# BC Cancer Protocol Summary For Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using DOCEtaxel, Oxaliplatin, Infusional Fluorouracil, and Leucovorin

***Protocol Code*** ***GIGFLODOC***

***Tumour Group*** ***Gastrointestinal***

***Contact Physician*** ***GI Systemic Therapy***

**ELIGIBILITY:**

- Histologically proven and as yet unresected adenocarcinoma of the stomach, gastro-esophageal junction, or lower 1/3 of the esophagus, Stage 1B (T1N1 or T2N0) or greater
- Clinical staging supporting operability of the primary with no distant metastases
- ECOG performance status 0-1, Karnofsky performance status greater than or equal to 70%
- No previous chemotherapy
- Adequate hepatic, renal, marrow and cardiac function
- Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or 4) other serious medical illness.
- Caution in patients with symptomatic peripheral neuropathy

**EXCLUSIONS:**

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid oxaliplatin in patients with congenital long QT syndrome.
- Grade 2-4 peripheral neuropathy

**TESTS:**

- Baseline and prior to each cycle: CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium. Optional: CEA, CA 19-9
- 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.

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**PREMEDICATIONS:**

- Antiemetic protocol for high-moderate emetogenic chemotherapy (see SCNAUSEA)
- Dexamethasone 8 mg PO bid for 3 days, starting one day prior to each DOCEtaxel administration. Patient must receive minimum of 3 doses pre-treatment.
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration. (Frozen gloves recommendation with DOCEtaxel use has been removed because of the use of oxaliplatin.)**
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

**TREATMENT:**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| DOCEtaxel | 50 mg/m² | IV in 100 to 250 mL NS over 1 hour<br>(see Precaution #2)<br>Use non-DEHP equipment |
| oxaliplatin** | 85 mg/m$^2$ | IV in 250 to 500 mL of D5W over 2 hours |
| leucovorin** | 200 mg/m$^2$ | IV in 250 mL D5W over 2 hour |
| fluorouracil | 2600 mg/m$^2$ | IV over 24 h in D5W to a total volume of 240 mL by continuous infusion at 10 mL/h via appropriate infusor device*** |
| filgrastim (G-CSF)‡ | 5 mcg/kg/day (300 mcg or 450 mcg) every other day starting Day 5 for 5 doses | -- |

‡ Consider Pharmacare approval for filgrastim (G-CSF) as the treatment is with curative intent. Eliminate or adjust filgrastim doses as needed depending upon next neutrophil count. Reduce filgrastim treatment duration if ANC greater than 10 or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir (Day 5-14) from chemotherapy.

- Repeat every 14 days for 4 cycles prior to surgery and 4 cycles post surgery.
- Surgery should take place within 6 weeks after completion of Cycle 4.
- Cycle 5 should begin 6-12 weeks after surgery.

**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 200 mg/m$^2$ IV over 2 hours when concurrent oxaliplatin is omitted.*

*** *A*lternative administration:

- To a total volume of 240 mL by continuous infusion at 10 mL/h via Baxter LV10 INFUSOR®;
- Inpatients: 2600 mg/m$^2$/day in 1000 mL D5W by continuous infusion over 24 h

***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

**Table 1 - Dose 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 | 2600 mg/m$^2$ | 2000 mg/m$^2$ | 1600 mg/m$^2$ |
| DOCEtaxel | 50 mg/m$^2$ | 40 mg/m$^2$ | 30 mg/m$^2$ |

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

### A. Dose Modifications for oxaliplatin NEUROLOGIC Toxicity

**(DOCEtaxel may also cause neurologic toxicity. DOCEtaxel dose reductions in addition to oxaliplatin reductions will be determined by clinician at their discretion.)**

| 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<br>2nd time: ↓ 1 dose level | 1st time: ↓ 1 dose level<br>2nd time: ↓ 1 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 |

