

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.
- Adequate marrow reserve (ANC greater than or equal to $1.2 \times 10^9/L$, platelets greater than or equal to $100 \times 10^9/L$)
- Adequate renal (Creatinine less than or equal to $1.5 \times ULN$) and liver function (bilirubin less than or equal to 26 micromol/L; ALT and Alkaline Phosphatase less than or equal to $5 \times ULN$)
- 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)
- Caution in patients with symptomatic peripheral neuropathy

EXCLUSIONS:

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

TESTS AND MONITORING:

- Baseline: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, sodium, potassium, magnesium, calcium, 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/m² IV over 2 hours when concurrent oxaliplatin is omitted.**

** Alternative 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/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.

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 | 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/m². 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 | 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 | 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 |
| <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 | 1.0 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 |
| <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 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 | |
| <ul style="list-style-type: none"> 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 | |
| <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 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:

- 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 minutes30 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 SCORX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.
- 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. Janine Davies at (604) 877-6000 or 1-800-663-3333 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