

BCCA Protocol Summary for Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using Cisplatin, Infusional Fluorouracil and Trastuzumab

Protocol Code:

UGIGAVCFT

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 or ECHO 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:

- 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,
- 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 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
Fluorouracil	800 mg/m ² /day for 5 days (total dose = 4000 mg/m ² over 120h)	IV in D5W to a total volume of 240 mL by continuous infusion at 2 mL/h via appropriate infusor device*
Trastuzumab	8 mg/kg for 1 st cycle ONLY,	IV in 250 mL NS over 1 hour 30 min for 1 st cycle (Observe for 1 hour post-infusion)
	then 6 mg/kg with subsequent cycles	IV in 250 mL NS over 1 hour for 2 nd cycle and over 30 min for all subsequent cycles. (Observe for 30 minutes post-infusion**)

*Inpatients: 800 mg/m²/day in 1000 mL D5W by continuous infusion daily over 24 h for 5 days

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

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

- 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 with chemotherapy. (See protocol UGIGAVTR.)

DOSE MODIFICATIONS:**1. Hematology For Cisplatin and Fluorouracil**

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
greater than or equal to 1.5	and	greater than 100	100%
1.0-1.49	or	75-100	Delay* then 100% for 1 st event**
less than 1.0	or	less than 75	Delay* then 75%

*Delay until ANC greater than or equal to 1.5 x 10⁹/L and platelets greater than or equal to 75 x 10⁹/L

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

2. Gastrointestinal toxicity: For Fluorouracil

Grade	Stomatitis	Diarrhea	Dose Fluorouracil
Grade 1	Painless ulcers, erythema or mild soreness	Increase of 2-3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output	100%
Grade 2	Painful erythema, edema, or ulcers but can eat	Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	75%
Grade 3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Increase of greater than 7 stools/day or grossly bloody diarrhea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Discontinue or delay until toxicity resolved then resume at 50%.

3. Hand-Foot Syndrome for Fluorouracil

Grade	Hand-Foot Syndrome	Dose
Grade 1	Skin changes or dermatitis without pain e.g. erythema, peeling	100%
Grade 2	Skin changes with pain not interfering with function	75% until resolved then consider increasing dose by 10%
Grade 3	Skin changes with pain, interfering with function	Delay until resolved then resume at 75% (150 mg/m ² /24 hr)

4 Renal dysfunction: for Cisplatin

Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula	Cisplatin 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

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. 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 fluorouracil 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 fluorouracil). 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: 01 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.