

BCCA Protocol Summary for Adjuvant Combination Chemotherapy for Stage III Rectal Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin

Protocol Code: *GIRAJFFOX*

Tumour Group: *Gastrointestinal*

Contact Physician: *GI Systemic Therapy*

ELIGIBILITY:

- Resected Stage III (Node positive) rectal cancer
- ECOG performance status 0, 1 or 2
- Adequate marrow reserve (ANC greater than or equal to $1.2 \times 10^9/L$, platelets greater than $100 \times 10^9/L$)
- Adequate renal (Creatinine less than or equal to $1.5 \times \text{ULN}$) and liver function (bilirubin less than or equal to 26 micromol/L; AST/ Alkaline Phosphatase less than or equal to $5 \times \text{ULN}$)
- [A BCCA "Class II Drug Registration Form" form must be submitted](#)
- Caution in patients with significant co-morbidities (see Precautions)
- Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Caution in patients with symptomatic peripheral neuropathy
- NOTE: This protocol may be used following prior pelvic radiation (either radiation alone or in combination with Capecitabine (GIRCRT) or fluorouracil.

TESTS:

- Baseline: CBC and differential, Creatinine, Bilirubin, AST, Alkaline Phosphatase, tumour markers, appropriate imaging studies.
- Prior to each cycle: CBC, Creatinine, Bilirubin, AST, Alkaline Phosphatase
- At least every 2 cycles: physician review to evaluate for peripheral neuropathy and other toxicity.
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:

- Antiemetic protocol for high-moderate emetogenic chemotherapy. See [SCNAUSEA](#) protocol.
- Counsel patients to avoid cold drinks and exposure to cold air, especially on day of oxaliplatin.
- **Cryotherapy (ice chips) should NOT be used as may exacerbate Oxaliplatin-induced pharyngo-laryngeal dysesthesias.**
- **OPTIONAL:** Calcium Gluconate 1000 mg and Magnesium Sulfate 1000 mg given together in 250 ml D5W IV over 20 minutes Pre and Post Oxaliplatin to reduce neurotoxicity (See note and precautions below under Dose Modifications for Neurologic Toxicity)

TREATMENT:

A cycle equals

Drug	Dose	BCCA Administration Guidelines
Oxaliplatin*	85 mg/m ²	IV in 500 mL** of D5W over 2 hours
Leucovorin*	400 mg/m ²	IV in 250 ml D5W over 2 hours
Fluorouracil (5-FU)	400 mg/m ²	IV bolus, after Leucovorin, THEN
Fluorouracil (5-FU)	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***

****Oxaliplatin and Leucovorin may be infused over the same two hour period by using a Y-site connector placed immediately before the injection site. Oxaliplatin and Leucovorin should not be combined in the same infusion bag. Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.***

*****for oxaliplatin dose less than or equal to 104 mg, use 250 mL D5W***

******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.

Repeat every 14 days for the number of cycles specified:

1. For patients with prior pelvic radiotherapy without concomitant Capecitabine or fluorouracil:
Give 12 cycles; consider beginning at dose level -1 to assess for toxicity, increasing to dose level 0 from cycle 3 if tolerated
2. For patients with prior or planned pelvic radiotherapy with concomitant Capecitabine (GIRCRT) or fluorouracil:
Give 8 cycles; if prior pelvic radiotherapy, consider beginning at dose level -1 to assess for toxicity, increasing to dose level 0 from cycle 3 if tolerated.

DOSAGE MODIFICATIONS (A, B & C)

- A. Dose Modifications for NEUROLOGIC Toxicity
- B. Dose Modifications for HEMATOLOGIC Toxicity
- C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Table 1 - Dose Reduction Levels for All Toxicity

Agent	Dose Level +1	Starting Dose	Dose Level -1	Dose Level -2*
Oxaliplatin	85 mg/m ²	85 mg/m ²	65 mg/m ²	50 mg/m ²
Fluorouracil Bolus	400 mg/m ²	400 mg/m ²	320 mg/m ²	200 mg/m ²
Fluorouracil Infusion	3000mg/m ² **	2400 mg/m ²	1900 mg/m ²	1500 mg/m ²

