BCCA Protocol Summary for Palliative Therapy of Advanced Colorectal Cancer using Leucovorin and Fluorouracil

**Protocol Code:** GIFUFA

**Tumour Group:** Gastrointestinal

**Contact Physician:** GI Systemic Therapy

**ELIGIBILITY:**
- Metastatic or unresectable colorectal adenocarcinoma
- ECOG 0-2

**TESTS:**
- Baseline: CBC & diff, LFTs (if liver metastases), CEA, bilirubin
- Prior to each treatment: CBC & diff
- Every 2-3 cycles: CEA
- If clinically indicated: LFTs, bilirubin
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

**PREMEDICATIONS:**
- metoclopramide 10-20 mg po or prochlorperazine 10 mg po is usually adequate.

**TREATMENT:**
- See dose modification #1 for elderly infirm patients and dose modification #2 for particularly fit patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>leucovorin</td>
<td>20 mg/m²/day x 5 days (d1-5)</td>
<td>IV push prior to fluorouracil</td>
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<tr>
<td>(folinic acid)</td>
<td></td>
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<tr>
<td>fluorouracil</td>
<td>400 mg/m²/day x 5 days (d1-5)</td>
<td>IV push</td>
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<tr>
<td>(5FU)</td>
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</tbody>
</table>

Repeat every 28 days as long there is evidence of a favorable response.

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.

**DOSE MODIFICATIONS** for Fluorouracil:
1. For elderly (greater than 70 yr) or infirm (ECOG greater than or equal to 2) patients, escalate dose of fluorouracil as follows:
   - Cycle 1: 375 mg/m²/day x 5 days (d1-5).
   - Cycle 2: 400 mg/m²/day x 5 days (d1-5) if no side effects at starting dose.
2. For young, fit patients, the dose of fluorouracil may be started at (or escalated to) 425 mg/m²/day x 5 days (d1-5).
1. **Hematological:**

<table>
<thead>
<tr>
<th>ANC ($x 10^9/L$)</th>
<th>Platelets ($x 10^9/L$)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5</td>
<td>greater than or equal to 100</td>
<td>100%</td>
</tr>
<tr>
<td>less than 1.5</td>
<td>less than 100</td>
<td>delay treatment</td>
</tr>
</tbody>
</table>

2. **Toxicity:**

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>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, or nocturnal stools or moderate increase in loose watery colostomy output</td>
<td>Delay if still present, then 80%</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>As above but cannot eat, mucosal necrosis and/or requires enteral support, dehydration</td>
<td>Increase of greater than or equal to 7 stools/day or incontinence, malabsorption, severe increase in loose watery colostomy output, grossly bloody diarrhea, may require parenteral support</td>
<td>Delay if still present, then 70%</td>
</tr>
</tbody>
</table>

*Dose reductions for stomatitis and diarrhea are based on dose given in preceding cycle and continue for remaining cycles. If multiple toxicities are seen, the dose administered is based on the most severe toxicity experienced. The dose of leucovorin is not modified for chemotherapy toxicity.

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

**PRECAUTIONS:**

1. **Enterocolitis:** can occur in elderly patients and requires prompt attention, especially intravenous fluids, to ensure adequate hydration.
2. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively; increased risk of myelosuppression in elderly.
3. **Mucositis:** sucking ice chips is recommended, especially at higher doses of fluorouracil to reduce mucositis 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.
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). 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.
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 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.

8. **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: N/A

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