Regimen Monograph

A - Regimen Name

CISPFU+TRAS Regimen

CISplatin-Fluorouracil-Trastuzumab

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.

Rationale and Uses

For the palliative treatment of HER2-overexpressing (IHC3+ or IHC2+ confirmed by ISH) inoperable advanced (non-resectable; either locally advanced, recurrent or metastatic) adenocarcinoma of the stomach or the gastroesophageal junction, in patients who are ECOG 0-2, have a normal ejection fraction and have not received previous systemic treatment for metastatic disease.

Supplementary Public Funding

trastuzumab
New Drug Funding Program (Trastuzumab (Biosimilar) - Advanced Gastric, Gastroesophageal, or Esophageal Cancer)

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B - Drug Regimen

Note: Different trastuzumab products are **NOT INTERCHANGEABLE**

Trastuzumab Loading Dose:

trastuzumab[1]	8 mg /kg	IV	Day 1, cycle 1 only

THEN, Trastuzumab Maintenance Dose:

trastuzumab[1]	6 mg /kg	IV	Day 1, cycle 2 onwards

[1] In general, the dose of trastuzumab should be delayed if the chemotherapy cycle is delayed for scheduling convenience; if the delay is > 1 week, trastuzumab loading dose should be repeated.

AND

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

An alternative schedule for **fluorouracil** is 1000 mg/m^2/day IV over 24 hours as continuous infusion, on days 1 to 4.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Cisplatin-Fluorouracil: Up to 6 cycles unless evidence of disease progression or unacceptable toxicity occurs

Trastuzumab: Until evidence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: High

Other Supportive Care:

- To prevent recurrence of infusion-associated reactions, acetaminophen and diphenhydramine may be given as pre-medication. Refer to trastuzumab drug monograph for full details.
- Standard regimens for cisplatin premedication and hydration should be followed. Refer to local guidelines
- Fluorouracil: Topical emollients (e.g. hand creams, udder balm) or oral pyridoxine therapy 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.

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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.

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Dosage with toxicity

Worst Toxicity Grade/ **Counts (x 10^9/L) in Prior Cycle**	**Cisplatin Dose (% previous dose)**	**Fluorouracil (5FU) (% previous dose)**
Grade 4 platelets, grade 4 ANC ≥ 5 days, Febrile Neutropenia, Thrombocytopenic bleeding Grade 4 ANC ≥ 7 d	75%* for suspect drug	
Grade 2 neurotoxicity / ototoxicity	75%	No change
Grade 3 or 4 neurotoxicity / ototoxicity	Discontinue	No change
Cardiotoxicity**	No change	Discontinue
Grade 3 related non-hematologic/organ	75%* for suspect drug. Consider discontinuing cisplatin.	
Grade 4 related non-hematologic/organ	Discontinue	

* Do not retreat until toxicity has recovered to ≤ grade 2, and platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.
**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%.

Trastuzumab:

Dosage with myelosuppression: No adjustment required.

(Continued on next page)

Dosage with cardiotoxicity - Product Monograph recommendations

- Trastuzumab should be held with a fall in LVEF (product monograph suggests if LVEF falls ≥10 points from baseline and/or if LVEF falls to < 50%). Repeat LVEF in 3 weeks and consider discontinuing. Discontinue if clinically significant cardiac dysfunction or cardiac failure develops.

Dosage with cardiotoxicity - Canadian Consensus Guidelines

- Discontinue if symptomatic.

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Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

Relationship of LVEF to Lower Limit of Normal (LLN)	**Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline**		
	≤ 10 percentage points	**10-15 percentage points**	**≥ 15 percentage points**
Within facility's normal limits	Continue	Continue	**Hold** and repeat MUGA/ECHO after 4 weeks
1-5% below LLN	Continue [1]	**Hold** and repeat MUGA/ECHO after 4 weeks [1, 2]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks [3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]

[1] Consider cardiac assessment and starting ACEI therapy

[2] After 2 holds, consider permanent trastuzumab discontinuation

[3] Start ACEI therapy and refer to cardiologist

Dosage with other toxicity - Trastuzumab:

Toxicity	**Action**	**Comment**
Mild hypersensitivity	Decrease infusion rate	May consider re-challenge with premedication
Hypersensitivity (dyspnea, clinically significant hypotension)	Hold	May consider rechallenge with premedication
Pulmonary toxicity, severe or life-threatening hypersensitivity	Discontinue permanently	

Hepatic Impairment

No adjustment required for trastuzumab and 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

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Renal Impairment

No adjustment required for trastuzumab.

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

*Upon the discretion of the prescriber, less dose reduction may be suggested.

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea and vomiting • Nephrotoxicity (may be severe) • Neurotoxicity (ototoxicity), electrolyte changes • Myelosuppression ± infection, bleeding (may be severe) • Cardiotoxicity (may be severe) • Mucositis, diarrhea, anorexia • Hand-foot syndrome • Fatigue • Headache, musculoskeletal pain • Rash (including photosensitivity) • Infusion related reaction (may be severe); fever, chills	• Leukoencephalopathy, optic neuritis • Arterial thromboembolism • Venous thromboembolism • Raynaud's • Arrhythmia • Pancreatitis • Pneumonitis • Hemolytic-uremic syndrome, hemolysis, vasculitis • Secondary malignancies • Injection site reaction • ↑ LFTs • Renal failure

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

NOTE: Different trastuzumab products are **NOT INTERCHANAGEABLE**.

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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

- Clinical toxicity assessment (including mucositis, nausea/vomiting, neurotoxicity, ototoxicity, cardiotoxicity, infection, bleeding, skin and pulmonary toxicity, diarrhea, infusion reactions).
- CBC before each cycle.
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and regular
- Baseline and regular liver and renal function tests (including electrolytes and magnesium).
- Baseline and regular cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan); more frequent with asymptomatic reductions in LVEF, q3 months during treatment and then q6 months after trastuzumab discontinuation x 2 years
- 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	First Cycle: 5 hours; Subsequent cycles: 4 hours
Pharmacy Workload (average time per visit)	32.713 minutes
Nursing Workload (average time per visit)	72.083 minutes

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K - References

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.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

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

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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

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(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.

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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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