BC Cancer Protocol Summary for Adjuvant Combination Chemotherapy for Stage III and Stage IIB Colon Cancer using Oxaliplatin, Fluorouracil, and Leucovorin

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

ELIGIBILITY:

- Stage III colon cancer
- Stage IIB colon cancer (T4N0)
- 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.

EXCLUSIONS:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid oxaliplatin in patients with congenital long QT syndrome.

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 symptomatic peripheral neuropathy

TESTS AND MONITORING:

- Baseline: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, sodium, potassium, magnesium, calcium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), appropriate imaging study and optional CEA.
- Prior to each cycle: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, sodium, potassium, magnesium, calcium.
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.
- At least every 2 or 3 cycles: physician review to evaluate for peripheral neuropathy and other toxicity.

PREMEDICATIONS:

- Antiemetic protocol for high-moderate emetogenic chemotherapy. (See SCNAUSEA)
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

TREATMENT:

Drug	Dose	BC Cancer Administration Guidelines
oxaliplatin*	85 mg/m^2	IV in 250 to 500 mL of D5W over 2 hours
leucovorin*	400 mg/m^2	IV in 250 ml D5W over 2 hours
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 x 12 cycles for high-risk stage III colon cancer – (any T4 and/or N2).
Repeat every 14 days for 6 cycles for low-risk stage III colon cancer (T1-3/N1).
For low-risk disease, adjuvant treatment with mFOLFOX6 for 3 months is a recommended option due to the significantly lower risk of neurotoxicity. Treatment to a maximum of 6 months or 12 cycles may be considered if the treating oncologist feels the benefits outweigh the risks.

If necessary the schedule may be modified +/- 3 days.

**** 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. Leucovorin dose remains at 400 mg/m^2 IV over 2 hours when concurrent oxaliplatin 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.

DOSE MODIFICATIONS (A, B & C):

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

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	Starting Dose	Dose Level –1	Dose Level -2*
oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
Fluorouracil IV push	400 mg/m^2	320 mg/m^2	200 mg/m^2
fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2

Leucovorin dose remains fixed at 400 mg/m^2. Leucovorin is delayed or omitted if IV push fluorouracil is delayed or omitted

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

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

A. Dose Modifications for Oxaliplatin 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	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	Discontinue*
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Maintain dose level	N/A	N/A

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**
▪ If ANC less than 1.2 on Day 1of 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	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	Maintain dose level
	4	less than 0.5	↓ 1 dose level	omit IV push and ↓ 1 infusion dose level
	Grade	**Platelets (x10^9/L)**	**oxaliplatin**	**fluorouracil**
▪ 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 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 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**	
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. ▪ If diarrhea is less than Grade 2 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 IV push 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, IV push and infusional fluorouracil
	Grade	**Stomatitis**	
▪ 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 IV push and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of oxaliplatin, IV push 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 in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

2. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. 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	**Pharyngo-laryngeal 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. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
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 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.
6. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
7. **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.
8. 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.
9. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
10. **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.
11. 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.
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. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

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.
3. Hochster HS, Grothey A, Shpilsky A, et al. Effect of intravenous calcium and magnesium versus placebo on response to FOLFOX+bevacizumab in the CONcePT trial. 2008 Gastrointestinal Cancers Symposium, Abstract 280
4. Nikcevich DA, Grothey A, Sloan JA, et al. Intravenous calcium and magnesium prevents oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: Results of a phase III placebo-controlled, double-blind trial (N04C7). Proc Am Soc Clin Oncol 2008; 26: Abstract 4009.
5. 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