BC Cancer Protocol Summary for Palliative Therapy of Advanced Gastrointestinal Cancer using Capecitabine

Protocol Code	*GIAVCAP*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Metastatic or unresectable cancer, not curable with surgery or radiation, and one of the following indications:
  - Colorectal adenocarcinoma,
  - Pancreatic adenocarcinoma previously treated with gemcitabine-based therapy,
  - Biliary tract (cholangiocarcinoma or gallbladder) cancer, previously treated with at least one prior line of therapy,
  - Gastric carcinoma, not fit enough for combination chemotherapy per provider discretion

Patients should have:

- ECOG performance status 0 to 2
- Ability to report any severe toxicity such as diarrhea, hand/foot syndrome, stomatitis

EXCLUSIONS:

Patients must not have:

- 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 & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, random glucose, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline if clinically indicated: ECG, GGT, CEA, CA 19-9
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: alkaline phosphatase, albumin, GGT, sodium, potassium, random glucose, ECG, CEA, CA 19-9
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle

Activated: 1 Mar 2002 (as UGIAVCAP) Revised: 1 Jul 2024 (Title, eligibility, tests, antiemetic risk category, and references updated)

- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
capecitabine	1000 to 1250 mg/m^2 BID x 14 days (Days 1 to 14) (Total daily dose = 2000 to 2500 mg/m^2/day)	PO

* Starting dose of 1000 mg/m^2 BID recommended for elderly, poor performance status or extensively pretreated patients. Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 21 days until disease progression or unacceptable toxicity.

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 treatment 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 (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort 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 to 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 (i.e., 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 to 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 to 1

Toxicity Criteria:

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0 to 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 the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19(8):2282-92.
2. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19(21):4097-106.
3. Cartwright TH, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002;20(1):160-4.
4. Heinemann V, et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). Gut 2013;62(5):751-9.
5. Boeck S, et al. Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer Oncology. 2007;73(3-4):221-7.
6. Tempero MA, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines J Natl Compr Canc Netw. 2014;12(8):1083-93.
7. Lamarca A, Palmer DH, Wasan HS, et al. Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701
8. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol. 2004 Sep;15(9):1344-7.