

# **BCCA 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:**

- 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  $1.5 \times \text{ULN}$ ) and liver function (bilirubin less than or equal to  $26 \text{ micromol/L}$ ; AST/ Alkaline Phosphatase less than or equal to  $5 \times \text{ULN}$ )
- A "Class II Drug Registration Form" must be submitted at the time of initiation of treatment.

## **EXCLUSIONS:**

- 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, differential & platelets, calculated creatinine clearance, LFTs (Bilirubin, AST, Alkaline Phosphatase)
- During treatment: CBC, differential and platelets, creatinine weekly
- After treatment: CBC, differential and platelets, creatinine weekly for 2 weeks after chemoradiation

## **PREMEDICATIONS:**

- Treatment is high to moderately emetogenic. See SCNAUSEA protocol.

**TREATMENT:**

Drug	Dose	BCCA Administration Guideline
Mitomycin	12 mg/m <sup>2</sup> on Day 1 Week 1 (Maximum dose = 20 mg)	IV push
Capecitabine	825 mg/m <sup>2</sup> BID on each RT day (Days 1-5, 8-12, 15-19, 22-26, 29-33 and 36-40) (Total daily dose=1650 mg/m <sup>2</sup> )	PO with food. Second dose should be taken 10-12 hours after the first dose

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	X Days 36-40
Mitomycin C	X Day 1					

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

**DOSE MODIFICATIONS:**

**For Capecitabine:**

**1. Hematological**

ANC (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> Event 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<sup>9</sup>/L and platelets greater than or equal to 75 x 10<sup>9</sup>/L

**Hand-Foot Skin Reaction:**

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	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> Event Dose
1	Skin changes with discomfort (eg, numbness, dysesthesia, paresthesia, tingling, erythema) not disturbing normal activities	100%	100%	100%	100%
2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	Severe skin changes (eg, 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

**2. 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	Painful 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	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> 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

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

4. **Renal dysfunction:**

Creatinine Clearance mL/min	Dose
greater than 50	100%
30-50	75%
less than 30	0%

Cockcroft-Gault Equation:

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

N = 1.23 male  
N = 1.04 female

**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. **Possible interactions with warfarin, phenytoin and fosphenytoin** have been reported with capecitabine and may occur at any time. Close monitoring is recommended (e.g. for warfarin, monitor **INR weekly during capecitabine therapy and for 1 month after stopping capecitabine.**
4. **Myocardial ischemia and angina** occur rarely in patients receiving Capecitabine (overall incidence = 3%, severe 1%). Development of cardiac symptoms, including signs of cardiac ischemia or new arrhythmia should prompt discontinuation of capecitabine.
5. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly. Refer to BCCA Febrile Neutropenia Guidelines.
6. **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.
7. **Extravasation:** Mitomycin causes pain and tissue necrosis if extravasated out of vein. Refer to BCCA Extravasation Guidelines.

- 8. 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<sup>2</sup> are at greatest risk.

**Call the GI Systemic Therapy physician at your regional cancer centre or Dr. Bal Johal at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.**

Date activated: February 1, 2010

Date revised: 01 Nov 2011 (minor typos corrected in Treatment and Precautions sections)

**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.