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:
- Squamous cell or Cloacogenic carcinoma of the anal canal
- T any, N any, M0
- At increased risk of hematologic toxicity from Mitomycin C, including known HIV infection
- ECOG performance status less than or equal to 2

EXCLUSIONS:
- 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

CAUTIONS:
- Adequate marrow reserve, renal and liver function

TESTS:
- Baseline: CBC, diff and platelets, creatinine, serum albumin, bilirubin, ALT, alkaline phosphatase. Optional: CEA, SCC
- During chemotherapy treatment: CBC, diff and platelets, creatinine, sodium, potassium before chemotherapy Weeks 1 and 5
- During radiation therapy: CBC, Diff and platelets weekly
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:
Treatment is high to moderately emetogenic. See SCNAUSEA protocol.

Activated: 1 Feb 2009 Revised: 1 Oct 2021 (ST chair name, contact information and Eligibility updated. Moved cautions from Eligibility to separate heading “Cautions”.)
Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/legal.htm

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, 1g magnesium sulfate, 30 g mannitol over 1 hour
fluorouracil	1000 mg/m^2/day for 4 days (Days 1-4 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/m^2/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:

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. **Renal dysfunction**

Calculated Cr Clearance (mL/min) 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 :

Estimated creatinine clearance: (mL/min) = N (140-age) wt (kg) / Serum creatinine (micromol/L)

N = 1.23 male
N = 1.04 female

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

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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 nutritionist 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.

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