Regimen Monograph

A - Regimen Name

MFOLFIRINOX Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan-Oxaliplatin

Disease Site	Gastrointestinal Pancreas
Intent	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	Treatment of locally advanced unresectable or metastatic pancreatic adenocarcinoma in patients with good performance status

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B - Drug Regimen

oxaliplatin	85 mg /m²	IV over 2 hours	Day 1
THEN,			
leucovorin	400 mg /m²	IV over 2 hours	Day 1
30 minutes after starting leucovorin, give:			
irinotecan	150 mg /m²	IV over 90 minutes, concurrently with leucovorin	Day 1
Then,			
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours (single dose)	Start on Day 1

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Continue until disease progression or unacceptable toxicity; in the clinical trial 12 cycles were recommended for responding patients, while the median number of cycles was 10 (range 1-47).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- For irinotecan cholinergic adverse effects (early diarrhea):
  - Unless contraindicated, atropine 0.25-1mg IV/SC may be given
  - Prophylactic atropine may be considered in patients who have experienced cholinergic symptoms
- Loperamide must be provided. Diarrhea (including abdominal cramps) may be severe and delayed with irinotecan.
- Give loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours. During the night the patient may take 4mg of loperamide every 4 hours.
- May consider GCSF as secondary prophylaxis for neutropenia (Conroy et al, 2011).
- May consider antibiotics for patients with ileus, fever or febrile neutropenia.
- Avoid mucositis prophylaxis with ice chips as cold temperatures can precipitate or exacerbate acute neurological symptoms of oxaliplatin.

Premedication for oxaliplatin (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).

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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

Do not start new cycle until platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L, recovery from diarrhea (to baseline without loperamide for at least 24 hours), and other non-hematologic toxicities have recovered to ≤grade 2.

Doses should be adjusted based on the worst preceding toxicity. Do not re-escalate dose if reduced for toxicity.

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

Dose Levels:

Drug	**Dose level 0 (mg/m^2)**	**Dose level -1* (mg/m^2)**
Irinotecan	150	120
Oxaliplatin	85	60
Fluorouracil infusion	2400	1800

* If further dose reduction is required, consider a 20% dose reduction or discontinuing the regimen.

Dose Modifications:

Toxicity	**Occurrence**	**Irinotecan dose[a,b]**	**Oxaliplatin dose[a,b]**	**Fluorouracil dose[a,b]**
Febrile neutropenia OR Grade 4 ANC > 7 d OR Delay 1-2 weeks for ≥ Grade 2 ANC	1st	↓ 1 dose level	No change	No change
	2nd	Maintain same dose level	↓ 1 dose level	
	3rd	Discontinue		

	≥ grade 3 platelets OR Delay 1-2 weeks for platelets <100 x 10^9/L	1st	No change	↓ 1 dose level	no change	
		2nd	↓ 1 dose level	Maintain same dose level	↓ 1 dose level	
		3rd	Discontinue			
	Diarrhea ≥ grade 3 OR Diarrhea with fever or ≥ Grade 3 ANC	1st	↓ 1 dose level	No change	No change	
		2nd	Maintain same dose level	↓ 1 dose level	↓ 1 dose level	
		3rd	Discontinue			
	Grade 3 or 4 mucositis or hand-foot syndrome	-	No change	No change	↓ 1 dose level	
	Grade 2 persistent neurotoxicity	-	No change	↓ 1 dose level	No change	
	Grade 3 neurotoxicity (recovers prior to next cycle)	-	No change	↓ 1 dose level	No change	
	Grade 3 persistent neurotoxicity OR Grade 4 neurotoxicity	Any	No change	Discontinue	No change	
	Grade 2 other non-hematological	-	Consider ↓	Consider ↓	Consider ↓	
	Grade 3 other non-hematological	-	↓ 1 dose level	↓ 1 dose level	↓ 1 dose level	
	Pneumonitis	Any	Discontinue	Discontinue	Discontinue	
	Grade 4 other non-hematological OR RPLS OR Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia	Any	Discontinue	Discontinue	Discontinue	

Pharyngolaryngeal dysesthesia	Any	-	↑ infusion to 6 hours	-

[a] Do not treat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, diarrhea resolved to baseline and other toxicity ≤ grade 2. Do not re-escalate dose if reduced for toxicity.
[b] Consider discontinuing if cycle delayed for > 2 weeks.

Management of Oxaliplatin Infusion-Related Reactions:

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

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

Transaminases		Bilirubin^	Irinotecan dose	Oxaliplatin dose	5FU dose
		1 to 1.5 x ULN or Gilbert's	Consider ↓	No change	No change
> 3 to 5 X ULN*	and/or	>1.5 to 4 X ULN	Omit	No change	Consider ↓ (e.g. 75% of previous dose)
>5 to 10 X ULN	and/or	>1.5 to 4 X ULN	Omit	No change	Consider ↓ (e.g. 50-75% of previous dose)
> 10 X ULN	and/or	> 4 X ULN	Omit	No info found	Omit
* or >5 X ULN with liver metastases					

^ If bilirubin ↑, consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent.

