

BC Cancer Protocol Summary for Curative Combined Modality Therapy for Carcinoma of the Anal Canal using CISplatin, Infusional Fluorouracil and Radiation Therapy

Protocol Code

GIFUPART

Tumour Group

Gastrointestinal

Contact Physician

GI Systemic Therapy

ELIGIBILITY:

Patients should have:

- Squamous cell or cloacogenic carcinoma of the anal canal (T any, N any, M0)
- Increased risk of hematologic toxicity from mitomycin C

Patients should have:

- ECOG less than or equal to 2

EXCLUSIONS:

Patients must have:

- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Uncontrolled HIV infection

CAUTIONS:

- Adequate marrow reserve, renal and liver function

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, DPYD test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline if clinically indicated: CEA, CA19-9, SCC, GGT, ECG
- Weekly during treatment: CBC & Diff, creatinine
- Weekly if clinically indicated: total bilirubin, ALT
- If clinically indicated: CEA, CA19-9, SCC, alkaline phosphatase, GGT, albumin, sodium, potassium, ECG
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Drug	Dose/m ²	BC Cancer Administration Guideline
CISplatin	60 mg/m ² on Day 1 Week 1 & Week 5	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
fluorouracil	1000 mg/m ² /day for 4 days (Days 1 to 4 on Weeks 1 and 5) (total dose = 4000 mg/m ² over 96 h)	IV in D5W to a total volume of 480 mL by continuous infusion at 5 mL/h via appropriate infusor device*

*Inpatients: 1000 mg/m²/day in 1000 mL D5W by continuous infusion daily over 24 h for 4 days

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

Week	1	2	3	4	5	6
Radiation therapy**	X	X	X	X	X	1/2
Infusional fluorouracil	X Days 1-4				X Days 1-4	
CISplatin	X Day 1				X Day 1	

** Radiotherapy: 50.4Gy in 28 fractions (over 5 ½ weeks, no gap)

DOSE MODIFICATIONS:**Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)**

Refer to “Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)” on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

1. Hematological

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than 100	100%
1.0 to less than 1.5	or	75 to 100	75%
Less than 1.0	or	Less than 75	Delay

2. Non-Hematologic Toxicities:

Prior to administration of chemotherapy, inform the physician if any signs of stomatitis, hand-foot skin reaction and/or diarrhea (Grade 1 to 4) are present.

Toxicity Criteria

Grade	Diarrhea	Stomatitis	Palmar-plantar erythrodysesthesia
0 to 1	Increase of 2 to 3 stools/day or nocturnal stools	Painless ulcers, erythema or mild soreness	Skin changes with discomfort (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting normal activities
2	Increase of 4 to 6 stools/day or nocturnal stools	Painful erythema, edema or ulcers but can eat	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	Painful erythema, edema or ulcers and cannot eat	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	Mucosal necrosis, requires parenteral support	--

Toxicity	Action
Stomatitis Grades 2 to 4	Hold fluorouracil until symptoms resolved to grade 0 to 1. Resume at the same dose for Grade 2 stomatitis, at 75% dose for Grade 3 stomatitis, or at 50% dose for Grade 4 stomatitis. Consider discontinuing infusion if symptoms are not resolved to grade 0 to 1 after 3 weeks of holding.
Diarrhea Grades 3 to 4	Hold fluorouracil until resolved to Grade 0 to 1. Notify the attending radiation oncologist (RO) and RO may hold radiation therapy until resolved to grade 0 to 1. Then resume at 25% dose, or lower at physician's discretion. Caution: if diarrhea persists or recurs, consider discontinuing the fluorouracil infusion and attempt to complete the radiation on schedule (at RO's discretion)
Palmar-plantar erythrodysesthesia (PPE) Grades 2 to 3	Hold fluorouracil until symptoms resolved to grade 0 to 1, then resume at 75% dose for Grade 2 PPE, or at 50% dose for Grade 3 PPE

If multiple toxicities are present, the dose administered is based on the most severe toxicity experienced. Continue at the same dose for grade 1 to 2 toxicities. However, for grade 3 to 4 toxicities, dose reduction is at physician's discretion. Viral infection, alopecia, fatigue, anorexia and nausea/vomiting controlled by antiemetics require no dose modification. All other non-hematologic toxicities are managed in the same manner as diarrhea. Dose reductions continue for remaining cycles.

3. Renal dysfunction

Calculated creatinine clearance (mL/minute) by Cockcroft/Gault formula	CISplatin dose
Greater than or equal to 60	100%
45 to 59	75%
Less than 45	Hold CISplatin or delay with additional IV fluids

Cockcroft/Gault formula :

$$\text{Estimated creatinine clearance: (mL/minute)} = \frac{N (140 - \text{age}) \text{ wt (kg)}}{\text{Serum creatinine (micromol/L)}}$$

N = 1.23 male

N = 1.04 female

4. **Hepatic dysfunction:** Omit fluorouracil if total bilirubin greater than 85 micromol/L unless secondary to biliary obstruction (BC Cancer Drug Manual).

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Nausea and vomiting** are common and patients should be treated with ondansetron and dexamethasone before each dose of CISplatin (see premedication section)
3. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
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 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.
6. **CNS toxicity** such as tinnitus, mild high frequency hearing loss and delayed peripheral neuropathy may occur secondary to CISplatin.
7. **Nutrition:** It is important to maintain weight if possible and early consultation with a dietitian to advise about aggressive oral nutritional support and/or an enteral feeding tube is recommended.
8. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity to fluorouracil-stomatitis, diarrhea, neutropenia, neurotoxicity-secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.
9. **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.

10. **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 Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

REFERENCES:

1. Vuong, Te et al. Conformal Therapy Improves the Therapeutic Index of Patients with Anal Canal Cancer Treated with Combined Chemotherapy and External Beam Radiotherapy. *Int J Radiation Oncology Biol Phys* 2007;67(5):1394-1400.
2. James, R et al. ACT II: The second UK Phase III Anal Cancer Trial. A Randomised Trial of Chemoradiation using Mitomycin or Cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus. ASCO Abstract 30894, May 2009.