

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

Protocol Code
Tumour Group
Contact Physician

GIFUART
Gastrointestinal
GI Systemic Therapy

ELIGIBILITY:

- Squamous cell or Cloacogenic carcinoma of the anal canal
- T any, N any, M0
- ECOG performance status less than or equal to 2
- 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 $1.5 \times ULN$) and liver function (bilirubin less than or equal to 26 micromol/L; **ALT**/ Alkaline Phosphatase less than or equal to $5 \times ULN$)

EXCLUSIONS:

- 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
- Known HIV positive

TESTS:

- Baseline: CBC, diff and platelets, creatinine, serum albumin, bilirubin, **ALT**, alkaline phosphatase. Optional: CEA, SCC
- During treatment: CBC, diff and platelets, weekly before chemotherapy & during radiation therapy
- If indicated clinically: bilirubin, creatinine
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:

- Treatment is low-moderate emetogenic. See SCNAUSEA protocol.

TREATMENT:

Drug	Dose/m ²	BC Cancer Administration Guideline
mitomycin	10 mg/m ² on Day 1 Week 1 and (Optional) Week 5 (Maximum dose = 20 mg)	IV push
fluorouracil	1000 mg/m ² /day for 4 days (Days 1-4 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/m²/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:

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

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

4. GI Toxicity:

(a) **Stomatitis:** Grade 3-4 (painful erythema, edema or ulcers and cannot eat). Decrease dose of Fluorouracil infusion by 25%.

(b) **Diarrhea:** Grade 4 (increase of greater than or equal to 10 stools/day or grossly bloody diarrhea; dehydration). Decrease dose of Fluorouracil infusion by 25%.

PRECAUTIONS:

- Extravasation:** Mitomycin causes pain and tissue necrosis if extravasated out of vein. Refer to BCCA Extravasation Guidelines.
- 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.
- 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/m² are at greatest risk.
- 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. Janine Davies at \(604\) 877-6000 or 1-800-663-3333](#) 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.