GIFUBC Cancer Protocol Summary for Curative Combined Modality Therapy for Carcinoma of the Anal Canal using Mitomycin, Infusional Fluorouracil and Radiation Therapy

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

ELIGIBILITY:

Patients must have:

- Squamous cell or cloacogenic carcinoma of the anal canal (T any, N any, M0)

Patients should have:

- ECOG performance status less than or equal to 2
- Adequate marrow reserve, renal and liver function

EXCLUSIONS:

Patients must not have:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Uncontrolled HIV infection

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline if clinically indicated: CEA, CA19-9, SCC, GGT, ECG
- Weekly before chemotherapy and weekly during radiation therapy: CBC & Diff
- Weekly if clinically indicated: total bilirubin, ALT
- If clinically indicated: CEA, CA19-9, SCC, alkaline phosphatase, albumin, GGT, creatinine, sodium, potassium, ECG
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy protocols for mitomycin in combination with fluorouracil (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
mitomycin	10 mg/m^2 on Day 1 Week 1and (Optional) Week 5 (Maximum dose = 20 mg)	IV push
fluorouracil	1000 mg/m^2/day for 4 days (Days 1 to 4 on Weeks 1 & 5) (total dose = 4000 mg/m^2 over 96 h)	IV in D5W to a total volume of 480 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 4 days

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

Week	1	2	3	4	5	6
Radiation therapy**	X	X	X	X	X	1/2
Infusional fluorouracil	X Days 1-4				X Days 1-4	
mitomycin	X Day 1				X Day 1 (mitomycin optional)	

**** Radiotherapy: 50.4 Gy in 28 fractions (over 5 ½ weeks, no gap)**

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**

   Day 1 counts:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 100	100%
Less than 1.5	or	Less than 100	Delay treatment

2. **Non-Hematologic Toxicities:**

Prior to administration of chemotherapy, inform the physician if any signs of stomatitis, hand-foot skin reaction and/or diarrhea (Grade 1 to 4) are present.

Toxicity Criteria

Grade	Diarrhea	Stomatitis	Palmar-plantar erythrodysesthesia
0 to 1	Increase of 2 to 3 stools/day or nocturnal stools	Painless ulcers, erythema or mild soreness	Skin changes with discomfort (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting normal activities
2	Increase of 4 to 6 stools/day or nocturnal stools	Painful erythema, edema or ulcers but can eat	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	Painful erythema, edema or ulcers and cannot eat	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	Mucosal necrosis, requires parenteral support	--

Toxicity	Action
Stomatitis Grades 2 to 4	Hold fluorouracil until symptoms resolved to grade 0 to 1. Resume at the same dose for Grade 2 stomatitis, at 75% dose for Grade 3 stomatitis, or at 50% dose for Grade 4 stomatitis. Consider discontinuing infusion if symptoms are not resolved to grade 0 to 1 after 3 weeks of holding.
Diarrhea Grades 3 to 4	Hold fluorouracil until resolved to Grade 0 to 1. Notify the attending radiation oncologist (RO) and RO may hold radiation therapy until resolved to grade 0 to 1. Then resume at 25% dose, or lower at physician's discretion. Caution: if diarrhea persists or recurs, consider discontinuing the fluorouracil infusion and attempt to complete the radiation on schedule (at RO's discretion)
Palmar-plantar erythrodysestheisa (PPE) Grades 2 to 3	Hold fluorouracil until symptoms resolved to grade 0 to 1, then resume at 75% dose for Grade 2 PPE, or at 50% dose for Grade 3 PPE

If multiple toxicities are present, the dose administered is based on the most severe toxicity experienced. Continue at the same dose for grade 1 to 2 toxicities. However, for grade 3 to 4 toxicities, dose reduction is at physician's discretion. Viral infection, alopecia, fatigue, anorexia and nausea/vomiting controlled by antiemetics require no dose modification. All other non-hematologic toxicities are managed in the same manner as diarrhea. Dose reductions continue for remaining cycles.

3. **Renal dysfunction**: Dose modification required for mitomycin if severe renal dysfunction (creatinine clearance less than 12 mL/min) (see BC Cancer Drug Manual).

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

PRECAUTIONS:

1. **Extravasation**: Mitomycin causes pain and tissue necrosis if extravasated out of vein. Refer to BC Cancer Extravasation Guidelines.
2. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. CBC should be checked 4-6 weeks post chemotherapy to verify that blood counts have returned to normal.
3. **Hemolytic Uremic Syndrome**: A syndrome of microangiopathic hemolytic anemia, thrombocytopenia, renal failure and hypertension has occurred in some patients receiving mitomycin in combination with fluorouracil. Patients treated for 6-12 months, and to cumulative doses of mitomycin greater than 50 mg/m^2 are at greatest risk.
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 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.
6. **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. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.
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.

Call the GI Systemic Therapy physician at your regional cancer centre or Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

REFERENCES:

1. Vuong, Te et al. Conformal Therapy Improves the Therapeutic Index of Patients with Anal Canal Cancer Treated with Combined Chemotherapy and External Beam Radiotherapy. Int J Radiation Oncology Biol Phys 2007;67(5):1394-1400.
2. James, R et al. ACT II: The second UK Phase III Anal Cancer Trial. A Randomised Trial of Chemoradiation using Mitomycin or Cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus. ASCO Abstract LBA4009, May 2009.