BC Cancer Protocol Summary for Palliative Chemotherapy for Upper Gastrointestinal Tract Cancer (Gastric, Esophageal, Gall Bladder, Pancreas Carcinoma and Cholangiocarcinoma) and Metastatic Anal using Infusional Fluorouracil and CISplatin

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

ELIGIBILITY:
- Metastatic or unresectable adenocarcinoma of the upper gastrointestinal tract (stomach, esophagus, gall bladder, pancreas, bile ducts)
- Metastatic squamous cell or cloacogenic carcinoma of the anal canal
- Metastatic esophageal squamous cell carcinoma
- ECOG 0 to 2

EXCLUSIONS:
- CNS metastases
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Inadequate hepatic function (total bilirubin greater than 35 micromol/L, ALT greater than 3x normal)
- Inadequate renal function (creatinine clearance less than 45 ml/min as calculated by Cockcroft/Gault formula – see page 3)

TESTS:
- Baseline: CBC, diff and platelets, creatinine, bilirubin, ALT, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine).
- Prior to each treatment: CBC, diff and platelets, creatinine
- If clinically indicated: bilirubin, appropriate imaging studies
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:
This regimen is high moderate in emetogenic potential. See SCNAUSEA protocol.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
CISplatin	25 mg/m^2 weekly on Days 1, 8, 15 and 22	IV in 100 to 250 mL NS over 30 minutes
fluorouracil	1000 mg/m^2/day for 2 days (total dose = 2000 mg/m^2 over 48 hours) weekly on Days 1, 8, 15 and 22 (Maximum dose = 5000 mg/48 hours)	IV in D5W to a total volume of 240 mL by continuous infusion at 5 mL/h via appropriate infusor device

(Inpatients: 1000 mg/m^2/day in 1000 mL D5W by continuous infusion daily over 24 h for 2 days)

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

Repeat every 28 days until disease progression or unacceptable toxicity. Most responding patients will manifest benefit by 6 to 8 cycles.

DOSE MODIFICATIONS:

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

1. **Hematological**:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (both drugs)
greater than or equal to 1.0	and	greater than or equal to 100	100%
less than 1.0	or	less than 100	delay

2. **Renal dysfunction**:
Delay for one week if serum creatinine greater than 3 x ULN. If serum Creatinine less than 3 x ULN adjust CISplatin dose as follows:

Creatinine Clearance (by Cockcroft/Gault formula	Dose - CISplatin only
greater than or equal to 60 mL/min	100%
45 to 59 mL/min	50%
less than 45 mL/min	delay

Cockcroft/Gault formula:

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

Where N = 1.04 for females, and 1.23 for males

3. **Gastrointestinal toxicity**:

Grade	Stomatitis	Diarrhea	Dose Fluorouracil
Grade 1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output	100%
Grade 2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	75%
Grade 3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Increase of greater than 7 stools/day or grossly bloody diarrhea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Discontinue or delay until toxicity resolved then resume at 50%.

4. **Hand-Foot Syndrome**

Grade	Hand-Foot Syndrome	Dose Fluorouracil
Grade 1	Skin changes or dermatitis without pain e.g. erythema, peeling	100%
Grade 2	Skin changes with pain not interfering with function	75% until resolved then consider increasing dose by 10%
Grade 3	Skin changes with pain, interfering with function	Delay until resolved then resume at 75%

5. **Hepatic dysfunction**: Omit treatment if bilirubin greater than 85 micromol/L unless secondary to biliary obstruction. Refer to BC Cancer Drug Manual.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
3. **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.
4. **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.
5. **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.
6. **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.
7. **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 Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.