Regimen Monograph

A - Regimen Name

FU(CIV-RT) Regimen

Fluorouracil

Disease Site

Gastrointestinal
Colorectal

Intent

Neoadjuvant
Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

Concurrent with radiation, for neoadjuvant treatment of stage II or III rectal cancer, or in the palliative setting. The addition of chemotherapy to radiation improves local control rates ± survival. Neoadjuvant / preoperative treatment appears to be better tolerated and superior to post-operative chemotherapy in terms of local control.

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B - Drug Regimen

fluorouracil	225 mg /m²/day	IV over 24 hours as continuous infusion	Concurrently with radiotherapy

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C - Cycle Frequency

During entire course of radiotherapy

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Toxicity or Counts (x10^9/L)	**During Cycle**	**For Next cycle**
Platelets < 80 or ANC < 1.5	Hold*	May consider ↓
Bleeding, febrile neutropenia	Hold*	↓ by 25%
≥ grade 3 GI	Hold*	↓ by 25%
CNS	Hold*	↓ by 25%
Cardiac	Hold*	Consider discontinuing
* Do not retreat until AGC ≥ 1.5 x 10^9/L , platelets ≥ 100 x 10^9/L and organ toxicity ≤ grade 2. With severe toxicity, consider testing for DPD deficiency prior to rechallenge.		

Hepatic Impairment

Suggested example:

Bilirubin		**AST/ALT**	**Fluorouracil (% previous dose)**
< 2 x ULN	and	3-5 x ULN	75 %
2-4 x ULN	or	5-10 x ULN	50-75%
≥ 4 x ULN	or	≥ 10 x ULN	Discontinue

Renal Impairment

No adjustment required, although reduction may be considered with severe renal insufficiency.

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F - Adverse Effects

Refer to fluorouracil drug monograph(s) for additional details of adverse effects

Prolonged 5FU infusion regimens have more Hand-Foot Syndrome and less myelosuppression and GI effects, compared to bolus regimens.

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection, bleeding • Hand-foot syndrome • Stomatitis • Diarrhea • Anorexia • Photosensitivity • Rash	• Cardiotoxicity • Arterial thromboembolism • Venous thromboembolism • Leukoencephalopathy • Optic neuritis • Hemolysis / hemolytic uremic syndrome • ↑ LFTs

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G - Interactions

Refer to fluorouracil drug monograph(s) for additional details

Fluorouracil is a known radiosensitizer. Patients should be carefully monitored for gastrointestinal toxicity when they are receiving concurrent 5FU-Radiation therapy

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H - Drug Administration and Special Precautions

Refer to fluorouracil drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and before each dose
- Liver function tests; baseline and as clinically indicated
- Clinical toxicity assessment and grading of stomatitis, diarrhea, bleeding, infection, local site toxicity, skin effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Renal function tests; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	22.05 minutes
Nursing Workload (average time per visit)	45 minutes

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K - References

Bosset JF, Collette L, Calais G, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-23.

Fluorouracil drug monograph, Cancer Care Ontario.

Gerard J, Bonnetain F, Conroy T, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. J Clin Oncol. 2006;24:4620-5.

O'Connell MJ, Martenson JA, Weiand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502-7.

Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Eng J Med 2004;351:1731-40.

Smalley SR, Benedetti J, Williamson S, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol 2006;24:3542-7.

Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980-7.

PEBC Advice Documents or Guidelines

- Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer

April 2023 Updated DPD deficiency information in the Dose Modifications section and fluorouracil antidote information in the Other Notes section.

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L - Other Notes

Schedule pump teaching session BEFORE the first day of infusion.

Antidote for Fluorouracil Overdose:

Uridine triacetate is a prodrug of uridine and is a specific antidote for treating fluorouracil overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies). Uridine triacetate (Vistogard®) is supplied by its manufacturer in the United States (Wellstat Therapeutics).

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

Additional resources on the management of fluorouracil infusion overdose:

- Management of Fluorouracil Infusion Overdose Guideline (Alberta Health Services)
- Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance (BC Cancer Agency)

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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