, Masci G, Fallini M, Morenghi E, Santoro A. Irinotecan and raltitrexed: an active combination in advanced colorectal cancer. Ann Oncol. 2002 Sep;13(9):1424-1429.
5. Feliu J, Castanon C, Salud A, Mel JR, Escudero P, Pelegrin A, Lopez-Gomez L, Ruiz M, Gonvalez E, Juarez F, Lizon J, Castro J, Gonvalez-Baron M, Oncopaz Cooperative Group Spain. Phase ll randomized trial of raltitrexed-oxaliplatin vs. raltitrexed-irinotecan as first-line treatment in advanced colorectal cancer. Br J Cancer 2005 Nov, 93(11): 1230-1235.
6. Liu Y, Teng Z, Qu Z, Zhang YQ, Zheng Z, Wen F et al. The efficacy and safety of irinotecan plus raltitrexed as second-line treatment in advanced colorectal cancer (ACC) patients: An interim analysis of a multicenter, phase II trial. J Clin Oncol 2019 May, 37(15) supplement.
7. Ulrich-Pur H, Raderer M, Verena Kornek G, Schüll B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W. Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer. 2003 Apr 22;88(8):1180-1184.