

BCCA Protocol Summary for Second Line Palliative Combination Chemotherapy for Metastatic Gastric or Esophageal Adenocarcinoma Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)

Protocol Code	<i>GIGFOLFIRI</i>
Tumour Group	<i>Gastrointestinal</i>
Contact Physician	<i>GI Systemic Therapy</i>

ELIGIBILITY:

- Second line therapy for locally advanced, locally recurrent or metastatic gastric or esophageal adenocarcinoma, not curable with surgery or radiation
- 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 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 12 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, Creatinine, LFTs (Bilirubin, AST, Alkaline Phosphatase) appropriate imaging study and tumor markers.
- CBC, Creatinine, LFTs (Bilirubin, AST, 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.

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 ²	IV in 500 mL of D5W over 1 hour 30 min
Folinic Acid (Leucovorin)*	400 mg/m ²	IV in 250 ml D5W over 1 hour 30 min
Fluorouracil	400 mg/m ²	IV bolus, after Folinic Acid, THEN
Fluorouracil	2400 mg/m ²	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 12 cycles.

Infusional Fluorouracil dose may be escalated to 3000 mg/m² 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/m²/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 ²	180 mg/m ²	150 mg/m ²	120 mg/m ²	Discontinue Therapy
Folinic Acid* (Leucovorin)	400 mg/m ²	400 mg/m ²	400 mg/m ²	400 mg/m ²	Discontinue Therapy
FLUOROURACIL BOLUS	400 mg/m ²	400 mg/m ²	320 mg/m ²	240 mg/m ²	Discontinue Therapy
FLUOROURACIL INFUSION	3000 mg/m ²	2400 mg/m ²	2000 mg/m ²	1600 mg/m ²	Discontinue Therapy

****Folinic Acid (Leucovorin) dose does not require dose adjustment; Folinic Acid (leucovorin) is delayed or omitted if bolus 5FU is delayed or omitted***

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
<ul style="list-style-type: none"> ▪ 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 – 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
	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
<ul style="list-style-type: none"> ▪ 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 – 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"> ▪ 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	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"> ▪ 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:

- 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: 1 Sep 2008

Date revised: 01 June 2011 (Infusion section revised)

References:

1. Sym SJ, Ryu MH, Lee JL, et al. Salvage chemotherapy with biweekly irinotecan, plus 5-fluorouracil and leucovorin in patients with advanced gastric cancer previously treated with fluoropyrimidine, platinum, and taxane. *Am J Clin Oncol*. 2008 Apr;31(2):151-6.
2. Kim ST, Kang WK, Kang JH, et al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. *Br J Cancer*. 2005 May 23;92(10):1850-4.
3. N. Fazio, G. Zampino, F. Nolè, et al. Irinotecan combined with infusional 5-fluorouracil and folinic acid (folfiri) in patients with metastatic gastric cancer resistant to cisplatin-containing chemotherapy. *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 4146.