***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***

**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):<br>Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe | |

**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** | **DOCEtaxel** |
| ▪ If ANC less than 1.5 on Day 1of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. If delayed 2 weeks and on filgrastim, consider discontinuing.<br>▪ 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).<br>▪ 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 | Maintain dose level |
| | 2 | 1.0 to less than 1.5 | Maintain dose level | Maintain dose level | Maintain dose level |
| | 3 | 0.5 to less than 1.0 | ↓ 1 dose level | Maintain dose level | ↓ 1 dose level |
| | 4 | less than 0.5 | ↓ 1 dose level | ↓ 1 infusion dose level | ↓ 1 dose level |
| | | | | | |
| | **Grade** | **Platelets (x10$^9$/L)** | **oxaliplatin** | **fluorouracil** | **DOCEtaxel** |
| ▪ If platelets less than 100 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.<br>▪ If platelets greater than or equal to 100 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s).<br>▪ If platelets remain less than 100 after 2 weeks, discontinue treatment. | 1 | greater than or equal to 100 | Maintain dose level | Maintain dose level | Maintain dose level |
| | 2 | 50 to less than 100 | Maintain dose level | Maintain dose level | Maintain dose level |
| | 3 | 10 to less than 50 | ↓ 1 dose level | Maintain dose level | ↓ 1 dose level |
| | 4 | less than 10 | ↓ 2 dose levels | Maintain dose level | ↓ 1 dose level |

Secondary prophylaxis with filgrastim can be used to prevent treatment delays in patients who, in a previous cycle, have experienced febrile neutropenia, Grade 4 neutropenia, or delay of scheduled treatment because of neutropenia

*Decrease DOCEtaxel and oxaliplatin to 75% of initial dose if patient experiences an episode of febrile neutropenia (despite the use of GCSF), thrombocytopenia causing bleeding, or any other clinically significant hematologic dose limiting toxicity during the prior cycle of treatment. Subsequent hematologic dose limiting toxicities lead to a further dose reduction to 50% of the initial dose. If dose limiting toxicities reoccur at the 50% dose level, the clinician may remove one or more of the drugs.

**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 2 times.<br>▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced.<br>▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment. | 1 | Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output | Maintain dose level |
| | 2 | Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output | Maintain dose level |
| | 3 | Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output | ↓ 1 dose level of 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 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.<br>▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced.<br>▪ 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 infusional fluorouracil |
| | 4 | As above but mucosal necrosis and/or requires enteral support, dehydration | ↓ 1 dose level of oxaliplatin and infusional fluorouracil |

**Hepatic dysfunction for DOCEtaxel:**

| Bllirubin | | Alkaline Phosphatase | | AST or ALT | Dose |
|---|---|---|---|---|---|
| less than or equal to ULN | and | less than 2.5 x ULN | and | less than or equal to 1.5 x ULN | 100% |
| less than or equal to ULN | and | 2.5 to 5 x ULN | and | 1.6 to 6 x ULN | 75% |
| greater than ULN | or | greater than 5 x ULN | or | greater than 5 ULN | discuss with contact physician |

ULN = upper limit of normal

**Renal Function:** Oxaliplatin should be omitted when Cr Cl is below 30 mL/min

**PRECAUTIONS:**

1. **Fluid retention**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention due to DOCEtaxel.
2. **DOCEtaxel Hypersensitivity**: Reactions are common to DOCEtaxel but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer Hypersensitivity Guidelines.
3. **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 hypersensitivity reaction 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.
4. **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated. Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
6. **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated ALT) may lead to increased toxicity and usually requires a dose reduction.
7. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia due to oxaliplatin 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;<br>Fluids and vasopressors if appropriate |

8. **QT prolongation and torsades de pointes** has been 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.
9. 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.
10. **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.
11. **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.
12. 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.

13. **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.
14. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity to fluorouracil – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
15. **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.
16. **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. ran SE, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GE) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol 2017;35(15 supply):4004-4004.
2. Al-Batran et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-esophageal junction adenocarcinoma (FLOT4-AIO):results from the phase 2 part of a multicentre, open-label, randomized phase 2/3 trial. Lancet Oncology 2016:17:1697-1708.
3. Al-Fakeeh et al. A pilot trial of FLOT neoadjuvant chemotherapy for resectable esophagogastric junction adenocarcinoma. Med Oncol 2016: 33 (62)
4. Al-Batran et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008: 26 (9): 1435-1442.