BC Cancer Protocol Summary for Palliative Therapy of Metastatic or Locally Advanced Anal Squamous Cell Carcinoma using CISplatin and Capecitabine

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

ELIGIBILITY:
- Metastatic or locally advanced anal squamous cell carcinoma SCC.
- ECOG performance status 0 -1, Karnofsky performance status greater than or equal to 70%.
- Adequate marrow reserve, hepatic, renal and cardiac function.

NOTE: For palliative treatment of metastatic or locally advanced gastric, gastroesophageal junction or esophageal adenocarcinoma use GIGAVCOX.

EXCLUSIONS:
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- CNS metastases.
- Suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)

CAUTION:
- Patients over 75 years of age

TESTS:
- Baseline: CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium. Optional: CEA, CA19-9, SCC.
- Prior to each treatment: CBC and differential, platelets, creatinine and sodium, potassium.
- If clinically indicated: LFTs (bilirubin, ALT, alkaline phosphatase), CEA, CA 19-9, SCC.
- 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 highly emetogenic chemotherapy. May not need any antiemetic with capecitabine. (see SCNAUSEA).

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
CISplatin	80 mg/m^2	Prehydrate with 1000 mL NS over 1 hour, then give CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour
capecitabine*	1000 mg/m^2 BID x 14 days (Total daily dose = 2000 mg/m^2/day	PO BID

* 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 6-8 cycles.

DOSE MODIFICATIONS:

1. **Hematological**

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (all drugs)
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to less than 1.5	or	75 to 100	75%
less than 1.0	or	less than 75	Delay

2. Hand-Foot Skin Reaction: for capecitabine

- 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

3. Other Non-Hematologic Toxicity: for capecitabine

- 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 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

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

4. **Renal dysfunction:** for CISplatin and capecitabine

Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula	CISplatin and capecitabine dose
Greater than or equal to 60	100%
45 to 59	75%
30 to 44	Hold CISplatin or delay with additional IV fluids Continue with 75% capecitabine
Less than 30	Hold CISplatin and capecitabine

Cockcroft/Gault formula:

$$CrCl = \frac{N\ (140\text{-age}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

Where N = 1.04 for females, and 1.23 for males

5. **Hepatic Dysfunction:** Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Renal Toxicity:**. Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycosides.
3. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.

4. **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.
5. **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.
6. **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.
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 Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Kang YK et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy inpatients with advanced gastric cancer: a randomised phase III noninferiority trial