BC Cancer Protocol Summary for Palliative Chemotherapy of Metastatic Colorectal Cancer using Weekly Irinotecan

Protocol Code	*GIIRINALT*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

INDICATIONS:

- For patients with high risk features such as advanced age, prior pelvic irradiation, or impaired hepatic function, who may not tolerate the q3weekly irinotecan schedule of GIIR. The risk of diarrhea is the same as with GIIR, but the risk of severe neutropenia may be lower, as the dosage can be adjusted more accurately to the patient's demonstrated tolerance.

ELIGIBILITY:

Patients must have

- Metastatic colorectal cancer requiring palliative therapy in patients who may not tolerate the 3-weekly irinotecan (GIIR)

Patients should have:

- ECOG performance status 0 to 2 if age 18 to 75 years, or 0 to 1 if age greater than 75 years

Note: For other indications, or for more than 6 cycles, a BC Cancer Compassionate Access Program (CAP) request must be approved

EXCLUSIONS:

- Inadequate hepatic function (bilirubin greater than or equal to 35 micromol/L or ALT or alkaline phosphatase greater than or equal to 5 x ULN)
- Greater than 3 loose stools per day in patients without colostomy or ileostomy

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium
- Baseline if clinically indicated: CEA, CA19-9, GGT, ECG
- Prior to each treatment: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: CEA, CA19-9, alkaline phosphatase, albumin, GGT, sodium, potassium, ECG

PREMEDICATIONS:

- Antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
irinotecan	125 mg/m^2 weeks 1 to 4 of a 6 week cycle (Treatment on Days 1, 8, 15 and 22 – no treatment on Days 29 and 36 of a 42 day cycle)	IV in 500 mL D5W over 1 hour 30 min

- Treatments omitted for toxicity in weeks 1 to 4 can be given on week 5 or 6 of the same cycle (Maximum of 4 treatments in a 6 week period)

- Repeat every 42 days for 6 cycles unless disease progression or unacceptable toxicity. If the patient tolerates treatment uneventfully, consideration should be given to changing to the GIIR protocol
- Discontinue if no clinical benefit after 2 cycles.
- All patients should be advised to obtain an adequate supply of Loperamide (IMODIUM®) with explicit instructions for the management of diarrhea.

DOSE MODIFICATIONS:

Note that there are two different dose adjustment schedules to be considered.
Note re-escalation of the dose following a dose reduction is at the discretion of the physician, irrespective of whether the dose reduction occurred within a cycle or at the beginning of a new cycle.

PRIOR TO A NEW CYCLE

Doses modifications are based upon clinical assessment and lab results on the scheduled Day 1 of treatment and upon maximum toxicity encountered in the previous cycle.

1. Hematological

If ANC less than 1.5 (x10^9/L) or platelets less than 75 (x10^9/L) at start of a cycle, hold treatment and check blood count weekly, then treat with dose reduction based on the Day 1 toxicity.

If ANC less than 1.5 (x10^9/L) or platelets less than 75 (x10^9/L), 2 weeks after a new cycle should begin, discontinue therapy.

Grade	ANC (x10^9/L)		Platelets (x10^9/L)	Dose
1	Greater than or equal to 1.5	and	Greater than or equal to 75	100%
2	1.0 to less than 1.5	or	50 to less than 75	100%
3	0.5 to less than 1.0	or	25 to less than 50	Decrease 25 mg/m^2 from the Day 1 dose used in the previous cycle
4	Less than 0.5	or	Less than 25	Decrease 50 mg/m^2 from the Day 1 dose used in the previous cycle

2. **Neutropenic Fever**:
Once resolved, decrease 50 mg/m^2 from the Day 1 dose used in the previous cycle.

3. **Diarrhea**

Once resolved to Grade 1, proceed with dose reduction based on the Day 1 toxicity.

Grade	Diarrhea	Dose
1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	100%
2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	100% if the only Grade 2 toxicity
3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Decrease 25 mg/m^2 from the Day 1 dose of the previous cycle if the only Grade 3 toxicity
4	Increase of 10 or more stools/day or grossly bloody diarrhea or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Decrease 50 mg/m^2 from the Day 1 dose of the previous cycle

DURING A CYCLE OF THERAPY

1. If multiple toxicities are seen, the dose administered should be based on the most severe toxicity experienced. Dose is calculated based on last dose received. If not recovered after 2 weeks, consider discontinuing treatment.

2. **Hematological**

Grade	ANC (x10^9/L)		Platelets (x10^9/L)	Dose
1	Greater than or equal to 1.5	and	Greater than or equal to 75	100%
2	1.0 to less than 1.5	or	50 to less than 75	Decrease dose by 25 mg/m^2 from the last dose received
3	0.5 to less than 1.0	or	25 to less than 50	Omit dose, then decrease 25 mg/m^2 from the last dose received when resolved to at least Grade 2
4	Less than 0.5	or	Less than 25	Omit dose, then decrease by 50 mg/m^2 from the last dose received when resolved to at least Grade 2

3. **Neutropenic Fever**:

Omit dose, then decrease 50 mg/m^2 from the last dose received when resolved.

4. **Diarrhea**

Grade	Diarrhea	Dose
1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	100%
2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Decrease dose 25 mg/m^2 from the last dose received
3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Omit dose, then decrease 25 mg/m^2 from the last dose received when resolved to at least Grade 2
4	Increase of 10 or more stools/day or grossly bloody diarrhea or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	Omit dose, then decrease 50 mg/m^2 from the last dose received when resolved to at least Grade 2

PRECAUTIONS:

1. **Diarrhea** may be life-threatening and requires prompt, aggressive treatment.
   - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
   - **Late diarrhea** has a median onset of 5 days post-treatment with this regimen and must be treated with **loperamide** (eg, IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
     - **4 mg stat**
     - **then 2 mg every 2 hours until diarrhea-free for 12 hours**
     - may take 4 mg every 4 hours at night
2. **Other cholinergic symptoms** may occur during or shortly after infusion of irinotecan, including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Gilbert's Syndrome** increases the risk of irinotecan-induced toxicity (Ann Oncol 1997;8:1049-51). A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
5. **Hepatic Dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or AST greater than 3x the upper limit of normal if no liver metastases, or AST greater than 5x the upper limit of normal with liver metastases.
6. **Pulmonary Toxicity:** Severe pulmonary toxicity has been reported rarely. Supportive care is required.
7. **Prior pelvic radiation** or radiation to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.

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. Conti JA, Kemeny NE, Saltz LB, et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 1996; 14: 709-15.