BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer using Irinotecan and Capecitabine in Patients Unsuitable for GIFOLFIRI

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

ELIGIBILITY:

- First line treatment for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation
- Consideration of first line oxaliplatin-based therapy (GICAPOX) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities
- Patients who have received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy.
- Patients who have progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired.
- ECOG performance status less than or equal to 2

EXCLUSIONS:

- Severe renal impairment (Creatinine Clearance less than 30 mL/min – calculated using a weight-based formula (eg: Cockcroft-Gault) or formally measured by renogram or 24 h urine collection. Non-weight based calculations of creatinine clearance (such as that provided by provincial laboratory based on serum creatinine alone) are not considered sufficiently accurate to determine renal insufficiency for this protocol
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)

CAUTIONS:

- Adequate marrow reserve, renal and liver function
- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Patients with baseline greater than 3 loose BM 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 AND MONITORING:

- Baseline CBC and differential, creatinine, bilirubin, ALT, alkaline phosphatase, appropriate imaging study. Optional : CEA, CA 19-9.
- CBC, creatinine, bilirubin, ALT, alkaline phosphatase prior to each cycle.
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.
- Consider weekly evaluations by phone or clinic visit for first 2 cycles (6 weeks) to assess for toxicity.
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.
- If clinically indicated : CEA, CA 19-9

Activated: 1 Apr 2004 Revised: 1 Oct 2021 (ST chair and contact, Eligibility, tests and monitoring updated. Moved cautions from Eligibility to separate heading "Cautions".)

PREMEDICATIONS:

- Antiemetic protocol for high-moderate emetogenic chemotherapy with irinotecan, may not need any anti-emetic with capecitabine (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
irinotecan	200 mg/m^2	IV in 500 mL of D5W over 1 hour 30 min
capecitabine*	800 mg/m^2 BID	PO x 14 days

*Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 21 days for a maximum of 16 cycles.

All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for the management of diarrhea.

DOSAGE MODIFICATIONS

Dose Levels for Toxicities

	Dose Level +1	Dose Level 0 (Starting Dose)	Dose Level -1	Dose Level -2
irinotecan	250 mg/m^2	200 mg/m^2	150 mg/m^2	Discontinue Therapy
capecitabine	1000 mg/m^2	800 mg/m^2	500 mg/m^2	Discontinue Therapy

Patients who go through Cycle 1 at the Starting Dose without significant toxicity can be treated at Dose Level +1 on subsequent cycles.

A. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**irinotecan**	**capecitabine**
▪ 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	Maintain dose level	Maintain dose level
	3	0.5 to less than1.0	↓ 1 dose level	↓ 1 dose level
	4	less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia and greater than or equal to Grade 2 fever		↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Platelets (x10^9/L)**	**irinotecan**	**capecitabine**
▪ 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 75	Maintain dose level	Maintain dose level
	2	50 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 1 dose level	↓ 1 dose level
	4	less than 10	↓ 2 dose levels	↓ 2 dose levels

B. Dose Modifications for NON-HEMATOLOGIC Toxicity

If Grade 2, 3 or 4 toxicities occur, daily administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to Grade 1.

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Diarrhea**	**irinotecan**	**capecitabine**
▪ 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 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	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Stomatitis**	**irinotecan**	**capecitabine**
▪ 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 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	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Maintain dose level	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)	irinotecan	capecitabine
▪ If hand-foot skin reaction greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If hand-foot skin reaction less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If hand-foot skin reaction remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	Maintain dose level	Maintain dose level
	2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	Maintain dose level	Maintain dose level
	3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Maintain dose level	↓ 1 dose level

Renal dysfunction:

Creatinine Clearance mL/min	Capecitabine Dose only
greater than 50	100%
30 to 50	75%
less than 30	Discontinue Therapy

Cockcroft-Gault Equation:

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

(mL/min)

N = 1.23 male
N = 1.04 female

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 – 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.
   - **Late diarrhea** has an onset of 5 - 11 days post-treatment, a duration of 3-7 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 (0.25 mg – 0.5 mg) 0.3 mg – 0.6 mg IV or SC. This dose may be repeated at the physician's discretion. Blood pressure and heart rate should be monitored. 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 syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome 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 17-35 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. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.
8. **Potential Drug Interactions:** 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.
9. **Possible drug interaction with capecitabine and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during capecitabine therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of capecitabine, repeat INR weekly for one month.
10. **Possible drug interaction with capecitabine and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Capecitabine may increase the serum concentration of these two agents.
11. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
12. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or

capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

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[1-6]:

1. Patt YZ, Lin E, Liebman J, et al. Capecitabine plus irinotecan: A highly active first-line treatment for metastatic colorectal cancer. Proc Am Soc Clin Oncol 2003;22:281a (abstract 1130).
2. Kerr DJ, Ten Bokkel Huinink WW, Ferry DR, et al. A phase I/II study of CPT-11 in combination with capecitabine as first line chemotherapy for metastatic colorectal cancer. Proc Am Soc Clin Oncol 2002;21:100a (abstract 643).
3. Delord P, Pierga JY, Dieras V, et al. Dose escalation and pharmacokinetic study of capecitabine (Xeloda) and irinotecan (CPT-11) in gastro-intestinal tumors: preliminary results. Proc Am Soc Clin Oncol 2002;21:100a (abstract 397).
4. Bajetta E, Di Bartolomeo M, Mariani L, et al. Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. Cancer 2004;100(2):279-87.
5. Wasserman E, Myara A, Lokiec F, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8(10):1049-51.
6. Mathijssen RHJ, Verweij J, de Bruijn P, et al. Effects of St. John's Wort on irinotecan metabolism. J Natl Cancer Inst 2002;94(16):1247-9.