Regimen Monograph

A - Regimen Name

FLOX Regimen

Fluorouracil-Leucovorin-Oxaliplatin

Disease Site

Gastrointestinal
- Colorectal
- Small bowel and appendix

Intent

Adjuvant

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

Adjuvant treatment of stage III and high risk stage II colorectal cancer

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B - Drug Regimen

oxaliplatin[1]	85 mg /m²	IV in 500mL D5W over 120 minutes	Days 1, 15 and 29
leucovorin[1]	500 mg /m²	IV diluted in D5W over 120 minutes (after oxaliplatin infusion on days 1, 15, and 29)	Days 1, 8, 15, 22, 29 and 36
fluorouracil	500 mg /m²	IV as bolus, 1 hour after leucovorin infusion has begun	Days 1, 8, 15, 22, 29, 36

[1] Oxaliplatin and leucovorin were not given concurrently in the trial.

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C - Cycle Frequency

REPEAT EVERY 56 DAYS
For a maximum total of 3 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate (Days 1, 15, 29)
Low (Days 8, 22, 36)

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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

No dose adjustments required for leucovorin.

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

Neurotoxicity Grade	Adjuvant
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	↓ from 85 → 75 mg/m^2	No change
Transient(1) Grade 3 Neurotoxicity	↓ from 85 → 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 or 4 Platelets OR Grade 3 or 4 Neutropenia (including febrile neutropenia)*	↓ from 85 → 75 mg/m^2 *	Reduce by 20% *

Sepsis / septic shock	Discontinue	Discontinue[4]
Other ≥ grade 3 related organ toxicity[(2)]	↓ from 85 → 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[4]	
PRES or hemolytic uremic anemia or any signs of microangiopathic hemolytic anemia	Discontinue permanently[4]	

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

[1] Transient = 7-14 days; persistent = ≥ 14 days

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

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

[4] Do not give leucovorin if fluorouracil is omitted.

* Discontinue if septic shock.

Hepatic Impairment

Bilirubin		**AST/ALT**	**oxaliplatin (% previous dose)**	**fluorouracil (% previous dose)**	**leucovorin (% previous dose)**
1-2 x ULN			No change	Caution	No change
>2-4 x ULN	And/or	2-4 x ULN	No change	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 (% prevoius dose)	leucovorin (% prevoius dose)
50 - 80	No change	No change	No change
30 - <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.

Dosage based on gender:

Women may be at higher risk of severe (grades 3-4) neutropenia in adjuvant treatment of colorectal cancer.

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Neuropathy (may be severe) • Nausea, vomiting • ↑ LFTs (may be severe) • Diarrhea (may be severe) • Fatigue • Mucositis • Abdominal pain • Myelosuppression ± infection, bleeding (may be severe)	• Arterial thromboembolism • Venous thromboembolism • Hypersensitivity • Cardiotoxicity, arrhythmia • Hemolytic uremic syndrome • Nephrotoxicity • Pancreatitis • Pneumonitis • Rhabdomyolysis

• Rash, photosensitivity • Hand-foot syndrome • Pharyngolaryngeal dysesthesia • Edema • Alopecia • Anorexia • Constipation (diarrhea more common) • Electrolyte abnormalities • Injection site reaction • Hypersensitivity	• PRES • Obstruction • Hemolysis • ↑ LFTS • Leucoencephalopathy

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G - Interactions

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

- Avoid concomitant use of drugs affecting hepatic metabolism (i.e. cimetidine) due to increased serum concentrations and toxicity of fluorouracil
- Avoid metronidazole use as it may decrease the clearance of fluorouracil
- Fluorouracil may increase phenytoin levels and toxicity; monitor levels and patient
- Avoid thiazide diuretics as they may decrease renal excretion of fluorouracil
- Warfarin clearance may be reduced. Monitor INR closely and adjust warfarin dose as necessary

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H - Drug Administration and Special Precautions

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

Drug Administration

Oxaliplatin:

- Oxaliplatin should always be administered before fluorouracil.
- May be mixed in 250-500 mL bag (D5W only - not NS, chloride containing or alkaline solutions, and should not be mixed with fluorouracil) and given 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 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 should be given prior to fluorouracil
- Dilute in D5W and infuse IV over 120 minutes

Fluorouracil:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse over 15 min.
- Protect from light

Contraindications

- Severe myelosuppression induced by prior chemotherapy or radiotherapy
- Patients with poor nutritional state
- Patients with potentially serious infections
- Oxaliplatin is contraindicated in patients with hypersensitivity to the drug or to other platinum agents (e.g. cisplatin, carboplatin) and in patients with severe renal impairment (Clcr < 30 mL/min).
- Fluorouracil is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.

Other Warnings/Precautions

- Patients should be warned about cold avoidance prior to treatment and ice for mucositis prophylaxis should not be used.
- Oxaliplatin may result in dizziness or visual disturbrances (including transient vision loss) in some patients; patients should exercise caution in driving or operating machinery.
- Use with extreme caution in patients who have undergone recent major surgery, with renal or hepatic impairment, widespread bone marrow involvement, or are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Avoid live vaccines; use may result in serious infections in immunocompromised patients.

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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.

Recommended Clinical Monitoring

- CBC; baseline and before each treatment
- Electrolytes, including magnesium; baseline and before each cycle
- INR, if patient on anticoagulants; as clinically indicated
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- Clinical assessment of GI effects, neurotoxicity, infection, bleeding, stomatitis, diarrhea, skin effects, thromboembolism, hypersensitivity, local reactions, respiratory or ophthalmic effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	Days 1, 15, 29: 4.5 hours; Days 8, 22, 36: 2.5 hours
Pharmacy Workload (average time per visit)	22.062 minutes
Nursing Workload (average time per visit)	47.917 minutes

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K - References

Fluorouracil, oxaliplatin, leucovorin drug monographs, Cancer Care Ontario.

Kuebler JP, Wieand S, O'Connel MJ et al. Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07. JCO 25(16) June 2007: 2198-2204.

PEBC Advice Documents or Guidelines

- Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection
- 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 and Special Precautions sections and fluorouracil antidote information in the Other Notes section.

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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)

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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.

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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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