

# BCCA Protocol Summary for First Line 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
- Consideration of first line oxaliplatin-based therapy (UGIFOLFOX) 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
- Adequate marrow reserve (ANC greater than or equal to  $1.5 \times 10^9/L$ , platelets greater than  $100 \times 10^9/L$ )
- Adequate renal (Creatinine less than or equal to  $1.5 \times ULN$ ) and liver function (bilirubin less than or equal to  $35 \text{ micromol/L}$ ; AST/ Alkaline Phosphatase less than or equal to  $5 \times ULN$ )
- "Class II Drug Registration" form must be completed at the start of the first 24 cycles. For further cycles, a BCCA "Compassionate Access Program" or "Undesignated Indication" request with appropriate clinical information for each patient must be approved prior to treatment.
- 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)

## TESTS AND MONITORING:

- Baseline CBC and differential, Platelets, Creatinine, LFTs (Bilirubin, AST, Alkaline Phosphatase) appropriate imaging study and tumour markers.
- **Prior to each cycle:** CBC and differential, Platelets
- **Each time seen by physician:** LFT's (Bilirubin, AST, Alkaline Phosphatase), Creatinine
- 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.

## 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                   | BCCA Administration Guidelines                                                                                   |
|--------------|------------------------|------------------------------------------------------------------------------------------------------------------|
| Irinotecan*  | 180 mg/m <sup>2</sup>  | IV in 500 mL of D5W over 1 hour 30 min                                                                           |
| Leucovorin*  | 400 mg/m <sup>2</sup>  | IV in 250 ml D5W over 1 hour 30 min                                                                              |
| Fluorouracil | 400 mg/m <sup>2</sup>  | IV bolus, after leucovorin, THEN                                                                                 |
| Fluorouracil | 2400 mg/m <sup>2</sup> | IV over 46 h in D5W to a total volume of 92 mL by continuous infusion at 2 mL/h via appropriate infusor device** |

Repeat every 14 days for a maximum of 24 cycles. If there is continued evidence of response or stable disease by imaging or tumour markers, apply for additional cycles via the BCCA Compassionate Access Program. Discontinue if no response after 2 cycles.

Infusional Fluorouracil dose may be escalated to 3000 mg/m<sup>2</sup> at Cycle 3 if the patient has experienced less than or equal to Grade 2 toxicity.

***\*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.***

***\*\*for total dose greater than 4400 mg, to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 infusor.***

*(Inpatients: 1200 mg/m<sup>2</sup>/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 +1          | Dose Level 0 (Starting Dose) | Dose Level -1          | Dose Level -2          | Dose Level -3       |
|-----------------------|------------------------|------------------------------|------------------------|------------------------|---------------------|
| Irinotecan            | 180 mg/m <sup>2</sup>  | 180 mg/m <sup>2</sup>        | 150 mg/m <sup>2</sup>  | 120 mg/m <sup>2</sup>  | Discontinue Therapy |
| Leucovorin*           | 400 mg/m <sup>2</sup>  | 400 mg/m <sup>2</sup>        | 400 mg/m <sup>2</sup>  | 400 mg/m <sup>2</sup>  | Discontinue Therapy |
| FLUOROURACIL BOLUS    | 400 mg/m <sup>2</sup>  | 400 mg/m <sup>2</sup>        | 320 mg/m <sup>2</sup>  | 240 mg/m <sup>2</sup>  | Discontinue Therapy |
| FLUOROURACIL INFUSION | 3000 mg/m <sup>2</sup> | 2400 mg/m <sup>2</sup>       | 2000 mg/m <sup>2</sup> | 1600 mg/m <sup>2</sup> | Discontinue Therapy |

***\*If bolus Fluorouracil is delayed/omitted, Leucovorin may also be delayed/omitted or reduced to 20 mg/m<sup>2</sup> IV push.***

**A. Dose Modifications for HEMATOLOGIC Toxicity**

| Prior to a Cycle<br>(Day 1)                                                                                                                                                                                                                                                                                                                                                                                         | Toxicity                                                                |                              | Dose Level For<br>Subsequent Cycles |                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------|-------------------------------------|---------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                     | Grade                                                                   | ANC (x10 <sup>9</sup> /L)    | Irinotecan                          | Fluorouracil        |
| <ul style="list-style-type: none"> <li>▪ If ANC less than 1.5 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.</li> <li>▪ If ANC is greater than or equal to 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest ANC</b> result of the delayed week(s).</li> <li>▪ If ANC remains less than 1.5 after 2 weeks, discontinue treatment.</li> </ul> | 1                                                                       | greater than or equal to 1.5 | Maintain dose level                 | Maintain dose level |
|                                                                                                                                                                                                                                                                                                                                                                                                                     | 2                                                                       | 1 – 1.49                     | Maintain dose level                 | Maintain dose level |
|                                                                                                                                                                                                                                                                                                                                                                                                                     | 3                                                                       | 0.5 – 0.99                   | ↓ 1 dose level                      | ↓ 1 dose level      |
|                                                                                                                                                                                                                                                                                                                                                                                                                     | 4                                                                       | less than 0.5                | ↓ 2 dose levels                     | ↓ 2 dose levels     |
|                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>Grade 4 neutropenia &amp; greater than or equal to Grade 2 fever</b> |                              | ↓ 2 dose levels                     | ↓ 2 dose levels     |

| Prior to a Cycle<br>(Day 1)                                                                                                                                                                                                                                                                                                                                                                                                          | Toxicity |                                 | Dose Level For<br>Subsequent Cycles |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------|-------------------------------------|---------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                      | Grade    | Platelets (x10 <sup>9</sup> /L) | Irinotecan                          | Fluorouracil        |
| <ul style="list-style-type: none"> <li>▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.</li> <li>▪ If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest platelets</b> result of the delayed week(s).</li> <li>▪ If platelets remain less than 75 after 2 weeks, discontinue treatment.</li> </ul> | 1        | greater than or equal to 75     | Maintain dose level                 | Maintain dose level |
|                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2        | 50 – 74.9                       | Maintain dose level                 | Maintain dose level |
|                                                                                                                                                                                                                                                                                                                                                                                                                                      | 3        | 10 – 49.9                       | ↓ 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        |
| <ul style="list-style-type: none"> <li>▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> <li>▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul> | 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                       | Fluorouracil        |
| <ul style="list-style-type: none"> <li>▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> <li>▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul> | 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:

- 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.
- 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 – 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.
- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
- Hepatic dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or AST greater than 3x the upper limit of normal if no liver metastases, or AST 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.
- Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely. Supportive care is required.
- 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.
- 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.
- 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. **Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).

**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.**

Date activated: 01 Dec 2002

Date revised: 1 June 2011 (Infusion section revised)

**References<sup>1-6</sup>:**

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.