BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin

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

ELIGIBILITY:

- First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and for adenocarcinoma of the appendix and small bowel.
- Consideration of first line oxaliplatin-based therapy (GIFOLFOX) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities
- Second line therapy if oxaliplatin-based combination used first line for locally advanced, recurrent or metastatic colorectal adenocarcinoma
- ECOG performance status less than or equal to 2
- 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.
- Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L)
- Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 35 micromol/L; ALT/ Alkaline Phosphatase less than or equal to 5 x ULN)
- Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)

EXCLUSIONS:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)

TESTS AND MONITORING:

- Baseline: CBC and differential, Platelets, Creatinine, LFTs (Bilirubin, ALT, Alkaline Phosphatase) appropriate imaging study. Optional: CEA, CA 19-9
- **Prior to each cycle**: CBC and differential, Platelets
- **Each time seen by physician**: LFT's (Bilirubin, ALT, Alkaline Phosphatase), Creatinine
- If clinically indicated: CEA, CA 19-9
- For patients on warfarin, weekly INR during fluorouracil therapy 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.

PREMEDICATIONS:

- Antiemetic protocol for high-moderate 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
irinotecan*	180 mg/m^2	IV in 500 mL of D5W over 1 hour 30 min
leucovorin*	400 mg/m^2	IV in 250 ml D5W over 1 hour 30 min
fluorouracil	400 mg/m^2	IV push, after leucovorin, THEN
fluorouracil	2400 mg/m^2	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR **

Repeat every 14 days until progression. Discontinue if no response after 2 cycles.

Irinotecan and leucovorin may be infused at the same time by using a y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag. Leucovorin dose remains at 400 mg/m^2 IV over 1 hour and 30 minutes when concurrent irinotecan is omitted.

****** *A*lternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside** dose banding range are **prepared as ordered**)**:**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m^2/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

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

Agent	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2	Dose Level –3
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	Discontinue Therapy
leucovorin*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue Therapy
fluorouracil IV push	400 mg/m^2	320 mg/m^2	240 mg/m^2	Discontinue Therapy
fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue Therapy

If IV push fluorouracil is delayed/omitted, leucovorin may also be delayed/omitted or reduced to 20 mg/m^2 IV push.

A. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**irinotecan**	**fluorouracil**
▪ 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 than 1.0	↓ 1 dose level	↓ 1 dose level
	4	less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia & 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	fluorouracil
▪ 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

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Diarrhea	irinotecan	fluorouracil
▪ 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 to 3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7 to 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**	**fluorouracil**
▪ 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	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

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 to 1.2 mg IV or SC. 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 to 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 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. **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. **Stomatitis**: Sucking ice chips may be considered for patients experiencing stomatitis. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches, which subside quickly.
9. **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.
10. **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.
11. **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.
12. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil 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 fluorouracil, repeat INR weekly for one month.
13. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References[1-6]:

1. Tournigand C, Louvet C, Quinaux E, et al. FOLFIRI followed by FOLFOX versus FOLFOX followed by FOLFIRI in metastatic colorectal cancer (MCRC): Final results of a phase III study. Proc Am Soc Clin Oncol 2001;20:abstract 494.
2. Tournigand C, Lovet C, Andre T, et al. Results of a Strategic Phase III study in Metastatic Colorectal Cancer: FOLFIRI then FOLFOX or Inverse Sequence? Proc Int Cong Anti-Cancer Treat 2002:137.
3. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355(9209):1041-7.
4. 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.
5. 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.
6. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22(2):229-37.