

BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Pancreatic Adenocarcinoma Using Irinotecan, Oxaliplatin, Fluorouracil and Folinic Acid (Leucovorin)

Protocol Code: *UGIFIRINOX*

Tumour Group: *Gastrointestinal*

Contact Physician: *GI Systemic Therapy*

ELIGIBILITY:

- First line therapy for metastatic pancreatic adenocarcinoma. Locally advanced disease only is not eligible.
- ECOG performance status less than or equal to 1
- Age 18 – 75 years
- Adequate marrow reserve (ANC greater than or equal to $1.5 \times 10^9/L$, platelets greater than $100 \times 10^9/L$)
- Adequate renal (Creatinine less than or equal to 1.5 x ULN) and liver function (bilirubin less than or equal to 26 micromol/L; AST/ Alkaline Phosphatase less than or equal to 5 x ULN)
- A BCCA “Compassionate Access Program” or “Undesignated Indication” request with appropriate clinical information for each patient must be approved prior to treatment

Exclusions:

- Ampullary Cancer
- CNS metastases

Caution:

- 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

TESTS AND MONITORING:

- Baseline CBC and differential, Platelets, Creatinine, LFTs (Bilirubin, AST, Alkaline Phosphatase) appropriate imaging study and tumour markers.
- Patients to be seen by physician at every cycle (every 2 weeks)
- **At the beginning of each cycle:** CBC and differential, Platelets, LFT’s (Bilirubin, AST, Alkaline Phosphatase), Creatinine
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at beginning of each cycle.
- Quantitative evaluation of disease response status every six to 10 weeks; discontinue therapy if any progression of disease.

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see precautions)

- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- 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 immediately followed by
Leucovorin (Folinic Acid)	400 mg/m ²	IV in 250 mL D5W over 2 hours with the addition after 30 minutes of
Irinotecan	180 mg/m ²	IV in 500 mL of D5W over 1 hour 30 minutes given through a Y connector placed immediately before the injection site. Immediately followed by
Fluorouracil (5-FU)	400 mg/m ²	IV bolus, followed by
Fluorouracil	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***

Repeat every 14 days for a maximum of 12 cycles.

*** 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.

All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for the management of diarrhea.

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*
Irinotecan	180 mg/m ²	150 mg/m ²	120 mg/m ²
Oxaliplatin	85 mg/m ²	65 mg/m ²	50 mg/m ²
Fluorouracil Bolus	400 mg/m ²	320 mg/m ²	200 mg/m ²
Fluorouracil Infusion	2400 mg/m ²	2000 mg/m ²	1600 mg/m ²

If bolus Fluorouracil is delayed/omitted, Folinic Acid (Leucovorin) should also be delayed/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

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. 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 Oxaliplatin NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle) Oxaliplatin
	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 based on day 1 CBC

	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan	Oxaliplatin	Leucovorin/Fluorouracil
ANC greater than or equal to $1.5 \times 10^9/L$ and Platelets greater than or equal to $75 \times 10^9/L$	No cycle delay	No dose reduction		
ANC greater than or equal to $1 \times 10^9/L$ and less than $1.5 \times 10^9/L$	Delay the treatment until ANC greater than or equal to $1.5 \times 10^9/L$ If no recovery in 2 weeks, discontinue the treatment* .	1st episode: dose reduction to 150 mg/m^2 2nd episode: maintain dose at 150 mg/m^2 3rd episode: discontinue the treatment	1st episode: no dose reduction 2nd episode: dose reduction to 65 mg/m^2 3rd episode: discontinue the treatment	1st episode: reduce the bolus fluorouracil and the infusional fluorouracil by one dose level 2nd episode – eliminate the bolus fluorouracil and leucovorin infusion and maintain infusional fluorouracil at dose level -1 3rd episode: discontinue the treatment
ANC greater than or equal to $0.5 \times 10^9/L$ and less than $1.0 \times 10^9/L$	Delay the treatment until ANC greater than or equal to $1.5 \times 10^9/L$ GCSF support should be considered If no recovery in 2 weeks, discontinue the treatment.	1st episode: dose reduction to 150 mg/m^2 2nd episode: dose reduction to 120 mg/m^2 3rd episode: discontinue the treatment	1st episode: no dose reduction 2nd episode: dose reduction to 65 mg/m^2 3rd episode: discontinue the treatment	1st episode: eliminate the bolus fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level 2nd episode: maintain the reduced dose 3rd episode: discontinue the treatment

