BC Cancer Protocol Summary for Curative Combined Modality Therapy for Carcinoma of the Anal Canal using Mitomycin, Capecitabine and Radiation Therapy

***Protocol Code**:*	*GICART*
***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 less than or equal to 2

EXCLUSIONS:

Patients must not have:

- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Uncontrolled HIV infection

CAUTIONS:

- Adequate marrow reserve, renal and liver function

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, GGT, ECG
- Weekly during treatment: CBC & Diff, creatinine
- Weekly if clinically indicated: total bilirubin, ALT
- If clinically indicated: CEA, CA19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy when mitomycin is given in combination with capecitabine.
- Antiemetics may not be needed with capecitabine monotherapy. See SCNAUSEA.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
mitomycin	10 mg/m^2 on Day 1 Week 1 and on Day 29 Week 5 (Week 5 mitomycin is optional) (Maximum dose = 20 mg)	IV push
capecitabine*	825 mg/m^2 BID **on each RT day** (Days 1-5, 8-12, 15-19, 22-26, 29-33 and continue until last day of RT) Note: capecitabine treatment is completed on the last day of RT (Total daily dose=1650 mg/m^2)	PO. Second dose should be taken 10-12 hours after the first dose

*Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Week	1	2	3	4	5	6
Radiation therapy**	X	X	X	X	X	1/2
capecitabine	X Days 1-5	X Days 8-12	X Days 15-19	X Days 22-26	X Days 29-33	Continue until last day of RT
mitomycin	X Day 1				X Day 29 (mitomycin optional)	

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

DOSE MODIFICATIONS:

Capecitabine 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 (x 10^9/L)		Platelets (x 10^9/L)	Mitomycin Dose
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

ANC (x 10^9/L)		Platelets (x 10^9/L)	1st Event Capecitabine Dose	2nd Event Capecitabine Dose	3rd Event Capecitabine Dose	4th Event Capecitabine Dose
Greater than or equal to 1.5	and	Greater than or equal to 75	100%	100%	100%	100%
1 – 1.49	or	50-74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25-49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
Less than 0.5	or	Less than 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L

2. Hand-Foot Skin Reaction: Capecitabine

If only chemotherapy is interrupted due to toxicity, retain the original stop and start dates (i.e., do not make up for missed doses when treatment is resumed).

Grade	Hand-Foot Skin Reaction	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
1	Skin changes with discomfort (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) not disturbing normal activities	100%	100%	100%	100%
2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Delay* then 75%	Discontinue or delay* then 50%	Discontinue	Discontinue

*Stop treatment immediately and delay until resolved to grade 0-1

3. **Other Non-Hematological Toxicity:**

If only chemotherapy is interrupted due to toxicity, retain the original stop and start dates (i.e., do not make up for missed doses when treatment is resumed).

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Increase of 2-3 stools/day or nocturnal stools	1 episode/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4-6 stools/day or nocturnal stools	2-5 episodes/day; intake decreased but can eat	Painlful erythema, edema or ulcers but can eat
3	Increase of 7-9 stools/day or incontinence, malabsorption	6-10 episodes/day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 episodes or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

Dose Adjustment

Toxicity Grade	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
0-1	100%	100%	100%	100%
2	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
3	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
4	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Stop treatment immediately and delay until toxicity resolved to grade 0-1

4. **Hepatic dysfunction:** Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction.

5. Renal dysfunction

A. Capecitabine

Creatinine Clearance (mL/min)	Dose
Greater than 50	100%
30 to 50	75%
Less than 30	0%

Cockcroft-Gault Equation:

Estimated creatinine clearance: (mL/min) = $\frac{\text{N (140-age) wt (kg)}}{\text{Serum creatinine (micromol/L)}}$

N = 1.23 male
N = 1.04 female

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

PRECAUTIONS:

Capecitabine:

1. Patients may experience severe toxicity while receiving concurrent Chemotherapy and Radiation Therapy. Capecitabine and radiation may have to be interrupted until toxicity has improved to grade 1 or less. The dose of capecitabine should be adjusted according to the tables upon restarting chemoradiation. It is important that the patient receive the full Radiation Therapy component. The major toxicity during concurrent Chemotherapy and Radiation Therapy is severe diarrhea, usually during week 4. The patient should be monitored to ensure that dehydration does not occur.
2. **Hand-foot syndrome** may also occur and should be monitored with treatment interruption and dose reductions as indicated in the dose modification section.
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). If patient is taking capecitabine, it should be stopped until given direction by the physician. 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. **Dipyrimidine dehydrogenase deficiency** may result in severe and unexpected toxicity-stomatitis, diarrhea, neutropenia, neurotoxicity. This deficiency is thought to be present in about 3% of the population.
6. **Possible drug interaction with capecitabine and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during capecitabine 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 capecitabine, repeat INR weekly for one month.
7. **Possible drug interaction with capecitabine and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Capecitabine may increase the serum concentration of these two agents.
8. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly. Refer to BC Cancer Febrile Neutropenia Guidelines.
9. **Extravasation:** Mitomycin causes pain and tissue necrosis if extravasated out of vein. Refer to BC Cancer Extravasation Guidelines.
10. **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.

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.

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):1394-400.
2. Glynn-Jones, R et al. A multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiation Oncology Biol Phys 2008;72 (1):119-26.
3. 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.