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

Protocol Code:	*GIRLCRT*
Tumour Group:	*Gastrointestinal*
Contact Physician:	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Colorectal adenocarcinoma planned for combination chemoradiotherapy

Note: GIRLCRT may be given neoadjuvantly (before or after GIRNACOXand GIRNAFFOX) or adjuvantly.

EXCLUSIONS:

Patients must not have:

- Unresectable metastatic disease
- 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 & 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
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- Weekly during radiation therapy: CBC & Diff, creatinine
- Weekly if clinically indicated during radiation therapy: 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 low emetogenic chemotherapy. May not need any antiemetic with capecitabine. See SCNAUSEA protocol.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
Radiation: 25 fractions over 5 weeks*		
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 RT, beginning on the first day of RT and ending on the last day of RT.

*May take 5-6 weeks

**Select dose per Dose Banding Table (appendix).

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 ($x10^9$/L)		Platelets ($x10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th 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 10^9/L, and platelets greater than or equal to 75 x 10^9/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	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 disrupting 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 capecitabine 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	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. Refer to BC Cancer Drug Manual.

5. **Renal Dysfunction:**

Creatinine Clearance (mL/min)	Dose
Greater than or equal to 50	100%
30 to less than 50	75%
Less than 30	Withhold

Cockcroft-Gault Equation:

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

N = 1.23 male
N = 1.04 female

PRECAUTIONS:

1. Patients may experience severe toxicity while receiving concurrent chemotherapy and RT. 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 RT component. The major toxicity during concurrent chemotherapy and RT 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 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 Viol 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.
3. Bahadoer RR, Dijkstra EA, Etten B, et al. Short-course Radiotherapy Followed by Chemotherapy Before Total Mesorectal Excision (TME) versus Preoperative Chemoradiotherapy, TME, and Optional Adjuvant Chemotherapy in Locally Advanced Rectal Cancer (RAPIDO): A Randomized, Open-label, Phase 3 Trial. Lancet Oncology 2021 Jan;22(1):29-42.
4. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ Preservation in Patients with Rectal Adenocarcinoma Treated with Neoadjuvant Therapy. Journal of Clinical Oncology 2022 Apr;40(23):2546-2557.
5. Schrag D, Shi Q, Weiser MR et al. Preoperative Treatment of Locally Advanced Rectal Cancer. New England Journal of Medicine 2023 June;389:322-334.

Appendix. CAPECITABINE DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)	Number of Tablets Per Dose	
From:	To:		150 mg	500 mg
226	375	300	2	
376	475	450	3	
476	575	500		1
576	725	650	1	1
726	900	800	2	1
901	1075	1000		2
1076	1225	1150	1	2
1226	1400	1300	2	2
1401	1575	1500		3
1576	1725	1650	1	3
1726	1900	1800	2	3
1901	2075	2000		4
2076	2225	2150	1	4
2226	2400	2300	2	4
2401	2575	2500		5
2576	2725	2650	1	5
2726	2900	2800	2	5
2901	3075	3000		6
3076	3225	3150	1	6
3226	3400	3300	2	6
3401	3575	3500		7
3576	3725	3650	1	7
3726	3900	3800	2	7