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

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

ELIGIBILITY:
- Stage II & III rectal adenocarcinoma, either pre-operative or post-operative
- Ability to manage infusional fluorouracil treatment
- Patients with a colostomy/ileostomy who have tried capecitabine and cannot tolerate it due to output issues.

EXCLUSIONS:
- Metastatic disease should be excluded by chest x-ray and abdominal ultrasound (and any other necessary investigations)
- Unstable or uncontrolled angina/coronary artery disease, neurological or psychiatric disorders and active infection
- Severe renal impairment (calculated creatinine clearance less than 30 ml/min)
- Suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (See Precautions)

TESTS:
- Baseline: CBC, differential & platelets, creatinine, BUN, bilirubin, ALT, alkaline phosphatase. Optional: CEA
- Prior to each treatment: CBC, differential & platelets, creatinine
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each chemotherapy cycle.
- Weekly during radiation therapy: CBC & differential & platelets, INR (for patients on warfarin)

PREMEDICATIONS:
Antiemetic protocol for low emetogenic chemotherapy with capecitabine and rare emetogenic chemotherapy with fluorouracil. May not need any antiemetic with capecitabine. See SCNAUSEA protocol.

TREATMENT:
Chemotherapy
Option 1: Cycle 1 during radiation treatment, and cycles 2-5 following radiation treatment

OR

Option 2: Cycle 1 prior to radiation treatment, cycle 2 during radiation treatment and cycles 3-5 following radiation treatment

OR

Option 3: Cycle 1 & 2 prior to radiation treatment, Cycle 3 during radiation treatment and Cycle 4 & 5 following radiation treatment

PRE-OPERATIVE: surgery to be scheduled 6 -8 weeks after completion of combined modality chemotherapy and radiation; i.e. therapy is interrupted after the chemoradiation 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.

CYCLE: WEEK	CHEMOTHERAPY		
Option 1	**Drug**	**Dose**	**BC Cancer Administration Guideline**
Radiation: 25 fractions over 5 weeks* (weeks 1-5)			
Cycle 1	fluorouracil	**225** mg/m^2/day continuously for the duration of Radiation Therapy or to a total of 35 calendar days, whichever comes first, beginning on the first day of RT and ending on the last day of RT	IV in D5W to a total volume of 252 mL in each 7-day infusor by continuous infusion at 1.5 mL/h via appropriate infusor device* via central venous access device
SURGERY			
Cycle 2: Week 10** Cycle 3: Week 13 Cycle 4: Week 16 Cycle 5: Week 19 Cycle 6: Week 22 Cycle 7: Week 25	capecitabine^{Ŧ}	1250 mg/m^2 BID (Total daily dose = 2500 mg/m^2) x 14 days	PO with food

*may take 5-6 weeks **cycle 2 starts 4-8 weeks after surgery. Cycle is 21 days.
Ŧ Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

CYCLE: WEEK	CHEMOTHERAPY		
Option 2	**Drug**	**Dose**	**BC Cancer Administration Guideline**
Cycle 1*	capecitabine^{Ŧ}	1250 mg/m^2 BID (Total daily dose = 2500 mg/m^2) x 14 days	PO with food
Radiation: 25 fractions over 5 weeks (weeks 4-8)**			
Cycle 2	fluorouracil	**225** mg/m^2/day continuously for the duration of Radiation Therapy or to a total of 35 calendar days, whichever comes first, beginning on the first day of RT and ending on the last day of RT	IV in D5W to a total volume of 252 mL in each 7-day infusor by continuous infusion at 1.5 mL/h via appropriate infusor device* via central venous access device
SURGERY			
Cycle 3*** Cycle 4 Cycle 5 Cycle 6 Cycle 7	capecitabine^{Ŧ}	1250 mg/m^2 BID (Total daily dose = 2500 mg/m^2) x 14 days	PO with food

*cycle is 21 days **may take 5-6 weeks ***cycle 3 starts 4-8 weeks after surgery. Cycle is 21 days.
Ŧ 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**
Cycle 1 & 2*	capecitabine[Ŧ]	1250 mg/m^2 BID (Total daily dose = 2500 mg/m^2) x 14 days	PO with food
Radiation: 25 fractions over 5 weeks (weeks 7-11)**			
Cycle 3	fluorouracil	**225** mg/m^2/day continuously for the duration of Radiation Therapy or to a total of 35 calendar days, whichever comes first, beginning on the first day of RT and ending on the last day of RT	IV in D5W to a total volume of 252 mL in each 7-day infusor by continuous infusion at 1.5 mL/h via appropriate infusor device* via central venous access device
SURGERY			
Cycle 4*** Cycle 5 Cycle 6 Cycle 7	capecitabine[Ŧ]	1250 mg/m^2 BID (Total daily dose = 2500 mg/m^2) x 14 days	PO with food

