Regimen Monograph

A - Regimen Name

CISPFU Regimen

CISplatin-Fluorouracil

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

Adjuvant
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

CISplatin	80 mg /m²	IV	Day 1
fluorouracil	800 mg /m²/day	IV over 24 hours as continuous infusion	Days 1 to 5

Alternative schedule:

CISplatin	80 mg /m²	IV	Day 1
fluorouracil	1000 mg /m²	IV over 24 hours as continuous infusion	Days 1 to 4

back to top

C - Cycle Frequency

REPEAT EVERY 21 TO 28 DAYS

Until disease progression or unacceptable toxicity occurs; usually up to 6 cycles due to cumulative cisplatin toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: High

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

• Standard regimens for Cisplatin premedication and hydration should be followed. Refer to local guidelines.

- Fluorouracil: Topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome in patients; Supportive care should be provided, including loperamide for diarrhea.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

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 grade 2-4 acute toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Worst Toxicity in Previous Cycle	Cisplatin (% previous dose)*	Fluorouracil (% previous dose)*
Grade 4 platelets, grade 4 ANC ≥ 5 days, thrombocytopenic bleeding or febrile neutropenia	75%	75%
Grade 2 neurotoxicity /ototoxicity	75%	100%
Grade 3 or 4 neurotoxicity/ototoxicity	Discontinue	Discontinue
Cardiotoxicity**	No change	Discontinue
Other grade 3 non-hematologic/organ toxicity	↓ 25% for suspect drug(s)	
Other grade 4 non-hematologic/organ toxicity (including stomatitis); delay > 2 weeks	Discontinue	
Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions	Discontinue	Discontinue

* Do not retreat until platelets ≥100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, toxicity has recovered to ≤ grade 2 (grade 1 for neurotoxicity) and creatinine ≤ grade 1.

**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

Hepatic Impairment

No dose adjustment required for cisplatin.

Bilirubin		AST	5FU (% previous)
1-2 x ULN	Or	2-4 x ULN	Consider ↓ dose in moderate-severe hepatic impairment
2-4 x ULN	Or	> 4 x ULN	
> 4 x ULN			OMIT

Renal Impairment

Creatinine clearance (mL/min)	Cisplatin (% previous dose)	5FU (% previous dose)
45-60	75%	No change
30-45	50%	No change
10-30	OMIT	Consider ↓ dose
< 10	OMIT	↓ dose

back to top

F - Adverse Effects

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

Prolonged 5FU regimens have more Hand-Foot Syndrome but less myelosuppression and GI effects compared to bolus infusions.

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life Threatening
• Nausea and vomiting • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Myelosuppression ± infection / bleeding (may be severe) • Hand-foot syndrome • Stomatitis, diarrhea • Hyperuricemia • Anorexia	• Arterial thromboembolism • Arrhythmia, cardiotoxicity • Leukoencephalopathy • Hemolytic uremic syndrome, vasculitis • Secondary malignancies • ↑ LFTs • Hypersensitivity • Raynaud's • Hemolysis • Venous thromboembolism

back to top

G - Interactions

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

back to top

H - Drug Administration and Special Precautions

Refer to CISplatin, 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

- Audiogram; as clinically indicated
- CBC; baseline and regular
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and regular
- Renal and liver function tests; baseline and regular
- Clinical toxicity assessment (infection, stomatitis, diarrhea, hand-foot syndrome, thromboembolism, infection, local toxicity, bleeding, nausea/vomiting, neurotoxicity, ototoxicity, cardiac, hepatic or other GI toxicity); at each visit

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

back to top

J - Administrative Information

Approximate Patient Visit	Day 1: 3 to 4 hours; 5FU-only days: 0.5 hour
Pharmacy Workload (average time per visit)	30.694 minutes
Nursing Workload (average time per visit)	59.167 minutes

back to top

K - References

Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326(24):1593-8.

Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26(7):1086-92.

Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376(9742): 687-97.

Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008;19(8):1450-7.

Kang YK, Kang WK, Shin D, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009;20(4):666-73.

Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 2003;21(1):54-9.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma
- Preoperative or Postoperative Therapy for Resectable Esophageal Cancer

April 2023 Updated DPD deficiency information in the Dose Modifications section and antidote information in Other Notes section.

back to top

L - Other Notes

Schedule pump teaching session BEFORE first day of infusion.

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