

BCCA Protocol Summary for Adjuvant Combination Chemotherapy for Stage III and Stage IIB Colon Cancer Using Oxaliplatin and Capecitabine

Protocol Code: UGIAJCAPOX

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
- Adequate marrow reserve
- Adequate renal and liver function
- A BCCA “Compassionate Access Program” 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

EXCLUSIONS:

- Severe renal impairment (Creatinine Clearance less than 30 mL/min)
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Severe pre-existing peripheral neuropathy

TESTS AND MONITORING:

- Baseline CBC and differential, creatinine, LFTs (bilirubin, AST, alkaline phosphatase) appropriate imaging study and tumour 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.

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.**
- **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	130 mg/m ²	IV in 500 mL* of D5W over 2 hours
Capecitabine	1000 mg/m ² BID	PO x 14 days

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

Repeat every 21 days for a maximum of 8 cycles.

Capecitabine Dose Calculation Table

Single Dose (mg)	Number of tablets per dose	
	150 mg	500 mg
1500	0	3
1650	1	3
1800	2	3
2000	0	4
2150	1	4
2300	2	4

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

DOSAGE MODIFICATIONS (Sections A, B & C)

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

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).

Table 1 - Dose Levels for NEUROLOGIC Toxicity (Section A)

Agent	Dose Level 0 (Starting Dose)	Neurotoxicity Dose Level -1N	Neurotoxicity Dose Level -2N	Neurotoxicity Dose Level -3N
Oxaliplatin	130 mg/m ²	100 mg/m ²	65 mg/m ²	Discontinue Therapy

**If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (ie if hematologic toxicity mandates dose -2 reduction (85 mg/m²) and neurologic toxicity mandates dose -2N reduction (65 mg/m²), then 65 mg/m² is given.*

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 one neurotoxicity dose level
Grade 3	↓1 neurotoxicity dose level	↓1 neurotoxicity dose level	Discontinue therapy
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Increase duration of infusion to 6 hours	N/A	N/A

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	

Table 2 Dose Levels for NON-NEUROLOGIC TOXICITY (Sections B & C)

Agent	Dose Level 0 (Starting dose)	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	130 mg/m ²	100 mg/m ²	85 mg/m ²	Discontinue Therapy
Capecitabine	1000 mg/m ² bid	750 mg/m ² bid	500 mg/m ² bid	Discontinue Therapy

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x10 ⁹ /L)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> ▪ If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.2 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 1.2 after 2 weeks, discontinue treatment. 	1	greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1.0 – 1.19	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	Platelets (x10 ⁹ /L)	Oxaliplatin	Capecitabine
<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 10.0	↓ 2 dose levels	↓ 2 dose levels

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

If Grade 2, 3 or 4 toxicities occur, daily administration of Capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade 1.

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Diarrhea	Oxaliplatin	Capecitabine
<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	Maintain 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	↓ 1 dose level	Discontinue Therapy
	Grade	Stomatitis		
<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	↓ 1 dose level	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)	Oxaliplatin	Capecitabine
<ul style="list-style-type: none"> ▪ If hand-foot skin reaction is greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If hand-foot skin reaction is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. ▪ If hand-foot skin reaction remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment. 	1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	Maintain dose level	Maintain dose level
	2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	Maintain dose level	Maintain dose level
	3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Maintain dose level	↓ 1 dose level

Renal dysfunction:

Creatinine Clearance mL/min	Capecitabine Dose only
greater than 50	100%
30 - 50	75%
less than 30	Discontinue Therapy

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance:} = \frac{N (140 - \text{age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L)}} \text{ (mL/min)}$$

N = 1.23 male
N = 1.04 female

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 table 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 pre-medication:

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)

- 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 1/3 the 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

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- 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.
- Possible drug interactions with Capecitabine 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 capecitabine therapy and for 1 month after stopping capecitabine).
- Myocardial** ischemia and angina occurs rarely in patients receiving Capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.
- 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.
- Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BCCA Extravasation Guidelines.
- 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.
- 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.

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 Oct 2011

Date revised:

References:

1. Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350(23):2343-51.
2. Haller D, Taberero J, Maroun J, et al. First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study) (abstract). Data presented at the joint ECCO/ESMO Multidisciplinary Congress, Berlin, Germany, September 2009.
3. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol.* 2007;25(16):2198-204.