BC Cancer Protocol Summary for Adjuvant Therapy of Colon Cancer using Capecitabine

Protocol Code *GIAJCAP*

Tumour Group *Gastrointestinal*

Contact Physician *GI Systemic Therapy*

ELIGIBILITY:

- Resected Stage III or high risk Stage II colon cancer
- ECOG performance status 0-2
- Patient must be able to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis

EXCLUSIONS:

- Severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under Dose Modifications)
- suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)

CAUTIONS:

- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS:

- Baseline: CBC and differential, creatinine, ALT, alkaline phosphatase, bilirubin, albumin, GGT, BUN. Optional: CEA
- Prior to each cycle: CBC and differential, Creatinine
- If clinically indicated: ALT, alkaline phosphatase, bilirubin, albumin, GGT, BUN
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:

- Antiemetic protocol for low moderate emetogenic chemotherapy (see SCNAUSEA)

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
capecitabine	1250 mg/m^2 BID x 14 days (d 1 to 14) (Total daily dose = 2500 mg/m^2/day)	PO with food

*Starting dose of 1000 mg/m^2 bid recommended for elderly or those with ECOG 2 performance status. Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 21 days for 8 cycles.

DOSE MODIFICATIONS:

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 (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort 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)

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 to 3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4 to 6 stools/day or nocturnal stools	2 to 5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	6 to 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 50	100%
30 to 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. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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.
3. **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.
4. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. 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.

Call the GI Systemic Therapy physician at your regional cancer centre or 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. Cassidy J, Scheithauer W, McKendrick J, et al. Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): efficacy results of a phase III trial. Proc ASCO 2004, abstr 3509.
2. Scheithauer W, McKendrick J, Begbie S et al. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. Ann Oncol 2003; 14:1735-43