ANC less than $0.5 \times 10^9/L$	Delay the treatment until ANC greater than or equal to $1.5 \times 10^9/L$ GCSF support should be considered If no recovery in 2 weeks, discontinue the treatment.	1st episode: dose reduction to 150 mg/m^2 2nd episode: dose reduction dose at 120 mg/m^2 3rd episode: discontinue the treatment	1st episode: dose reduction to 65 mg/m^2 2nd episode: dose reduction to 50 mg/m^2 3rd episode: discontinue the treatment	1st episode: eliminate the bolus fluorouracil and leucovorin infusion and reduce the infusional fluorouracil by one dose level 2nd episode: maintain the reduced dose 3rd episode: discontinue the treatment
Platelets greater than or equal to $50 \times 10^9/L$ and less than $75 \times 10^9/L$	Delay the treatment until recovery (platelets greater than or equal to $75 \times 10^9/L$). If no recovery in 2 weeks, discontinue the treatment.	1st episode: no dose reduction 2nd episode: reduce the dose to 150 mg/m^2 3rd episode: discontinue the treatment	1st episode: dose reduction to 65 mg/m^2 2nd episode: maintain the reduced dose 3rd episode: discontinue the treatment	1st episode: reduce the bolus fluorouracil and the infusional fluorouracil by one dose level 2nd episode: maintain the reduced dose 3rd episode: discontinue the treatment
Platelets less than $50 \times 10^9/L$	Delay the treatment until recovery (platelets greater than or equal to $75 \times 10^9/L$). If no recovery in 2 weeks, discontinue the treatment.	1st episode: no dose reduction 2nd episode: dose reduction to 150 mg/m^2 3rd episode: discontinue the treatment	1st episode: dose reduction to 65 mg/m^2 2nd episode: dose reduction to 50 mg/m^2 3rd episode: discontinue the treatment	1st episode: reduce the bolus fluorouracil and the infusional fluorouracil by one dose level 2nd episode – eliminate the bolus fluorouracil and leucovorin infusion and maintain the infusional fluorouracil at dose level -1 3rd episode: discontinue the treatment

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

At the Beginning of 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 2 times. 	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

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Diarrhea	
<ul style="list-style-type: none"> ▪ 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. 	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of irinotecan and infusional fluorouracil. Discontinue bolus fluorouracil and leucovorin.
	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. Discontinue irinotecan, bolus fluorouracil and leucovorin.
	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 oxaliplatin, irinotecan and infusional fluorouracil. Discontinue bolus fluorouracil and leucovorin.

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. **Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with oxaliplatin. Supportive care is required. 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**.
4. **Diarrhea:** may be life threatening and requires prompt, aggressive treatment.
 - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 - 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.
 - **Late diarrhea** has an onset of 5 - 11 days post-treatment, a duration of 3-7 days and must be treated promptly with **loperamide** (eg, IMODIUM[®]). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
 - **4 mg stat**
 - **then 2 mg every 2 hours until diarrhea-free for 12 hours**
 - may take 4 mg every 4 hours at night
 - The use of drinks such as GATORADE[®] or POWERADE[®] to replace fluid & body salts is recommended.
 - Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.
5. **Other cholinergic symptoms:** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg – 0.6 mg IV or SC. This dose may be repeated at the physician's discretion. Blood pressure and heart rate should be monitored. Prophylactic atropine may be required for subsequent treatments.

6. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. **GCSF support should be initiated for further cycles after an episode of febrile neutropenia.**
7. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
8. **Hepatic dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or AST greater than 3x the upper limit of normal if no liver metastases, or AST greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17-35 micromol/L.
9. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.
10. **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.
11. **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.
12. **Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BCCA [Extravasation Guidelines](#).
13. **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.
14. 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.
15. **Potential Drug Interactions:** Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. Carbamazepine, Phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.
Fluorouracil interactions with warfarin, phenytoin and fosphenytoin 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. Bal Johal at 604-930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

Date activated: June 1, 2011

Date revised:

References:

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6. Mathijssen RHJ, Verweij J, de Bruijn P, et al. Effects of St. John's Wort on irinotecan metabolism. J Natl Cancer Inst 2002;94(16):1247-9.