BCCA Protocol Summary for Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Patients with Peritoneal Carcinomatosis from Limited Advanced Colorectal and Appendiceal Carcinomas Using Oxaliplatin and Fluorouracil (5-FU)

Protocol Code	*GIHIPEC*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

The cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are to be carried out only at the Vancouver General Hospital with the participation of Medical Oncology BCCA.

ELIGIBILITY:

- All cases considered for cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) must be reviewed in a multidisciplinary tumour conference.
- Mucinous or non-mucinous peritoneal carcinomatosis arising from an appendiceal or colorectal primary tumour)
- Adequate marrow reserve (ANC greater than or equal to 1.2 x 10^9/L, platelets greater than 100 x 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)

ABSOLUTE CONTRAINDICATIONS:

- ECOG > 2
- Non appendiceal/colorectal/mesothelial primary tumour
- Unresectable disease on preoperative imaging
- Extra-abdominal metastases
- Multifocal malignant small bowel obstruction
- Co-morbidities precluding extensive surgery (renal failure, cardiac disease, COPD, irreversible hematological disorders, and other)

RELATIVE CONTRAINDICATIONS:

- Age > 70 years
- Extensive disease not amenable for R0/1 resection
- Synchronous liver metastases
- Disease progression while on chemotherapy
- High-grade adenocarcinoma
- Bilateral hydronephrosis

TESTS:

Before Each treatment:

- Baseline: CBC and differential, Creatinine, LFTs (Bilirubin, AST, Alkaline Phosphatase) and appropriate tumour markers.
- CT abdomen/pelvis to evaluate extent of disease
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each treatment.

PREMEDICATIONS:

- For most patients this regimen has low/moderate emetogenicity. Some patients may require pre-treatment antiemetics.
- See SCNAUSEA protocol.

TREATMENT:

Drug	Dosage	BCCA Administration Guidelines
fluorouracil (5-FU)	400 mg/m²	INTRAVENOUS over 10 minutes, starting 30 to 60 minutes prior to start of intraperitoneal perfusion (administered by anesthetist)
oxaliplatin	460 mg/m²	INTRAPERITONEAL mixed in 2 L/m² D5W and perfused for 30 to 60 minutes at intraperitoneal temperature 40-42°C using open "coliseum" technique and Belmont hyperthermia pump, flow rate 1000mL/minute

Alternate regimen*

mitomycin 10 mg/m² Maximum dose:20 mg	INTRAPERITONEAL mixed in 1.5 L/m² of 1.5% dextrose DIANEAL ® peritoneal dialysis solution with calcium 2.5 mEq/L and perfused for 60 minutes at intraperitoneal temperature 40-42°C using open "coliseum" technique and Belmont hyperthermia pump, flow rate 1000mL/min

***Alternate regimen** used in patients who have:

- Allergic reaction or significant documented toxicity from pre-existing platinum-based therapies
- Recurred following previous intraperitoneal treatment with oxaliplatin and are considered candidates for repeat CRS + HIPEC

Dose for oxaliplatin, mitomycin and fluorouracil to be based on ideal body weight (IBW):

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$$

Ideal Body Weight (IBW):

Males:

- IBW = 50 kg + 2.3 kg for each inch (2.54 cm) over 5 feet (152.4 cm)

Females:

- IBW = 45.5 kg + 2.3 kg for each inch (2.54 cm) over 5 feet (152.4 cm)

OR

Males:

- IBW (kg) = 51.65 + 0.73 (height in cm – 152.4)

Females:

- IBW (kg) = 48.67 + 0.65 (height in cm – 152.4)

DOSE MODIFICATIONS:

Clinical Criteria for Dose Modification	Dose
Age greater than 60y	75%

1. **Renal dysfunction:** If GFR is less than 0.2 mL/sec (12 mL/min), reduce dose of all chemotherapeutic agents to 75%.

   Cockcroft/Gault formula:

$$CrCl\ (mL/min) = \frac{N\ (140\text{-}age) \times weight\ (kg)}{serum\ creatinine\ (micromol/L)}$$

   Where N = 1.04 for females, and 1.23 for males

2. **Hepatic dysfunction:** Omit fluorouracil if bilirubin is greater than 85 micromol/L, unless secondary to biliary obstruction (BCCA Cancer Drug Manual)

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.
2. **Pulmonary toxicity**: Mitomycin is associated with pulmonary toxicity consisting of dyspnea and non-productive cough, with an incidence of 3-12%. Threshold dose for pulmonary toxicity is 50-60 mg/m^2.

3. **Renal toxicity**: Mitomycin is associated with a syndrome of renal failure and **microangiopathic hemolytic anemia**, with an incidence of 10%. Threshold dose for syndrome is 50-60 mg/m^2, usually appearing after 6 months of therapy.
4. **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.
5. **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 BCCA Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
6. **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.
7. **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.
8. **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.
9. **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.

Call Dr. Yarrow McConnell at 604-875-4111 or Dr. JP McGhie at (250) 519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

Date activated: 01 October 2013

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References:

1. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30(20):2449–56.
2. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15(9):2426–32.
3. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28(1):63–8.
4. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27(5):681–5.