

# **BCCA Protocol Summary for Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using CISplatin, Capecitabine and Trastuzumab**

**Protocol Code:**

*UGIGAVCCT*

**Tumour Group:**

*Gastrointestinal*

## **ELIGIBILITY:**

- Metastatic or inoperable locally advanced gastric or gastroesophageal junction adenocarcinoma
- ECOG performance status 0-2,
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio of greater than or equal to 2 per BCCA central laboratory
- No prior chemotherapy, 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 normal left ventricular ejection fraction (LVEF).
- Adequate marrow reserve, renal and liver function
- NOTE: A BCCA "Compassionate Access Program" form with appropriate clinical information for each patient must be submitted and approved prior to treatment.

## **EXCLUSIONS:**

- Inability to swallow Capecitabine tablets
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Baseline LVEF less than 50%

## **TESTS:**

- Baseline: CBC and differential, platelets, serum Creatinine, Bilirubin, AST/ALT, Alkaline Phosphatase,
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Prior to each treatment: CBC and differential, platelets, serum Creatinine, AST/ALT, Alkaline Phosphatase
- Radiologic evaluation is recommended after 2-3 cycles
- If clinically indicated: cardiac function assessment with MUGA scan or Echocardiogram

## **PREMEDICATIONS:**

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA protocol)
- Not usually required for trastuzumab

**TREATMENT:**

Drug	Dose	BCCA Administration Guideline
CISplatin	80 mg/m <sup>2</sup>	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 1 <sup>st</sup> cycle ONLY,	IV in 250 mL NS over 1 hour 30 minutes for 1 <sup>st</sup> cycle (Observe for 1 hour post-infusion)
	then 6 mg/kg with subsequent cycles	IV in 250 ml NS over 1 hour for 2 <sup>nd</sup> cycle and over 30 min for all subsequent cycles. (Observe for 30 minutes post-infusion**)
Capecitabine	1000 mg/m <sup>2</sup> bid x 14 days (Total daily dose = 2000 mg/m <sup>2</sup> /day)	PO bid with food

\*Observation period not required after 3 consecutive treatments with no reaction

- 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 UGIGAVTR).

**DOSE MODIFICATIONS:****1. Hematology** For CISplatin and Capecitabine

ANC (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Dose
greater than or equal to 1.5	and	greater than 100	100%
1 – 1.49	or	75-100	<b>Delay*</b> then 100% for 1 <sup>st</sup> event**
less than 1	or	less than 75	<b>Delay*</b> then 75%

\*Delay until ANC greater than or equal to 1.5 x 10<sup>9</sup>/L and platelets greater than or equal to 75 x 10<sup>9</sup>/L

\*\*Consider dose reduction to 75% for subsequent events and/ or prolonged delays of more than 2 wks

**2. 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	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> 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

**3. 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	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> 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

**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%
45-59	75%
less than 45	Hold cisplatin or delay with additional IV fluids

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. **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 Capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment.
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 BCCA 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. **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. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
8. **Possible drug interactions with Capecitabine and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping Capecitabine). A drug interaction with **Trastuzumab and warfarin** has also been reported.

**Call the GI Systemic Therapy physician at your regional cancer centre or Dr. Sanjay Rao at (250) 712-3900 or 1-888-563-7773 with any problems or questions regarding this treatment program.**

Date activated: February 1, 2010

Date revised: 1 June 2011 (Infusion section revised)

**Reference:**

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.