BC Cancer Protocol Summary for Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using CISplatin, Capecitabine and Trastuzumab

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

ELIGIBILITY:
- GIGAVCOXT is the preferred protocol. But for pre-existing neuropathy cisplatin protocol can be used.
- Metastatic or locally advanced (unresectable) gastric, gastroesophageal junction, or esophageal adenocarcinoma.
- ECOG performance status 0-2.
- HER-2 positive/overexpression defined as either IHC3+, or FISH amplification ratio of greater than or equal to 2 per BC Cancer central laboratory.
- No prior chemotherapy in the metastatic setting, greater than 6 weeks from prior radiation therapy, greater than 3 weeks from surgery.
  NOTE: Patients are still eligible for this protocol if they receive less than or equal to 3 cycles of standard chemotherapy while the results of HER-2 testing are pending.
- No signs or symptoms of cardiac disease. For patients with cardiac risk factors or history of cardiac disease, a MUGA scan or Echocardiogram should be done to document adequate left ventricular ejection fraction (LVEF).
- Adequate marrow reserve, renal and liver function

EXCLUSIONS:
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months), unstable angina, uncontrolled high blood pressure
- Baseline LVEF less than 50%
- Suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)

TESTS:
- Baseline: CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium. Optional: CEA, CA 19-9
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Prior to each treatment: CBC and differential, platelets, creatinine, sodium, potassium
- If clinically indicated: LFTs (bilirubin, ALT, alkaline phosphatase), cardiac function assessment with MUGA scan or Echocardiogram, CEA, CA 19-9
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle.
- Radiologic evaluation is recommended after 2-3 cycles
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA protocol)
- Not usually required for trastuzumab. May not need antiemetic with capecitabine.

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
trastuzumab	8 mg/kg for 1st cycle ONLY,	IV in 250 mL NS over 1 hour 30 minutes for 1st cycle (Observe for 1 hour post-infusion)
	then 6 mg/kg with subsequent cycles	IV in 250 ml NS over 1 hour for 2nd cycle and over 30 min for all subsequent cycles. (Observe for 30 minutes post-infusion**)
capecitabine**	1000 mg/m^2 BID x 14 days (Total daily dose = 2000 mg/m^2 /day)	PO BID

*Observation period not required after 3 consecutive treatments with no reaction
**Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

- Repeat every 21 days x 6 cycles
- Discontinue therapy if there is lack of response after 2-3 cycles
- Trastuzumab can be continued as single agent until disease progression following 6 cycles of chemotherapy (See protocol GIGAVTR).

DOSE MODIFICATIONS:

1. **Hematology** For CISplatin and capecitabine

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.5	and	greater than or equal to100	100%
1.0 to less than 1.5	or	75 to less than100	**Delay*** then 100% for 1st event**
less than 1.0	or	less than 75	**Delay*** then 75%

*Delay until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 100 x 10^9/L
**Consider dose reduction to 75% for subsequent events and/ or prolonged delays of more then 2 wks

2. **Hand-Foot Skin Reaction:** 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)

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
0-1	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

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

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:

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

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. **Cardiac toxicity**: Trastuzumab can produce ventricular dysfunction and congestive heart failure in less than 2% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but can be considered after 6 months of treatment with trastuzumab. If no significant decline in cardiac function, repeated testing is not generally necessary, unless clinically indicated. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias. **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.
2. **Trastuzumab infusion-associated symptoms,** usually chills and fever, can occur in some patients during the first trastuzumab infusion. Symptoms may be treated with acetaminophen, diphenhydramine and meperidine with or without an infusion rate reduction. Rarely, serious infusion-related reactions have been reported. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
4. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
5. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
6. **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.
7. **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.
8. **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.

9. **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.
10. A drug interaction with **trastuzumab and warfarin** has also been reported.

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. Van Cutsem E, Kang Y, Chung H, et al. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 2009; 27(15s): Abstract LBA4509.
2. Bang YJ, Chung HC, Xu JM, et al. Pathological features of advanced gastric cancer: relationship to human epidermal growth factor receptor 2 positivity in the global screening programme of the ToGA trial. J Clin Oncol 2009; 27(15s): Abstract 4556.