

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

Protocol Code: GICPART
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)
- Increased risk of hematologic toxicity from mitomycin C

Patients should have:

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

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

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 highly emetogenic chemotherapy for CISplatin
- May not need antiemetic with capecitabine (see protocol SCNAUSEA).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
CISplatin	60 mg/m ² on Day 1 Week 1 and Week 5	Prehydrate with 1000 mL NS over 1 hour, then give cisplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour
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 last day of RT (total daily dose=1650 mg/m ²)	PO. 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	Continue until last day of RT
CISplatin	X Day 1				X Day 1	

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

** Radiotherapy: 50.4Gy 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)	CISplatin Dose
Greater than or equal to 1.5	and	Greater than 100	100%
1.0 to 1.49	or	75 to 100	75%
Less than 1.0	or	Less than 75	Delay

- Consider decreasing to 75% if an episode of febrile neutropenia occurs with the prior treatment

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	1 st Event Capecitabine Dose	2 nd Event Capecitabine Dose	3 rd Event Capecitabine Dose	4 th Event Capecitabine Dose
Greater than or equal to 1.5	and	Greater than or equal to 75	100%	100%	100%	100%
1.0 to 1.49	or	50 to 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5 to 0.99	or	25 to 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 10⁹/L and platelets greater than or equal to 75 x 10⁹/L

2. Renal dysfunction

Calculated creatinine clearance (mL/minute) by Cockcroft/Gault formula	CISplatin and Capecitabine dose
Greater than or equal to 60	100%
45 to 59	75%
Less than 45	Hold cisplatin or delay with additional IV fluids Discontinue/hold Capecitabine

Cockcroft/Gault formula :

Estimated creatinine clearance:
(mL/minute)

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

N = 1.23 male
N = 1.04 female

3. 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 st Event Capecitabine Dose	2 nd Event Capecitabine Dose	3 rd Event Capecitabine Dose	4 th Event Capecitabine Dose
1	Skin changes with discomfort (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) not disturbing normal activities	100%	100%	100%	100%
2	Skin change (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

4. 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 st Event Capecitabine Dose	2 nd Event Capecitabine Dose	3 rd Event Capecitabine Dose	4 th Event Capecitabine 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

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

PRECAUTIONS:

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 doses 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. **Dihydropyrimidine 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. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
10. **Ototoxicity** and **sensory neural damage** should be assessed by history prior to each cycle.

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):1394-1400.
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.
3. 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): 119-126.