Regimen Monograph

A - Regimen Name

IRIN Regimen

Irinotecan

Disease Site

Gastrointestinal
Esophagus
Gastric / Stomach

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.

back to top

B - Drug Regimen

irinotecan	350 mg /m²	IV	Day 1

Alternative schedule:

irinotecan	150 mg /m²	IV	Days 1 and 15

back to top

C - Cycle Frequency

Standard schedule: REPEAT EVERY 21 DAYS

Alternative schedule: REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:
Also refer to CCO Antiemetic Summary

Irinotecan - Cholinergic adverse effects (early diarrhea):

- Prophylactic atropine may be considered in patients who have experienced cholinergic symptoms
- Diarrhea (including abdominal cramps) 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.
- Loperamide must be provided

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Patients should not be treated with irinotecan until they have recovered from prior toxicity: platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, GI toxicity recovered to baseline (without loperamide for at least 24 hours) and all other toxicities to Grade ≤ 1.

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

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.

Dosage with toxicity

All dose adjustments should be based on the worst preceding toxicity.

Dose Level	Dose (mg/m2)
0	350
-1	300
-2	250
-3	200

Toxicity grade[3]	**Suggested dose During treatment course of Weekly schedule[2]**	**At start of subsequent course[1]**
		3-weekly schedule[2]
1	No change	No change
2	↓ 25mg/m^2	Diarrhea alone – no change
		Hematologic alone – no change
		Other [3]: ↓ 50mg/m^2
3	Omit, then ↓ 25mg/m^2 when ≤	↓ 50mg/m^2

	grade 2	
4 or febrile neutropenia	Omit, then ↓ 50mg/m^2 when ≤ grade 2	↓ 50mg/m^2
Pneumonitis	Hold; investigate and if confirmed, discontinue.	

[1] Relative to the starting dose used in the previous cycle. Start a new cycle when the parameters below are met.

[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, ANC ≥ 1.5 x 10^9/L and and other toxicities recovered to ≤ Grade 1. If no recovery after a 2-week delay, consider discontinuing treatment.

[3] Excludes alopecia, anorexia, and fatigue

Hepatic Impairment

Elimination is decreased in hepatic impairment with increased exposure to SN-38. Patients with bilirubin 1-1.5 x ULN or Gilbert's syndrome are at an increased risk of myelosuppression.

Bilirubin [1]		**Transaminases**	**Irinotecan dose**
22-35 µmoL/L (1-1.5 x ULN) or with Gilbert's syndrome			Monitor closely; may consider dose reduction
> 35 µmoL/L	or	>3 x ULN (without liver metastases) or >5 x ULN (with liver metastases)	Not recommended.
[1]Consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent			

Renal Impairment

No specific studies, but as the kidney is not a major route of excretion, no adjustment anticipated to be required.

Dosage in the Elderly

Monitor patients ≥ 65 years closely for increased risk of diarrhea. Patients ≥ 70 years of age using the q3w schedule should receive 300mg/m^2

back to top

F - Adverse Effects

Refer to irinotecan 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
• Diarrhea (both early and late), may be severe • Nausea and vomiting • Fatigue • Alopecia • Abdominal pain • Anorexia	• Constipation • Cholinergic symptoms • Myelosuppression ± infection, bleeding (may be severe)	• Cough, dyspnea (may be severe) • Rhinitis • Headache/insomnia/dizziness • Musculoskeletal pain • Increased LFTs (may be severe) • Rash • Mucositis • Dyspepsia • Edema	• Arterial/venous thromboembolism • GI obstruction, perforation • Hypersensitivity • Pancreatitis • Pneumonitis • Tumour Lysis Syndrome • Renal failure

back to top

G - Interactions

Refer to irinotecan drug monograph(s) for additional details

- Azole antifungals are contraindicated with irinotecan (discontinue one week before the first dose of irinotecan)
- 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

back to top

H - Drug Administration and Special Precautions

Refer to irinotecan drug monograph(s) for additional details

Administration:

- Mix in 500mL bag (D5W-preferred or NS) in a concentration range between 0.12 to 3 mg/mL; infuse IV over 90 minutes
- Do not refrigerate admixtures in NS (may result in precipitation)
- 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.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during irinotecan treatment

Contraindications:

- Patients with a known hypersensitivity to the product or any of its ingredients
- Irinotecan should not be co-administered with azole antifungals (ketoconazole etc, see Interactions section)
- Avoid in patients with hereditary fructose intolerance since the product contains sorbitol
- Avoid the use of live or live attenuated vaccines

Other Warnings/Precautions:

- 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 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.

Pregnancy/Lactation:

- Irinotecan is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects unknown

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and before each dose
- Liver function tests; baseline and before each cycle
- Toxicity assessment and rating of diarrhea and other GI effects, cholinergic symptoms, pneumonitis, neurological, bleeding, infection, dehydration, fatigue, pancreatitis, thromboembolism; 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 as clinically indicated
Renal function tests; baseline and periodic

back to top

J - Administrative Information

Approximate Patient Visit	1.5 to 2 hours
Pharmacy Workload (average time per visit)	16.162 minutes
Nursing Workload (average time per visit)	38.333 minutes

back to top

K - References

Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013;31(35):4438-44.

Kanat O, Evrensel T, Manavoglu O, et al. Single-agent irinotecan as second-line treatment for advanced gastric cancer. Tumori. 2003 Jul-Aug;89(4):405-7.

Kang JH, Lee SI, Lim do H, et al. Salvage chemotherapy for pretreated gastric cancer: a

randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30:1513-8.

Thuss-Patience PC, Kretzschmar A, et al. Survival advantage for irinotecan versus best supportive care as second - line chemotherapy in gastric cancer -- a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47(15):2306-14.

Irinotecan drug monograph, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

November 2022 Added PEBC guideline link

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