*cycle is 21 days **may take 5-6 weeks ***cycle 4 starts 4-8 weeks after surgery. Cycle is 21 days.
Ŧ 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 fluorouracil:

1. **Hematological:**

ANC (x10^9/L)		Platelets (x10^9/L)	Action
less than 1.5	or	less than 50	Hold fluorouracil until counts recover. Radiation therapy at Radiation Oncologist's discretion.

2. Non-Hematologic Toxicities:
Inform the attending physician or designate prior to administration of chemotherapy if any signs of stomatitis and/or diarrhea (Grade 1-4) are present.

Toxicity	Action
Stomatitis Grades 2-4	Hold fluorouracil until resolved then resume at dose reduced by 50 mg/m^2/day. Consider discontinuing infusion if not resolved after 3 weeks on hold.
Diarrhea Grades 3-4	Hold fluorouracil and Radiation therapy until resolved then resume at previous dose. Caution: if diarrhea persists or recurs, consider discontinuing the fluorouracil infusion and attempt to complete the radiation on schedule (at Radiation Oncologist's discretion).
Palmar-plantar erythrodysesthesia Grades 2-4 (moderate paresthesias +/or – numbness with or without local dermatitis; painful swelling of distal phalanges)	Hold fluorouracil until resolved then resume with dose reduced by 50 mg/m^2 /day.

If multiple toxicities are seen, the dose administered is based on the most severe toxicity experienced. Viral infection, alopecia, fatigue, anorexia and nausea/vomiting controlled by antiemetics require no dose modification. All other non-hematologic toxicities are managed in the same manner as diarrhea. Dose reductions continue for remaining cycles.

3. **Hepatic dysfunction:** Omit treatment if bilirubin greater than 85 micromol/L unless secondary to biliary obstruction (BC Cancer Cancer Drug Manual).

DOSE MODIFICATIONS for capecitabine:

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 treatment is interrupted due to toxicity, retain the original stop and start dates (ie. 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 (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:

- see next table for toxicity grading criteria for diarrhea, nausea and vomiting, and stomatitis
- if treatment is interrupted due to toxicity, retain the original stop and start dates (ie. do not make up for missed doses when treatment is resumed)

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

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Increase of 2-3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4-6 stools/day or nocturnal stools	2-5 vomits/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 vomits/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 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

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:

For capecitabine:

1. **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.
2. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly.
3. **Hand-foot syndrome** may also occur and should be monitored with treatment interruption and dose reductions as indicated in the dose modification section.
4. **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.
5. **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.
6. **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.
7. **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.

For fluorouracil:

1. **Patients may experience severe toxicity** while receiving concurrent Chemotherapy and Radiation Therapy. Fluorouracil and radiation may have to be interrupted until toxicity has improved. If diarrhea persists or recurs, consider discontinuing the fluorouracil infusion and attempt to complete the radiation on schedule (at Radiation Oncologist's discretion).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. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly.
2. **Stomatitis**: sucking ice chips is recommended, especially at higher doses of Fluorouracil to reduce stomatitis following chemotherapy. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches which subside quickly.
3. **A GI syndrome** characterized by progression from mild GI symptoms to potentially fatal enterocolitis has been reported. Prompt attention, especially to ensure adequate hydration, is required. Diarrhea with cramping occurs more commonly in previously radiated patients especially in the elderly.
4. **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.
5. **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.

6. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil 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 fluorouracil, repeat INR weekly for one month.
7. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.
8. **Elderly Patients**
   Although several publications show that the benefit of adjuvant therapy is maintained in the elderly, it is also clear that increased toxicity is often seen in this population. While age alone should not be used as the sole criterion for dose modification, it is imperative that dose modifications be considered in the context of significant co-morbidities, impaired organ function (including physiologic age-related declines), tenuous nutritional status, poor performance status and the like.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. 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;17:246-251.