

BCCA Protocol Summary For Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, Cisplatin and Infusional Fluorouracil

Protocol Code:

GIGECF

Tumour Group:

Gastrointestinal

ELIGIBILITY:

- Histologically proven and as yet unresected adenocarcinoma of the stomach, gastro-esophageal junction, or lower 1/3 of the esophagus, Stage 1B (T1N1 or T2N0) or greater
- Clinical staging supporting operability of the primary with no distant metastases
- ECOG performance status 0-1, Karnofsky performance status greater than or equal to 70%
- No previous chemotherapy
- Adequate hepatic, renal, marrow and cardiac function

EXCLUSIONS:

- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia

TESTS:

- Baseline: CBC and differential, platelet, Creatinine, Bilirubin, AST/ALT, Alkaline Phosphatase
- Prior to each cycle: CBC and differential, platelet, Creatinine, electrolytes, AST/ALT, Alkaline Phosphatase
- Weekly while on Fluorouracil: CBC and differential, platelet
- If clinically indicated: MUGA scan or Echocardiogram

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy.(See SCNAUSEA protocol)

TREATMENT:

Drug	Dose	BCCA Administration Guideline
Epirubicin	50 mg/m ²	IV push
Cisplatin	60 mg/m ²	Prehydrate with 1000 mL NS over 1 h, then give Cisplatin IV in 500 mL NS with 20 mEq KCl, 1 g MgSO ₄ , 30 g mannitol over 1 h
Fluorouracil	200 mg/m ² /day for 21 days, dispensed as three 7-day infusors (total dose = 4200 mg/m ² over 504 h)	IV in D5W to a total volume of 252 mL in each 7-day infusor by continuous infusion at 1.5 mL/h via appropriate infusor device*

*Inpatients: 200 mg/m²/day in 1000 mL D5W by continuous infusion daily over 24 h for 21 days

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

- Repeat every 21 days for 3 cycles prior to surgery and 3 cycles post surgery. Surgery should take place 3-6 weeks after completion of Cycle 3 and Cycle 4 should begin 6-12 weeks after surgery.

DOSE MODIFICATIONS:

1. Hematology

Prior to each cycle -

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (day 1 Epirubicin & Cisplatin)*
greater than or equal to 1.5	and	greater than 100	100%
1-1.49	or	75 -100	75%
less than 1	or	less than 75	Delay
*Consider decreasing to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment			

During weekly Fluorouracil treatment -

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (weekly Fluorouracil)
0.5 – 1	or	10 - 50	75%
less than 0.5	or	less than 10	Hold
Weekly Fluorouracil infusion dose should be decreased to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment			

2. Gastrointestinal toxicity: for Fluorouracil

Grade	Stomatitis	Diarrhea	Dose
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. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.
2. **Renal Toxicity:** Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
3. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
4. **Cardiac Toxicity:** Clinical cardiac assessment is required prior to Epirubicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO).
5. **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.
6. **Extravasation: Epirubicin** causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
7. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity to fluorouracil – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.
8. **Possible interactions with warfarin, phenytoin and fosphenytoin** have been reported with fluorouracil/capecitabine and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil/capecitabine therapy and for 1 month after stopping fluorouracil/capecitabine).

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: 01 November 2007

Date revised: 1 June 2011 (Infusion section revised)

Reference:

1. Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *New Engl J Med* 2006;355 (1):11-9.

2. Findlay M et al. A Phase II study in advanced gastric cancer using epirubicin and cisplatin in combination with continuous 5-FU (ECF). *Ann Oncol* 1994; 5:609-616.