Regimen Monograph

A - Regimen Name

CAPECISP+TRAS Regimen

Capecitabine-CISplatin-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

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 with ECOG 0-2, a normal ejection fraction and who 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)

capecitabine
ODB - General Benefit (capecitabine)

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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
capecitabine	1000 mg /m²	PO	BID* Days 1 to 14

(*Total dose 2000 mg/m^2/day)
(Outpatient prescription in 150mg and 500mg tablets)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Cisplatin-Capecitabine: 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
No routine prophylaxis for capecitabine

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 cisplatin monograph
- Topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.
- 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.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. 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

Trastuzumab:

Dosage with myelosuppression*:* No adjustment required

Dosage with cardiotoxicity:

Product Monograph Recommendations

- Trastuzumab should be held with a fall in LVEF (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.

Canadian Consensus Guidelines

- Discontinue if symptomatic.

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

Trastuzumab - Dosage with other toxicity:

Toxicity	**Action**
Mild hypersensitivity reaction	↓ infusion rate (and/ or hold) and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate. Consider premedication for next infusion.
Moderate hypersensitivity reaction	Hold and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate; complete infusion at ↓ rate if possible. Use premedication for next infusion.
Severe hypersensitivity reaction or Pulmonary Toxicity	Hold and manage symptoms aggressively with beta-agonists, antihistamines, antipyretics, and/or corticosteroids. Discontinue permanently and do not rechallenge

CISplatin:

Worst Toxicity in Previous Cycle	CISplatin Dose for next cycle*
Grade 4 platelets, grade 4 ANC ≥ 5 days, thrombocytopenic bleeding or febrile neutropenia	↓ 25%
Grade 2 neurotoxicity /ototoxicity	↓ 25%
Grade 3 or 4 neurotoxicity/ototoxicity	Discontinue
Other grade 3 non-hematologic/organ toxicity	↓ 25%
Other grade 4 non-hematologic/organ toxicity	Discontinue
Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions, grade 3 or 4 ↑ LFTs	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 ≤ ULN.	

Capecitabine:

Do not start treatment with capecitabine unless baseline neutrophil counts are ≥ 1.5 x 10^9/L and/or platelet counts of ≥ 100 x 10^9/L. Patients should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.
Dose modifications are mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100%
2nd appearance	Interrupt until resolved to grade 0-1	75%
3rd appearance	Interrupt until resolved to grade 0-1	50%
4th appearance	Discontinue treatment permanently	--

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 3 1st appearance 2nd appearance 3rd appearance OR any evidence of Stevens-Johnson syndrome or Toxic Epidermal Necrolysis	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 75% 50% –
Grade 4 1st appearance, including SJS, TENS, OR cardiotoxicity OR acute renal failure 2nd appearance	 Discontinue permanently or If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to grade 0-1. Discontinue permanently	 Discontinue or 50% –

Hepatic Impairment

No adjustment required for trastuzumab and cisplatin.

Capecitabine:

- Use dose modification table above for increases in bilirubin.
- In patients with mild to moderate hepatic impairment due to liver metastases exposure is increased, but no dose adjustment is necessary, although caution should be exercised.
- The use of capecitabine in patients with severe hepatic impairment has not been studied.

Renal Impairment

No adjustment required for trastuzumab.

Creatinine clearance (mL/min)	Cisplatin (% previous dose)	Capecitabine (% previous dose)
> 60	No change	100%; monitor closely
> 50-60	75%*	100%; monitor closely
30-50	50%*	75%; use with caution
10-<30	Discontinue*	Discontinue
< 10	Discontinue*	Discontinue

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

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F - Adverse Effects

Refer to trastuzumab, CISplatin, capecitabine 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 • Abdominal pain • Hand-foot syndrome • Fatigue • ↑ LFTs • Headache, musculoskeletal pain • Rash (may be severe); photosensitivity • Infusion-related reaction (may be severe)	• GI obstruction/perforation • Seizures • Arterial thromboembolism • Venous thromboembolism • Raynaud's • Arrhythmia • ITP • Pancreatitis • Pneumonitis • Hemolytic-uremic syndrome, hemolysis, vasculitis • Renal failure • Secondary malignancies • Injection site reaction

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G - Interactions

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

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H - Drug Administration and Special Precautions

Refer to trastuzumab, CISplatin, capecitabine 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, dehydration, infusion reactions); at each visit
- CBC; baseline and before each cycle
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and regular
- Baseline and regular liver and renal function tests
- 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
- INR or PT; baseline and regular if on anticoagulants
- 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: 3.5 hours
Pharmacy Workload (average time per visit)	40.176 minutes
Nursing Workload (average time per visit)	62.5 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.

Capecitabine, cisplatin and trastuzumab drug monographs, Cancer Care Ontario.

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

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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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