Regimen Monograph

A - Regimen Name

FOLFIRI Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach
- Hepatobiliary / Liver / Bile Duct

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 advanced gastric cancer
- Treatment of metastatic cholangiocarcinoma

back to top

B - Drug Regimen

irinotecan	180 mg /m²	IV over 90 minutes	Day 1
leucovorin	400 mg /m²	IV over 120 minutes concurrently with irinotecan	Day 1
fluorouracil	400 mg /m²	IV bolus, after leucovorin	Day 1
THEN			
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours only	Start on Day 1

Irinotecan and leucovorin may be infused at the same time by using a y-connector, but not in the same bag, then fluorouracil.

back to top

C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until evidence of disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Irinotecan:

- Unless contraindicated, atropine 0.25-1mg IV/SC may be used for cholinergic adverse effects (early diarrhea)
- Diarrhea (abdominal cramp = diarrhea) may be severe and delayed with irinotecan; use loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours
- Patients with ileus, fever or febrile neutropenia should receive antibiotics.

5FU:

- May advise patients to suck on ice chips during bolus injection of 5FU, to reduce stomatitis

Also refer to CCO Antiemetic Summary

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

See general recommendations for hematologic toxicity.

FOLFIRI

Patients should not be re-treated with irinotecan until recovery (to baseline) from GI toxicity (without loperamide for at least 24 hours) has occurred, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L. All dose adjustments should be based on the worst preceding toxicity.

Patients with ileus, fever or febrile neutropenia should receive antibiotics.

Do not use in patients with ECOG PS of 3 or 4, nor in patients with moderate or severe increases in bilirubin.

Consider a reduction in the starting dose described below for elderly patients (≥ 70 years), patients with prior abdominal or pelvic irradiation, patients with a poor performance status (ECOG of 2), patients with mild increases in bilirubin (including Gilbert's syndrome), patients homozygous for UGT1A1*28 allele or patients with a history of myelosuppression with previous treatment.

Suggested Dose Levels:

Regimen	Drug	Starting dose (mg/m^2)	Dose level -1 (mg/m^2)	Dose Level -2 (mg/m^2)
FOLFIRI	Irinotecan	180	150	120
	Leucovorin infusion	400	No change	No change
	5-FU bolus	400	320	240
	5-FU infusion (start day 1 over 46h*)	2400	2000	1600

* This 5-FU dosing is not approved by Health Canada, but has been used in some phase III trials.

Dosage with Toxicity:

Dose Adjustments for Irinotecan in Combination with Fluorouracil:

Worst Toxicity Grade from Previous Cycle	At the start of subsequent cycles[1, 2] (FOLFIRI)
Hematologic	
Grade 1	No change
Grade 2	No change
Grade 3	reduce by 1 dose level
Grade 4 or febrile neutropenia	reduce by 2 dose levels
Diarrhea	
Grade 1: 2-3/day > pre-treatment	No change
Grade 2: 4-6/day > pre-treatment	No change

Grade 3: 7-9/day > pre-treatment	reduce by 1 dose level
Grade 4: ≥10/day > pre-treatment	reduce by 2 dose levels
Other Non-hematologic toxicities (excludes alopecia, anorexia and fatigue). For mucositis/stomatitis, decrease 5FU only.	
Grade 1	No change
Grade 2	Hold until ≤ grade 1, no change in dose
Grade 3	Hold until ≤ grade 2, reduce by 1 dose level
Grade 4	Hold until ≤ grade 2, reduce by 2 dose levels
[1] Relative to the starting dose used in the previous cycle. [2] Patients should not be retreated until GI toxicity resolved to baseline (without loperamide for at least 24 h), platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L. If no recovery after a 2-week delay, consider discontinuing treatment.	

Hepatic Impairment

No dose adjustment required for leucovorin. OMIT leucovorin if 5FU is omitted.

Transaminases	Bilirubin	Irinotecan	5FU
	1-1.5 X ULN or Gilbert's	Consider ↓	No change
> 3 X ULN*	2-4 X ULN	Omit	No change
	> 4 XULN	Omit	Omit
* or 5 X ULN with liver metastases; consider investigating for reversible causes such as biliary obstruction and reevaluate after stent			

Renal Impairment

No dose adjustment required for leucovorin.

Creatinine Clearance (mL/min)	Fluorouracil (% previous dose)	Irinotecan (% previous dose)
>60	No change	No change
30-60	No change	Caution; no data available
<30	Caution; consider dose ↓	Caution; no data available

Dosage in the Elderly

Consider reducing starting dose for patients ≥ 70 years. Monitor patients ≥ 65 years closely.

back to top

F - Adverse Effects

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

back to top

G - Interactions

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

back to top

H - Drug Administration and Special Precautions

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

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.

Recommended Clinical Monitoring

- CBC, electrolytes, liver & renal function tests; baseline and before each cycle
- Clinical toxicity assessment (including diarrhea, infection, dehydration, stomatitis, nausea and vomiting, fatigue and cardiac effects); at each visit
- Close monitoring of above parameters in elderly patients and patients who are receiving pelvic radiotherapy.

- 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 regular

back to top

J - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	37.403 minutes
Nursing Workload (average time per visit)	61.667 minutes

back to top

K - References

Caparica R, Lengelé A, Bekolo W, et al. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. Autops Case Rep 2019 Jun 24;9(2):e2019087.

Guion-Dusserre JF, Lorgis V, Vincent J, et al. FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. World J Gastroenterol 2015 Feb 21;21(7):2096-101.

Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup study. J Clin Oncol 2014;32(31):3520-6.

Mizrahi JD, Gunchick V, Mody K, et al. Multi-institutional retrospective analysis of FOLFIRI in patients with advanced biliary tract cancers. World J Gastrointest Oncol 2020 Jan 15;12(1):83-91.

Moretto R, Raimondo L, De Stefano A, et al. FOLFIRI in patients with locally advanced or metastatic pancreatic or biliary tract carcinoma: a monoinstitutional experience. Anticancer Drugs 2013 Oct;24(9):980-5.

Roussot N, Vincent J, Palmier R, et al. FOLFIRI-bevacizumab as a second-line treatment for advanced biliary tract cancer after gemcitabine-based chemotherapy. Front Oncol 2023 Nov 30;13:1293670.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

December 2024 Added cholangiocarcinoma to Rationale and Uses section

back to top

L - Other Notes

Diarrhea can be severe, with either immediate or delayed onset. Patients must be instructed in the use of Loperamide as treatment for diarrhea, and must have a supply of this drug upon starting Irinotecan treatments.

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).

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top