Regimen Monograph

A - Regimen Name

CISPFU Regimen

CISplatin-Fluorouracil

Disease Site Head and Neck

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.

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B - Drug Regimen

CISplatin	70 to 100 mg /m²	IV	Day 1
fluorouracil	1000 mg /m²/day	IV as continuous infusion	Days 1 to 4

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Up to 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Other Supportive Care:

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

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 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

Hematologic Toxicities

See appendix 6 for general recommendations.

GI Toxicities

Toxicity	Action
If Mucositis or Diarrhea ≥ Grade 3 in previous course	**REDUCE** to 2/3 dose of 5-FU
If Hand-Foot Syndrome ≥ Grade 2	**REDUCE** to 2/3 dose of 5-FU

Hepatic Impairment

Omit fluorouracil if bilirubin > 4 x ULN.

Renal Impairment

Creatinine Clearance or Serum Creatinine	Cisplatin Dose
If CrCl = 0.5 to 1 mL/sec or Serum Creatinine = 136-185µmol	**REDUCE*** Cisplatin to 50% dose
If CrCl < 0.5 mL/sec or Serum Creatinine > 185 µmol/L	**OMIT** Cisplatin dose

*Upon the discretion of the prescriber, less dose reduction may be suggested. See Cisplatin drug monograph.

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F - Adverse Effects

Refer to fluorouracil, CISplatin 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, vomiting • Nephrotoxicity • Hearing impaired • Myelosuppression +/- infection, bleeding • Abnormal electrolytes • Anorexia • Diarrhea • Mucositis • Neurotoxicity (may be severe) • Photosensitivity • Rash • Hand-foot syndrome	• Increased LFTs • Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Hypersensitivity • Hemolysis • Radiation recall reaction • Vasculitis

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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 cycle
- Baseline and regular liver and renal function (including electrolytes and magnesium) tests.
- Clinical toxicity assessment (including stomatitis, neurotoxicity, ototoxicity, and hand-foot syndrome); at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Audiogram; baseline and periodic

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J - Administrative Information

Approximate Patient Visit	Day 1-4: 3 to 4 hours
Pharmacy Workload (average time per visit)	30.694 minutes
Nursing Workload (average time per visit)	59.167 minutes

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K - References

Cisplatin and fluorouracil drug monographs, Cancer Care Ontario.

Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16(4):1310-7.

Browman GP, Cronin L. Standard chemotherapy in squamous cell head and neck cancer: what we have learned from randomized trials. Semin Oncol, 1994; 21: 311-319.

Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Study. J Clin Oncol, 1992; 10: 1245-1251.

Gibson MK, Li Y, Murphy B, et al. Randomized Phase III Evaluation of Cisplatin Plus Fluorouracil Versus Cisplatin Plus Paclitaxel in Advanced Head and Neck Cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005; 23: 3562-3567.

Taylor SG IV, Murthy AK, Vannetzel JM, et al. Randomized Comparison of Neoadjuvant Cisplatin and Fluorouracil Infusion Followed by Radiation Versus Concomitant Treatment in Advanced Head and Neck Cancer. J Clin Oncol 1994; 12:385-395.

Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116-27.

Vermorken JB, Stöhlmacher-Williams J, Davidenko I, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol. 2013 Jul;14(8):697-710.

PEBC Advice Documents or Guidelines

- The Management of Head and Neck Cancer in Ontario

April 2023 Updated DPD deficiency information in the Dose Modifications section and antidote information in Other Notes section; Modified Supportive Care section

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L - Other Notes

Schedule pump teaching session BEFORE first day of infusion. Home care arrangement if 5FU infusion is to be administered at home.

5FU CIV and Cisplatin regimen is associated with moderate toxicity risks and response rates of about 30% but no difference in survival when compared against methotrexate.

In patients with adequate performance status where standard chemotherapy would unlikely yield a good therapeutic index, consideration should be made for enrollment into a clinical trial of novel agent(s).

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.

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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