BC Cancer Protocol Summary for Adjuvant Therapy of Colon Cancer using Fluorouracil Injection and Infusion and Leucovorin Infusion

Protocol Code: *GIAJFL*

Tumour Group: *Gastrointestinal*

Contact Physician: *GI Systemic Therapy*

ELIGIBILITY:

- Resected Stage III or high risk Stage II colon cancer
- ECOG performance status 0-2
- Adequate marrow reserve, renal and liver function
- Caution in patients with recent MI, uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure or other serious medical illness
- Caution in patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Patient must be able to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis

EXCLUSIONS:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)

TESTS AND MONITORING:

- **Baseline:** CBC and differential, platelets, Creatinine, LFTs (Bilirubin, ALT, Alkaline Phosphatase) appropriate imaging study and optional CEA.
- **Prior to each cycle**: CBC and differential, platelets
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.
- Quantitative evaluation of disease response status every eight to twelve weeks; discontinue therapy if any progression of disease.

PREMEDICATIONS:

- Antiemetics are not usually required (see SCNAUSEA)

TREATMENT:

A cycle equals:

Drug	Dose	BC Cancer Administration Guidelines
leucovorin	400 mg/m^2	IV in 250 ml D5W over 2 hours
fluorouracil	400 mg/m^2	IV push, after Folinic Acid, THEN
fluorouracil	2400 mg/m^2	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR *

Repeat every 14 days for 12 cycles.

***** *A*lternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside** dose banding range are **prepared as ordered**)**:**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m^2/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

DOSAGE MODIFICATIONS

Agent	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2	Dose Level –3
leucovorin*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue Therapy
fluorouracil IV push	400 mg/m^2	320 mg/m^2	240 mg/m^2	Discontinue Therapy
fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue Therapy

****leucovorin dose does not require dose adjustment; leucovorin is delayed or omitted if fluorouracil is delayed or omitted***

A. Dose Modifications for HEMATOLOGIC Toxicity

<table>
<tr><th rowspan="2">Prior to a Cycle (Day 1)</th><th colspan="2">Toxicity</th><th>Dose Level For Subsequent Cycles</th></tr>
<tr><th>Grade</th><th>ANC (x10^9/L)</th><th>fluorouracil</th></tr>
<tr><td rowspan="5">▪ If ANC less than 1.0 on Day 1of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.
▪ If ANC is greater than or equal to 1.0 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s).
▪ If ANC remains less than 1.0 after 2 weeks, discontinue treatment.</td><td>1</td><td>greater than or equal to 1.5</td><td>Maintain dose level</td></tr>
<tr><td>2</td><td>1.0 to less than 1.5</td><td>Maintain dose level</td></tr>
<tr><td>3</td><td>0.5 to less than 1.0</td><td>↓ 1 dose level</td></tr>
<tr><td>4</td><td>less than 0.5</td><td>↓ 1 dose level</td></tr>
<tr><td colspan="2">Grade 4 neutropenia & greater than or equal to Grade 2 fever</td><td>↓ 1 dose level</td></tr>
<tr><td></td><td>Grade</td><td>Platelets (x10^9/L)</td><td>fluorouracil</td></tr>
<tr><td rowspan="4">▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times.
▪ If platelets greater than or equal to 75 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s).
▪ If platelets remain less than 75 after 2 weeks, discontinue treatment.</td><td>1</td><td>greater than or equal to 75</td><td>Maintain dose level</td></tr>
<tr><td>2</td><td>50 to less than 75</td><td>Maintain dose level</td></tr>
<tr><td>3</td><td>10 to less than 50</td><td>Maintain dose level</td></tr>
<tr><td>4</td><td>less than 10</td><td>Maintain dose level</td></tr>
</table>

B. Dose Modifications for NON-HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	**Diarrhea**	**fluorouracil**
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks of treatment delay, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level
	Grade	**Stomatitis**	**fluorouracil**
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 2 dose levels

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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.
3. **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.
4. **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.
5. **Stomatitis**: Sucking ice chips may be considered for patients experiencing stomatitis. 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.
6. **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.
7. **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 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.

REFERENCES: