BC Cancer Protocol Summary for Adjuvant Chemotherapy of Gastric Cancer patients with Completely Resected Gastric Cancer using CISplatin and Capecitabine and Radiation Therapy

Protocol Code:	*GIGAJCPRT*
Tumour Group:	*Gastrointestinal*
Contact Physicians:	*GI Systemic Therapy*

ELIGIBILITY:
- Resected gastric cancer stage IIA or higher and no distant metastases. **Note:** Patients with IB gastric cancer should be reviewed at GI conference for consideration of adjuvant fluorouracil chemotherapy with radiation therapy. Contact GI Tumour Group designate for protocol (GIGAIRT).
- Patients eligible for standard adjuvant chemoradiation
- Age 18 years or older
- ECOG 0 to 1
- Adequate hepatic, renal, marrow and cardiac function.
- Caution in patients with recent MI, uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness

EXCLUSIONS:
- Stage IA or IB (T2aN0) disease, microscopically positive resection margins, and involvement of M1 lymph node or distant metastases.
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under Dose Modifications)
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)

TESTS:
- Baseline: CBC & diff, platelets, creatinine, sodium, potassium, liver function tests (bilirubin, ALT, alkaline phosphatase), appropriate tumour marker(s),
- Prior to each treatment: CBC & diff, platelets, creatinine
- Weekly during radiation therapy: CBC & diff, platelets, creatinine
- If clinically indicated: liver function tests (bilirubin, ALT, alkaline phosphatase), sodium, potassium
- For patients on warfarin, weekly INR during capecitabine therapy until stable warfarin dose established, then INR prior to each cycle.
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS
- For cycles 1 to 2 and 4 to 5 containing cisplatin: Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA).
- For cycle 3 containing only capecitabine: Antiemetic protocol for low moderate emetogenic chemotherapy (see SCNAUSEA). Prochlorperazine or metoclopramide may be sufficient antiemetics for cycle 3 of treatment. However, radiation may induce nausea during this cycle and in such cases, antiemetics should be reevaluated.

TREATMENT

Chemotherapy is given in 5 cycles: cycle 1 and 2 are prior to radiation treatment, cycle 3 is during radiation treatment, and cycles 4 and 5 are following radiation treatment. Cycle 4 to start 2-4 weeks after Radiation complete.

CYCLE	CHEMOTHERAPY		
	Drug	**Dose**	**BC Cancer Administration Guidelines**
Cycle 1 and 2 Repeat every 21 days for 2 cycles. (Cycle 1: weeks 1 to 3) (Cycle 2: weeks 4 to 6)	CISplatin	60 mg/m^2 on Day 1 only	Prehydrate with NS 1000 mL over 1 hour, then give CISplatin IV in NS 500 mL with potassium chloride 20 mEq, magnesium sulphate 1 g, and mannitol 30 g over 1 hour.
	capecitabine	1000 mg/m^2 BID x 14 days (Total daily dose = 2000 mg/m^2)	PO BID
Radiation: 45 Gy in 25 fractions over 5 weeks (weeks 7 to 11)			
Cycle 3 (Weeks 7 to 11)	capecitabine	825 mg/m^2 BID **on each RT day only** (Total daily dose = 1650 mg/m^2)	PO BID. Second dose should be taken 10 to 12 hours after first dose. Given on the days that RT is given for the duration of Radiation Therapy, beginning on the first day of RT and ending on the last day of RT.
Cycle 4* and 5 Repeat every 21 days for 2 cycles (*Cycle 4 to start 2-4 weeks after Radiation complete)	CISplatin	60 mg/ m^2 on Day 1 only	Prehydrate with NS 1000 mL over 1 hour, then give CISplatin IV in NS 500 mL with potassium chloride 20 mEq, magnesium sulphate 1 g, and mannitol 30 g over 1 hour.
	capecitabine	1000 mg/ m^2 BID x 14 days (Total daily dose = 2000 mg/m2)	PO BID

Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

DOSE MODIFICATIONS:

1. **Hematology**:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 75	100%
Less than 1.5	or	Less than 75	Delay x 1 week

After 1 week of delay:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 75	100%
1.0 to less than 1.5	and	Greater than or equal to 75	Reduce **capecitabine only** by 25%
Less than 1.0	or	Less than 75	Delay x 1 week

After 2nd week of delay:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 75	Reduce **capecitabine only** by 25%
Less than 1.0	or	Less than 75	Delay x 1 week

After 3rd week of delay:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 75	Reduce **capecitabine only** by 50%
Less than 1.0	or	Less than 75	Omit Further Chemotherapy

- If after 3 weeks of delays counts have not recovered, stop 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	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

*stop treatment immediately and delay until resolved to grade 0 to 1

3. **Nausea:** for CISplatin

Grade	Nausea and Vomiting	Dose
0 to 1	1 vomit/day but can eat	100%
2	2 to 5 vomits/day; intake decreased but can eat	100%
3	6 to 10 vomits/day and cannot eat	75%
4	10 vomits or more per day or requires parenteral support; dehydration	75%

4. **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 to 1	Increase of 2 to 3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4 to 6 stools/day or nocturnal stools	2 to 5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	6 to 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 to 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 to 1

5. **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

6. **Hepatic dysfunction**: Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction.

PRECAUTIONS:

1. **Neutropenia**: Fever and other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside
3. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
4. **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. **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. **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.
8. **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 the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

REFERENCES:

1. Lee J, Lim D, Kim S et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: The ARTIST Trial. J Clin Oncol 2012;30:268-273.