BCCA Protocol Summary for Combined Modality Adjuvant Therapy for Completely Resected Gastric Adenocarcinoma using Fluorouracil + Folinic Acid (Leucovorin) + Radiation Therapy

Protocol Code: GIGAIRT

Tumour Group: Gastrointestinal

Contact Physicians: GI Systemic Therapy

ELIGIBILITY:
- Stage IB – IV M0 adenocarcinoma of the stomach or gastroesophageal junction who have undergone gastric resection with curative intent within 8-10 weeks and who have had a preop CT scan
- ECOG Performance Status 0-1; see Precautions patients with ECOG greater than or equal to 2
- Patients must have a Radiation Oncology consult before proceeding with this treatment

TESTS:
- Baseline: CBC and diff, LFTs,
- Prior to each treatment: CBC & diff
- Weekly during radiation therapy: CBC & diff
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:
Treatment is non-emetogenic. See SCNAUSEA protocol.

TREATMENT:
- Chemotherapy is given in 5 cycles: cycle 1 is prior to radiation treatment, cycles 2 and 3 are during radiation treatment, and cycles 4 & 5 are following radiation treatment.

Some patients may experience stomatitis and/or diarrhea during Days 1-5 requiring dose modifications and/or treatment discontinuation due to excessive sensitivity. It is essential that all patients be assessed for stomatitis and diarrhea at each treatment visit and that any signs of these toxicities be reported to the attending physician or designate prior to administering the chemotherapy for that day. Continuing chemotherapy in this setting may result in life threatening toxicity.
### Schema:

<table>
<thead>
<tr>
<th>CYCLE: WEEK: DAY</th>
<th>CHEMOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
</tr>
<tr>
<td>1:Wk 1:days 1-5</td>
<td>leucovorin</td>
</tr>
<tr>
<td></td>
<td>fluorouracil</td>
</tr>
<tr>
<td>2:Wk 5:days 29-32 (first 4 days of RT)</td>
<td>leucovorin</td>
</tr>
<tr>
<td></td>
<td>fluorouracil</td>
</tr>
<tr>
<td>3:Wk 9:days 59-61 (last 3 days of RT)</td>
<td>leucovorin</td>
</tr>
<tr>
<td></td>
<td>fluorouracil</td>
</tr>
<tr>
<td>4*:Wk 14:days 92-96</td>
<td>leucovorin</td>
</tr>
<tr>
<td>5:Wk 18: days 120-124</td>
<td>leucovorin</td>
</tr>
</tbody>
</table>

* Cycle 4 starts 28 days after radiation ends

**Radiation: 4500 cGy in 25 fractions over 5 weeks (weeks 5-9)**

**DOSE MODIFICATIONS:**

If the radiation therapy is delayed, the chemotherapy should be delayed similarly so that Cycles 2 and 3 are always given during the first and fifth week of radiation therapy.

The dose of folinic acid (leucovorin) is not modified for toxicity but is omitted if fluorouracil is omitted.

For Cycles 1, 2, 4 and 5:

1. **ANC (x 10⁹/L)**
   - greater than or equal to 1.5
   - less than 1.5

   **Platelets (x 10⁹/L)**
   - greater than or equal to 100
   - less than 100

   **Fluorouracil Dose**
   - 100%
   - delay treatment

For Cycle 3:

**ANC (x 10⁹/L)**
- less than 1.5

**Platelets (x 10⁹/L)**
- less than 75

**Fluorouracil Dose**
- omit treatment
- RTX at Radiation
- Oncologist’s discretion
2. Non-hematological Toxicity

(For Cycles 1, 2, 4 and 5)

Inform the attending physician or designate prior to administration of chemotherapy if any signs of stomatitis and/or diarrhea (Grade 1-4) are present.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Diarrhea</th>
<th>Stomatitis (if dose not reduced during previous cycle)</th>
<th>Percentage Dose of Fluorouracil for subsequent cycles based on interval toxicity</th>
<th>Dose Fluorouracil + Folinic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Increase of 2-3 stools/day or nocturnal stools; or mild increase in loose watery colostomy output</td>
<td>Painless ulcers, erythema or mild soreness</td>
<td>425 mg/m² Cycle 1, 4 &amp; 5 or 400 mg/m² Cycle 2 (or 100% of previous dose)</td>
<td>If greater than or equal to Grade 2 at start of cycle, hold and check weekly, then treat based on interval toxicity. If greater than or equal to Grade 2 after 2 weeks, discontinue.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output</td>
<td>Painful erythema, edema, or ulcers but can eat</td>
<td>340 mg/m² Cycle 1, 4 &amp; 5 or 320 mg/m² Cycle 2 (or 80% of previous dose)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Increase of greater than 7 stools/day or incontinence, malabsorption, severe increase in loose watery colostomy output, grossly bloody diarrhea, may require parenteral support</td>
<td>As above but cannot eat, mucosal necrosis and/or requires enteral support, dehydration</td>
<td>255 mg/m² Cycle 1, 4 &amp; 5 or 240 mg/m² Cycle 2 (or 60% of previous dose)</td>
<td></td>
</tr>
</tbody>
</table>

(For Cycle 3)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC less than 1.5 or Platelets less than 75</td>
<td>Omit Cycle</td>
</tr>
<tr>
<td>Stomatitis Grade 2-4</td>
<td>Omit Cycle</td>
</tr>
<tr>
<td>Diarrhea Grade 3-4</td>
<td>Omit Cycle</td>
</tr>
<tr>
<td>Interruption of Radiation due to diarrhea</td>
<td>Proceed with cycle once radiation resumes if toxicity has resolved. Chemotherapy should always be given on the first 4 days and the last 3 days of radiation therapy</td>
</tr>
</tbody>
</table>

If toxicity is greater than or equal to Grade 2 after treatment has been held for 2 weeks, **discontinue treatment.**

If multiple toxicities are seen, the dose administered is based on the most severe toxicity experienced. Viral infection, alopecia, fatigue, anorexia and nausea/vomiting controlled by antiemetics require no dose alteration. All other non-hematologic toxicities are managed in the same manner as diarrhea. Dose reductions continue for remaining cycles.

3. **Hepatic dysfunction:** Omit treatment if bilirubin greater than 85 micromol/L unless secondary to biliary obstruction (BCCA Cancer Drug Manual).
PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly.

2. **Sucking ice chips** is recommended, especially at higher doses of Fluorouracil, to reduce stomatitis following chemotherapy. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches which subside quickly.

3. **A GI syndrome** characterized by progression from mild GI symptoms to potentially fatal enterocolitis has been reported. Prompt attention, especially to ensure adequate hydration, is required.

4. Consideration should be given to a **dose reduction for elderly patients** (greater than 70 years of age, particularly female), patients with poor nutritional status and patients with an ECOG performance status of greater than or equal to 2. Starting Fluorouracil doses should be reduced to 375 mg/m², then increased by 25 mg/m² each cycle until the standard dose for that cycle is reached and there are no side effects at the previous dose.

5. **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.

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 BCCA 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. **Dipyrimidine dehydrogenase deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity. 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.

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.

Date activated: 01 August 2001 (as GIGAI)

Date revised: **1 Nov 2015 (addition of Diarrhea Precaution)**

REFERENCES: