

BC Cancer Protocol Summary for Palliative Therapy of Metastatic Colorectal Cancer using Capecitabine and Bevacizumab

Protocol Code:

GIAVCAPB

Tumour Group:

Gastrointestinal

Contact Physician:

GI Systemic Therapy

ELIGIBILITY:

Patients must have:

- Metastatic or unresectable colorectal adenocarcinoma, not curable with surgery or radiation

Patients should have:

- No major surgery within 28 days of administration of therapy
- No untreated CNS metastases
- ECOG performance status 0 to 2
- Adequate hematologic, renal and hepatic function (Caution in patients with severe hepatic dysfunction i.e., total bilirubin greater than 50 micromol/L)

Note: Patients with metastatic colorectal cancer without left-sided primary may receive either bevacizumab or PANitumumab based treatment, but not sequential use of these agents

EXCLUSIONS:

Patients must not have:

- Severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under Dose Modifications)

CAUTIONS:

- Patients with: 1) recent MI; 2) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, 3) renal disease including proteinuria, 4) bleeding disorders, 5) previous anthracycline exposure, or 6) other serious medical illness
- Patients with recent (less than 6 months) arterial thromboembolic event

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), dipstick or laboratory urinalysis for protein, Blood Pressure measurement
- Baseline if clinically indicated: CEA, CA 19-9, GGT, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, Blood Pressure measurement
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG
- Prior to each *even* numbered cycles: dipstick or laboratory urinalysis for protein
- 24 hour urine for protein if occurrence of proteinuria dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1 g/L
- Blood Pressure measurement to be taken pre and post dose for first 3 cycles only and then pre-therapy with each subsequent visit.
- For patients on warfarin, weekly INR 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 (see [SCNAUSEA](#)). May not need antiemetics.

TREATMENT:

One Cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
bevacizumab	7.5 mg/kg*	IV in 100 mL Normal Saline over 15 minutes**
capecitabine [‡]	1000 mg/m ² BID	PO x 14 days

Repeat every 21 days until disease progression or unacceptable toxicity.

*** The bevacizumab dose should be recalculated for patients who experience more than a 10% change in body weight.**

**** Observe for fever, chills, rash, pruritus, urticaria or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted then it should be given at an initial rate of 60 minutes or longer.**

If acute hypertension (increase in BP measurement of greater than 20 mm Hg diastolic or greater than 160/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at ½ the original rate of infusion if blood pressure returns to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab and subsequent infusions of bevacizumab should be given over 3 hours. Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

Line should be flushed with Normal Saline pre and post dose as bevacizumab should not be mixed with dextrose solutions.

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

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 (for capecitabine only):

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	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 $1.5 \times 10^9/L$ and platelets greater than or equal to $75 \times 10^9/L$

2. Hand-Foot Skin Reaction (for capecitabine only):

- 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	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th 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 0-1

3. Diarrhea, Stomatitis, Nausea and Vomiting or other non-hematological toxicity (for capecitabine only):

- 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	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

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)	capecitabine Dose only
Greater than or equal to 50	100%
30 - 50	75%
Less than 30	Discontinue Therapy

Cockcroft-Gault Equation:

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

N = 1.23 male

N = 1.04 female

6. Proteinuria:

There are 3 different measures of proteinuria that may be used to assess the need for modification of Bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24 hour urine collections for protein (measured in g/24 hours)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each even numbered cycle of therapy:

Degree of Proteinuria	
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below.
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection

24-Hour Urine Total Protein (g/24 hours)	Bevacizumab Dose
Less than or equal to 2	100%
Greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2 g/24 hour
Greater than 4	Discontinue Therapy

7. Hypertension:

Blood Pressure (mm Hg)	Bevacizumab Dose
Less than or equal to 160/100	100%
Greater than 160/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy*
Hypertensive Crisis	Discontinue Therapy

- **Antihypertensive therapy may include hydroCHLOROthiazide 12.5-25 mg PO once daily, ramipril (ALTACE®) 2.5-5 mg PO once daily, or amlodipine (NORVASC™) 5-10 mg PO once daily.**

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Gastrointestinal perforations and wound dehiscence:** Can be fatal. Typical presentation is reported as abdominal pain associated with symptoms such as constipation and vomiting. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.
3. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue bevacizumab. Patients with significant bleeding diatheses should not receive bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of bevacizumab. COX-2 inhibitors are permissible. **For patients on warfarin, see Thrombosis (for bevacizumab) and Drug Interactions (for capecitabine).**

4. **Thrombosis:** A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary embolus arises, hold bevacizumab for 2 weeks, then consider resumption of bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue bevacizumab. Patients on warfarin should have INR checked frequently, at least once per cycle, while receiving bevacizumab. In patients on warfarin with an elevated INR, it is recommended to **hold the bevacizumab if INR is greater than 3.0**
5. **Proteinuria:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. If proteinuria of greater than or equal to 2g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
6. **Hypertension:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. The most commonly used therapies are Calcium Channel Blockers, ACE Inhibitors and Diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
7. **Reversible Posterior Leukoencephalopathy Syndrome:** Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
8. **Congestive Heart Failure:** Has been reported in up to 3.5% of patients treated with bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.
9. **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.
10. **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.
11. **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.
12. **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.
13. **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. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomized phase 3 trial. *Lancet Oncol* 2013; 14: 1077-1085.
2. [CADTH \[Canada's Drug Agency \(CDA-AMC\)\] Reimbursement Review. Provisional Funding Algorithm. Metastatic colorectal cancer. May 2024.](#)