Regimen Monograph

A - Regimen Name

MFOLFOX6 Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Oxaliplatin

Disease Site	Gastrointestinal Colorectal (Rectal)
Intent	Neoadjuvant
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	Neoadjuvant treatment of locally advanced rectal cancer

back to top

B - Drug Regimen

oxaliplatin	85 mg /m²	IV over 2 hours	Day 1
leucovorin	400 mg /m²	IV over 2 hours (concurrently with oxaliplatin)	Day 1
fluorouracil	400 mg /m²	IV bolus, after leucovorin	Day 1
THEN			
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours (single dose)	Start on Day 1

back to top

C - Cycle Frequency

REPEAT EVERY 14 DAYS

For a usual total of **up to 8 cycles** unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Febrile Neutropenia Risk: Moderate

Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Avoid mucositis prophylaxis with ice chip as cold temperatures can precipitate or exacerbate acute neurological symptoms of oxaliplatin.

Oxaliplatin premedication (prophylaxis for infusion reactions):

- There is insufficient evidence that routine prophylaxis with pre-medications reduces IR rates.
- Consider corticosteroids and H1-receptor antagonists ± H2-receptor antagonists in high-risk patients (i.e. ≥ cycle 6, younger age, female gender, prior platinum exposure, platinum-free interval ≥ 3 years).

back to top

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

No dose adjustments required for leucovorin. Leucovorin should be omitted if fluorouracil is omitted.

Neurotoxicity was graded based on the following scales in some adjuvant colorectal cancer trials.

Neurotoxicity Grade	Description
1	No change or none
2	Mild paresthesias, loss of deep tendon reflexes
3	Mild or moderate objective sensory loss, moderate paresthesias
4	Severe objective sensory loss or paresthesias that interfere with function

Dose Modifications:

Toxicity Grade	Oxaliplatin^	Fluorouracil^
Persistent(1) Grade 2 Neurotoxicity	↓ to 75 mg/m^2	No change
Transient(1) Grade 3 Neurotoxicity	↓ to 75 mg/m^2	No change
Persistent(1) Grade 3 Neurotoxicity or any Grade 4 Neurotoxicity	Discontinue	No change
≥ Grade 3 GI toxicity (after prophylaxis) OR ≥ Grade 3 Platelets OR ≥ Grade 3 Neutropenia (including febrile neutropenia)	↓ to 75 mg/m^2	Reduce by 20%
Sepsis / septic shock	Discontinue	Discontinue
Other ≥ grade 3 related organ toxicity(2)	Consider ↓ to 75 mg/m^2	Reduce by 20%
Pharyngolaryngeal dysesthesia	Hold; then increase duration of infusion to 6 hours(3)	No change
Pneumonitis	Hold, investigate; discontinue permanently if confirmed.	
Anaphylactic-like reaction	Discontinue permanently	
PRES/RPLS		
Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia		
Disseminated intravascular coagulation (DIC)		
QT prolongation		

Intestinal ischemia or duodenal ulcer	
Symptoms of rhabdomyolysis	

^Do not re-treat until the ANC ≥ 1.5 x 10^9/L and the platelets ≥ 75-100 x 10^9/L, GI and neurotoxicities have resolved and other non-hematologic toxicities ≤ grade 1.

[1] Transient = >7days-<1 cycle; persistent = ≥ 1 cycle

[2] For skin toxicity, reduce 5FU dose only

[3] If oxygen saturation is normal, an anxiolytic agent may be given.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Oxaliplatin:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.

* Up to 50% of patients can experience recurrent reactions during re-challenge despite using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist).

Hepatic Impairment

Bilirubin		**AST/ALT**	**oxaliplatin (% previous dose)**	**fluorouracil (% previous dose)**	**leucovorin (% previous dose**)
1-2 x ULN			No adjustment required	Caution	No change
>2-4 x ULN	And/or	2-4 x ULN	No adjustment required	Caution	No change
>4 x ULN	And/or	4 x ULN	No data available	OMIT if Bilirubin > 4 x ULN	OMIT if 5FU omitted
ANY	Or	> 4 X ULN	No data available	OMIT if Bilirubin > 4 x ULN	OMIT if 5FU omitted

Renal Impairment

Creatinine Clearance (mL/min)	**oxaliplatin (% previous dose)**	**fluorouracil (% previous dose)**	**leucovorin (% previous dose)**
≥50	No adjustment needed	No change	No change
30 to <50	Caution	No change; monitor	No change
<30	Discontinue	Consider dose ↓	No change

Dosage in the Elderly

Patients ≥ 65 years had a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments were needed but caution should be exercised.

