

BC Cancer Protocol Summary for Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, CISplatin and Capecitabine

Protocol Code

GIGECC

Tumour Group

Gastrointestinal

Contact Physicians

GI Systemic Therapy

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:

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

TESTS:

- Baseline: CBC & diff, platelets, serum Creatinine, Bilirubin, ALT, Alkaline Phosphatase
- Prior to each treatment: CBC & diff, platelets, serum Creatinine, sodium, potassium, ALT, Alkaline Phosphatase
- If clinically indicated: MUGA scan or Echocardiogram
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see [SCNAUSEA](#))

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
epirubicin	50 mg/m ²	IV push
CISplatin	60 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 sulphate, 30 g mannitol over 1 hour
capecitabine*	625 mg/m ² bid x 21 days (Total daily dose = 1250 mg/m ² /day)	PO bid with food

* 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 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. Hematologic:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose
greater than or equal to 1.5	and	greater than 100	100%
1 to 1.5	or	75 to 100	75%
less than 1	or	less than 75	delay
*Consider decreasing to 75% if an episode of febrile neutropenia occurs with prior cycle of treatment			

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	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th 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

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	1 st Event Dose	2 nd Event Dose	3 rd Event Dose	4 th 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 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:

- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
- Renal Toxicity:** Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside
- Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
- 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). **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. **Extravasation: Epirubicin** causes pain and tissue necrosis if extravasated. Refer to BC Cancer [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 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.

Call the GI Systemic Therapy physician at your regional cancer centre or Dr. JP McGhie at (250) 519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Sumpter K. et al. Report of two planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005 92;1976-83.
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.
3. Cunningham D et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. NEJM 2008 358;1:36-46.