Renal Impairment

Creatinine Clearance (mL/min)	oxaliplatin (% previous dose)	fluorouracil (% previous dose)	irinotecan (% previous dose)
≥50	No change	No change	No change
30 to <50	Caution	No change	No change
<30	Discontinue	Consider dose reduction	Caution

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F - Adverse Effects

Refer to oxaliplatin, leucovorin, irinotecan, 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 • Myelosuppression ± infection, bleeding (may be severe) • Nausea/ vomiting • Fatigue • Alopecia • ↑ Bilirubin/ LFTs • Diarrhea (early 51%; late 88%; may be severe) • Anorexia, weight loss	• Mucositis • Pharyngolaryngeal dysesthesia • Constipation • Cholinergic symptoms • Conjunctivitis/tearing	• Cough/ dyspnea • Rash/dry skin/ photosensitivity • Anorexia • Insomnia • Headache • Dizziness • Edema • Rhinitis • Musculoskeletal pain • Hyperglycemia • Hand-foot syndrome • Flushing • Dyspepsia • Dysgeusia • Abnormal electrolytes (↓Ca, K, Na) • Injection site reaction • Hypersensitivity	• Cardiotoxicity • Arrhythmia/QT prolongation • Arterial/venous thromboembolism • DIC • ITP • Hypotension • Radiation recall reaction • GI ulceration/ ischemia/ obstruction/ perforation • Hemolysis • Hemolytic uremic syndrome • Hepatic necrosis • VOD • Pancreatitis • Acute cerebellar syndrome • Rhabdomyolysis • Guillain-Barre syndrome • Extrapyramidal disorder • Leukoencephalopathy • RPLS/PRES • Optic neuritis • Seizure • Renal failure • Pneumonitis • Hearing impairment

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G - Interactions

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

- Use of fluorouracil within 4 weeks of treatment with brivudine, sorivudine (and chemically related analogues) is **contraindicated**.
- Azole antifungals are **contraindicated** with irinotecan (discontinue one week before the first dose of irinotecan).
- Avoid concomitant use of metronidazole and fluorouracil if possible.
- Avoid concomitant use of strong CYP3A4 inhibitors and inducers with irinotecan.
- Avoid concomitant use of prochlorperazine (on same day of irinotecan treatment), turmeric and azatanavir with irinotecan.
- Thiazide diuretics may decrease renal excretion of fluorouracil; consider an alternative antihypertensive.
- 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 oxaliplatin is used with other drugs that are nephrotoxic, prolong QT or are associated with rhabdomyolysis.
- Caution with the concurrent use of cimetidine due to interference with fluorouracil metabolism; fatal cases have been reported.

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H - Drug Administration and Special Precautions

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

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 oxaliplatin 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.
- 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.
- 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 250 mL D5W.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

Irinotecan:

- Mix in 500mL bag D5W in a concentration range between 0.12 to 3 mg/mL; infuse IV over 90 minutes
- Infusion may be given at the same time as leucovorin in separate D5W bags using a Y-site.
- Avoid freezing irinotecan and its admixtures since this may result in drug precipitation.
- Do not admix with other drugs.
- Protect from light.
- Prior to the initial irinotecan treatment, patients should be given a sufficient supply of loperamide and instructed on its appropriate use.

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 at room temperature (15 to 25ºC). Protect from light.

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

Contraindications:

- Hypersensitivity to the fluorouracil, irinotecan, leucovorin, oxaliplatin or to other platinum agents (e.g. cisplatin, carboplatin) or to any component of the formulation.
- Patients with severe renal impairment (CrCl < 30 mL/min), with oxaliplatin
- Patients with poor nutritional state
- Patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration)
- Patients with potentially serious infections
- Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity, with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Avoid in patients with hereditary fructose intolerance since the irinotecan formulation contains sorbitol.
- Avoid the use of live or live attenuated vaccines.
- Fluorouracil should not be used within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues. (See interactions section)
- Irinotecan should not be co-administered with azole antifungals (ketoconazole etc. See Interactions section)

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.

- Do not give oxaliplatin intraperitoneally.
- Irinotecan is not recommended for use in patients with ECOG performance status 3 or 4, or in patients with moderate or severe increases in bilirubin.
- Carefully monitor and consider irinotecan dose reduction for elderly patients, patients with poor performance status (= 2), limited marrow reserve, 3rd space accumulation, Gilbert's syndrome and patients with reduced UGT1A1 activity; they may be more susceptible to the toxic effects of irinotecan.
- Concurrent administration of irinotecan with irradiation is not recommended. Patients with prior pelvic or abdominal irradiation are at an increased risk of severe myelosuppression following irinotecan therapy.
- 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.

Pregnancy/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

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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.

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
- Liver and renal function tests; baseline and before each cycle
- Electrolytes, including magnesium; baseline and before each cycle
- INR for patients on warfarin; baseline and as clinically indicated
- Routine toxicity rating of diarrhea and other GI effects, fatigue, cholinergic symptoms, hypersensitivity, pneumonitis, bleeding, infection, dehydration, pancreatitis, neuropathy, thromboembolism, local reactions, skin (including rash, hand-foot syndrome), ophthalmic and cardiac toxicity.
- 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

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J - Administrative Information

Approximate Patient Visit	4 hours
Pharmacy Workload (average time per visit)	39.92 minutes
Nursing Workload (average time per visit)	69.17 minutes

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K - References

Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395-406.

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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.

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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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