back to top

F - Adverse Effects

Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Sensory neuropathy (may be severe, including cranial) • Myelosuppression ± infection, bleeding • Nausea, vomiting • ECG changes (mostly asymptomatic) • ↑ LFTs • Diarrhea (may be severe)	• Fatigue • Mucositis (may be severe) • Pharyngolaryngeal dysesthesia • Alopecia (mostly mild)	• Anorexia, weight changes • Abdominal pain • Constipation • Edema • Hyperglycemia • Musculoskeletal pain • Rash, Hand-foot syndrome • Dysgeusia • Injection site reaction • Abnormal electrolyte(s) • Hypersensitivity	• Venous / arterial thromboembolism • QT prolongation, arrhythmia • Cardiotoxicity • Guillain-Barre syndrome • Optic neuritis • Extrapyramidal or cortical dysfunction, acute cerebellar syndrome • RPLS / PRES • Leukoencephalopathy • Nephrotoxicity • Pneumonitis • INR / prothrombin time increased • Disseminated intravascular coagulation • Hemolysis • Hemolytic uremic syndrome • Idiopathic thrombocytopenic purpura • Photosensitivity • Radiation recall reaction • GI obstruction / perforation / ulcer / ischemia • Pancreatitis

			• Veno-occlusive disease • Rhabdomyolysis • Hearing impaired • Eye disorders

back to top

G - Interactions

Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details.

- Use of fluorouracil within 4 weeks of treatment with brivudine, sorivudine (and chemically related analogues) is contraindicated.
- Thiazide diuretics may decrease renal excretion of fluorouracil; consider an alternative antihypertensive.
- Avoid concomitant use of metronidazole and fluorouracil if possible.
- Monitor INR closely while on concomitant warfarin and fluorouracil or oxaliplatin; adjust warfarin dose accordingly.
- Monitor phenytoin levels if used concurrently with fluorouracil.
- Monitor for toxicity when using oxaliplatin with other nephrotoxic drugs, QT -prolonging drugs or drugs associated with rhabdomyolysis.
- Caution with the concurrent use of cimetidine due to interference with fluorouracil metabolism; fatal cases have been reported.

back to top

H - Drug Administration and Special Precautions

Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details.

Administration

Oxaliplatin:

- Oxaliplatin is administered by intravenous infusion.
- Oxaliplatin should always be administered before fluorouracil.
- May be mixed in 250-500 mL bag of D5W only. **Do not** mix with NS, chloride containing or alkaline solutions, or with fluorouracil.
- Administer by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Do not mix oxaliplatin with other drugs in the same infusion bag or infusion line.
- Infusion may be given at the same time as leucovorin in separate D5W bags using a Y-site, providing trometamol is not used as an excipient. Do not administer concurrently with fluorouracil.
- If another drug is given before oxaliplatin, flush infusion line with D5W before giving oxaliplatin. Flush the line with D5W after oxaliplatin before giving a subsequent drug (e.g. fluorouracil).
- The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

Leucovorin:

- Leucovorin may be diluted in 250mL D5W if given concurrently with oxaliplatin (over 2 hours) using Y-site administration.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

Fluorouracil bolus:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse IV over 15 minutes.
- Store unopened vials at room temperature (15-25ºC). Protect from light.

Fluorouracil IV continuous infusion:

- Refer to local guidelines on preparation of fluorouracil IV infusion.
- Continuous infusion via central line or PICC using CADD infusion pump, infusor bottle or similar device.
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents.
- Store unopened vials at room temperature (15 to 25ºC). Protect from light.

Refer to **Section L - Other Notes** section for Information on the **Antidote for Fluorouracil Overdose**.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- patients with poor nutritional state
- patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration)
- patients with potentially serious infections
- patients with known hypersensitivity to the drug, other platinum agents (e.g. cisplatin, carboplatin), or any of their excipients
- patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity, with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- severe renal impairment (CrCl < 30 mL/min), with oxaliplatin
- fluorouracil should not be used within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues.

Warnings/Precautions:

- Oxaliplatin may result in dizziness or visual disturbances (including transient vision loss) in some patients; patients should exercise caution in driving or operating machinery.
- Use fluorouracil with extreme caution in patients who:
  - have undergone recent major surgery,
  - have renal or hepatic impairment,
  - have widespread bone marrow involvement,
  - have previous use of other myelosuppressive chemotherapeutic agents,
  - have a history of high dose irradiation to bone marrow-bearing areas,
  - have a history of heart disease,
  - or are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Avoid the use of live vaccines.

Pregnancy and Lactation:

- This regimen is **contraindicated** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is **contraindicated** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Yes

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Electrolytes, including magnesium; baseline and before each cycle
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- INR, if patient on anticoagulants; baseline and as clinically indicated
- Clinical assessment of GI effects, neurotoxicity, infection, bleeding, stomatitis, diarrhea, skin effects, thromboembolism, hypersensitivity, local reactions, respiratory, cardiovascular or ophthalmic effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose, especially in patients with diabetes; Baseline and regularly

back to top

J - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	38.381 minutes
Nursing Workload (average time per visit)	69.167 minutes

back to top

K - References

Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol 2018 Jun 14;4(6):e180071. doi: 10.1001/jamaoncol.2018.0071.

Deng Y, Chi P, Lan P, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. J Clin Oncol 2019 Dec 1;37(34):3223-33.

Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery, and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. Annal of Oncol 2015. 26:1722-8.

Oxaliplatin, fluorouracil and leucovorin drug monographs, Ontario Health (Cancer Care Ontario).

November 2023 Modified Pregnancy/lactation section

back to top

L - Other Notes

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)

back to top

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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back to top