Leucovorin dose remains fixed at 400 mg/m². Leucovorin is delayed or omitted if bolus fluorouracil is delayed or omitted

*** For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.**

**** Infusional Fluorouracil dose may be escalated to 3000 mg/m² at Cycle 3 if the patient has experienced Grade 2 toxicity or less.**

Table 2 - Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with Oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

There is evidence that infusions of Calcium gluconate and Magnesium sulphate prior to and following Oxaliplatin may reduce the incidence and severity of Oxaliplatin-induced peripheral neuropathy. Concerns about the Ca/Mg infusion reducing the efficacy of FOLFOX chemotherapy raised previously by an unscheduled interim analysis of the CONcept trial have been refuted.⁵⁻⁷ Physicians are encouraged to consider this therapy, especially in patients in whom peripheral neuropathy develops on treatment. CAUTION: Calcium and Magnesium therapy is NOT recommended in those patients with known hypercalcemia or those receiving therapy with Digitalis or Thiazide diuretics (See Premedications above for administration directions).

A. Dose Modifications for NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 – 7 days	greater than 7 days	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	1 st time: ↓ 1 dose level 2 nd time: ↓ 1 dose level	1 st time: ↓ 1 dose level 2 nd time: ↓ 1 dose level	Discontinue*
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Maintain dose level	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x10 ⁹ /L)	Oxaliplatin	Fluorouracil
<ul style="list-style-type: none"> If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 4 times. If ANC is greater than or equal to 1.2 within 4 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 1.2 after 4 weeks, discontinue treatment. 	1	greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1 – 1.19	Maintain dose level	Maintain dose level
	3	0.5 – 0.99	↓ 1 dose level	Maintain dose level
	4	less than 0.5	↓ 1 dose level	omit bolus and ↓ 1 infusion dose level
	Grade	Platelets (x10 ⁹ /L)	Oxaliplatin	Fluorouracil
<ul style="list-style-type: none"> If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 4 times. If platelets greater than or equal to 75 within 4 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 4 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	Maintain dose level
	4	less than 10	↓ 2 dose levels	Maintain dose level

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Diarrhea	
<ul style="list-style-type: none"> ▪ If diarrhea greater than or equal to Grade 1 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. ▪ If diarrhea is less than Grade 1 within 4 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 4 weeks, discontinue treatment. 	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of bolus and infusional fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level of oxaliplatin, bolus and infusional fluorouracil
	Grade	Stomatitis	
<ul style="list-style-type: none"> ▪ If stomatitis greater than or equal to Grade 2 on Day 1 of 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
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level of bolus and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of both oxaliplatin, bolus and infusional fluorouracil

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see below)
For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication:

45 minutes prior to Oxaliplatin:

- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes

30 minutes prior to Oxaliplatin:

- Diphenhydramine 50 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed in bag).

2. **Laryngo-pharyngeal dysesthesia** is an unusual dysesthesia characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table.)

Clinical Symptoms	Laryngo-pharyngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O ₂ saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **Prior Pelvic Radiotherapy:** As pelvic radiotherapy may lessen bone marrow reserve, consideration should be given to a level 1 dose reduction on the initial 1-2 cycles post radiation, to assess for tolerance. Thereafter, as tolerated, the dose may be increased to dose level 0.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Myocardial** ischemia and angina occurs rarely in patients receiving Fluorouracil. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.
6. **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.

7. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
8. **Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BCCA Extravasation Guidelines.
9. **Venous Occlusive Disease** is a rare but serious complications that has been reported in patients (0.02%) receiving Oxaliplatin in combination with Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
10. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, Oxaliplatin should be permanently discontinued.
11. **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 February 2008

Date revised: 1 Jan 2012 (CAP approval replaced by Class II form in Eligibility)

References:

1. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. *N Engl J Med* 350:2343-2351, 2004.
2. Grothey A, Hart L, Rowland K, et al. Intermittent oxaliplatin administration improved time-to-treatment failure in metastatic colorectal cancer: Final results of the phase III CONcePT trial. *Proc Am Soc Clin Oncol* 2008; 26: Abstract 4010