**BC Cancer** Summary for Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using CISplatin, Infusional Fluorouracil and Trastuzumab (HERCEPTIN)

**Protocol Code:** GIGAVCFT

**Tumour Group:** Gastrointestinal

**Contact Physician:** GI Systemic Therapy

**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

**EXCLUSIONS:**
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months), *unstable angina, uncontrolled high blood pressure*
- Baseline LVEF less than 50%
- Suspected Dihydropyrimidine Dehydrogenase (DPD) deficiency (see Precautions)

**TESTS:**
- Baseline: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase, sodium, potassium. Optional: CEA, CA 19-9
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram, or MUGA scan)
- Prior to each treatment: CBC and differential, platelets, creatinine, sodium, potassium
- If clinically indicated: bilirubin, ALT, alkaline phosphatase, cardiac function assessment with MUGA scan or Echocardiogram, CEA, CA 19-9
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.
- Radiologic evaluation is recommended after 2-3 cycles

**PREMEDICATIONS:**
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA protocol)
- Not usually required for trastuzumab
### TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISplatin</td>
<td>80 mg/m²</td>
<td>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</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>800 mg/m²/day for 5 days (total dose = 4000 mg/m² over 120h)</td>
<td>IV in D5W to a total volume of 240 mL by continuous infusion at 2 mL/h via appropriate infusor device*</td>
</tr>
<tr>
<td>Trastuzumab (HERCEPTIN)</td>
<td>8 mg/kg for 1st cycle ONLY, then 6 mg/kg with subsequent cycles</td>
<td>IV in 250 mL NS over 1 hour 30 min for 1st cycle (Observe for 1 hour post-infusion) for 1st cycle and over 30 min for all subsequent cycles. (Observe for 30 minutes post-infusion**)</td>
</tr>
</tbody>
</table>

*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 GIGAVTR.)

### DOSE MODIFICATIONS:

1. **Hematology** For CISplatin and fluorouracil

<table>
<thead>
<tr>
<th>ANC (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than or equal to 100</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>1.0 to less than 1.5 or 75 to less than 100</td>
<td>Delay* then 100% for 1st event**</td>
<td></td>
</tr>
<tr>
<td>less than 1.0 or less than 75</td>
<td>Delay* then 75%</td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stomatitis</th>
<th>Diarrhea</th>
<th>Dose Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>Increase of 2-3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Painful erythema, edema, or ulcers but can eat</td>
<td>Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output</td>
<td>75%</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>As above, but cannot eat, mucosal necrosis, requires parenteral support.</td>
<td>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</td>
<td>Discontinue or delay until toxicity resolved then resume at 50%.</td>
</tr>
</tbody>
</table>

3. **Hand-Foot Syndrome** for fluorouracil

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hand-Foot Syndrome</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Skin changes or dermatitis without pain e.g. erythema, peeling</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Skin changes with pain not interfering with function</td>
<td>75% until resolved then consider increasing dose by 10%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Skin changes with pain, interfering with function</td>
<td>Delay until resolved then resume at 75% (150 mg/m²/24 hr)</td>
</tr>
</tbody>
</table>

4. **Renal dysfunction**: for CISplatin

<table>
<thead>
<tr>
<th>Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula</th>
<th>CISplatin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>100%</td>
</tr>
<tr>
<td>45-59</td>
<td>75%</td>
</tr>
<tr>
<td>less than 45</td>
<td>Hold CISplatin or delay with additional IV fluids</td>
</tr>
</tbody>
</table>

*Cockcroft/Gault formula:*

\[
CrCl = \frac{N (140-age) \times weight (kg)}{serum creatinine (micromol/L)}
\]

*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 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.

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 BC Cancer 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. **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). 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.

7. **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.

8. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur
at any time. For patients on warfarin, weekly INR during fluorouracil 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 fluorouracil, repeat INR weekly for one month.

9. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been
reported and may occur at any time. Close monitoring is recommended. Fluorouracil may
increase the serum concentration of these two agents.

10. A drug interaction with **trastuzumab and warfarin** has also been reported.

**Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic
Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or
questions regarding this treatment program.**

**Reference:**

trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2

human epidermal growth factor receptor 2 positivity in the global screening programme of the ToGA trial.