

BC Cancer Protocol Summary for Combined Modality Adjuvant Therapy for High Risk Rectal Carcinoma using Capecitabine and Radiation Therapy

Protocol Code:

GIRCRT

Tumour Group:

Gastrointestinal

Contact Physician:

GI Systemic Therapy

ELIGIBILITY:

- Stage II & III rectal adenocarcinoma, either pre-operative or post-operative
- Stage IV pre-operative rectal adenocarcinoma

EXCLUSIONS:

- Metastatic disease should be excluded by CEA, chest x-ray and abdominal ultrasound (and any other necessary investigations).
- Unstable or uncontrolled angina/coronary artery disease
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min)
- Suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)

TESTS:

- Baseline: CBC, differential & platelets, creatinine, bilirubin, ALT, alkaline phosphatase, and optional CEA
- Prior to each treatment: CBC, differential, & platelets, creatinine
- Weekly during radiation therapy: CBC & differential, platelets, creatinine, INR (for patients on warfarin)
- 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 low emetogenic chemotherapy. May not need any antiemetic with Capecitabine. See [SCNAUSEA](#) protocol.

TREATMENT:

Chemotherapy:

Option 1: Cycle 1 during radiation treatment, and cycles 2-7 following radiation treatment

OR

Option 2: Cycle 1 prior to radiation treatment, cycle 2 during radiation treatment, and cycles 3-7 following radiation treatment

OR

Option 3: Cycle 1 & 2 prior to radiation treatment, Cycle 3 during radiation treatment, and cycles 4-7 following radiation treatment

PRE-OPERATIVE: Surgery should be scheduled 6-8 weeks after completion of combined modality chemotherapy and radiation; i.e., therapy is interrupted after the chemoradiation cycle and the remaining cycles are given post-operatively, 4-8 weeks after surgery.

NOTE:

Pre-operative combined modality chemotherapy and radiation has been shown to be less toxic and more effective than post-operative therapy. Every effort should be made to give chemoradiation pre-operatively.

See dose modification for patients with significant co-morbid conditions, poor performance status or increased creatinine clearance

CYCLE: WEEK Option 1	CHEMOTHERAPY		
	Drug	Dose	BC Cancer Administration Guideline
Radiation: 25 fractions over 5 weeks*			
Cycle 1	capecitabine [†]	825 mg/ m ² BID on each RT day (Total daily dose=1650 mg/m ²)	PO. Second dose should be taken 10-12 hours after the first dose. Given on the days that RT is given for the duration of Radiation Therapy, beginning on the first day of RT and ending on the last day of RT.
SURGERY			
Cycles 2–7**	capecitabine [†]	1250 mg/m ² BID (Total daily dose = 2500 mg/m ²) x 14 days	PO

*May take 5-6 weeks

**Cycle 2 starts 4-8 weeks after surgery. Cycle is 21 days.

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

CYCLE: WEEK Option 2	CHEMOTHERAPY		
	Drug	Dose	BC Cancer Administration Guideline
Cycle 1*	capecitabine [†]	1250 mg/m ² BID (Total daily dose = 2500 mg/m ²) x 14 days	PO
Radiation: 25 fractions over 5 weeks**			
Cycle 2**	capecitabine [†]	825 mg/ m ² BID on each RT day (Total daily dose=1650 mg/ m ²)	PO. Second dose should be taken 10-12 hours after the first dose. Given on the days that RT is given for the duration of Radiation Therapy, beginning on the first day of RT and ending on the last day of RT.
SURGERY			
Cycles 3–7***	capecitabine [†]	1250 mg/m ² BID (Total daily dose = 2500 mg/m ²) x 14 days	PO

* Cycle is 21 days

**May take 5-6 weeks

***Cycle 3 starts 4-8 weeks after surgery. Cycle is 21 days.

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

CYCLE: WEEK Option 3	CHEMOTHERAPY		
	Drug	Dose	BC Cancer Administration Guideline
Cycles 1 & 2 *	capecitabine [†]	1250 mg/m ² BID (Total daily dose = 2500 mg/m ²) x 14 days	PO
Radiation: 25 fractions over 5 weeks**			
Cycle 3**	capecitabine [†]	825 mg/ m ² BID on each RT day (Total daily dose=1650 mg/ m ²)	PO. Second dose should be taken 10-12 hours after the first dose. Given on the days that RT is given for the duration of Radiation Therapy, beginning on the first day of RT and ending on the last day of RT.
SURGERY			
Cycles 4–7***	capecitabine [†]	1250 mg/m ² BID (Total daily dose = 2500 mg/m ²) x 14 days	PO

*Cycle is 21 days

**May take 5-6 weeks

***Cycle 4 starts 4-8 weeks after surgery. Cycle is 21 days.

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

Pelvic Irradiation:

- 4500 cGy in 25 fractions over 5 weeks
- Followed at the Radiation Oncologist's discretion by a boost of 540 cGy to the tumour bed and immediately adjacent lymph nodes, plus 2 cm.
- When feasible, a final boost of 360 cGy may be given to the tumour bed, plus 2 cm. No small bowel may be treated within this volume.

DOSE MODIFICATIONS:

For capecitabine:

1. Hematological:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose
Greater than or equal to 1.5	and	Greater than or equal to 75	100%	100%	100%	100%
1.0 to less than 1.5	or	50 to less than 75	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5 to less than 1.0	or	25 to less than 50	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. 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 Dose	2 nd Event Dose	3 rd Event Dose	4 th Event Dose
1	Skin changes with discomfort (eg, numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting 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

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	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 Dose	2 nd Event Dose	3 rd Event Dose	4 th 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:**

Creatinine Clearance mL/min	Dose
Greater than or equal to 50	100%
30 to less than 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:

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. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.
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. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly.
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. **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.

8. **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.

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

REFERENCES:

1. Yu, CS et al. Optimal time Interval between capecitabine intake and radiotherapy in preoperative chemoradiation for locally advanced rectal cancer. *Int J Radiation Oncology Biol Phys* 2007;67(4):1020-6.
2. De Paoli, A, et al. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. *Ann Onc* 2006;17:246-51.