Regimen Monograph

A - Regimen Name

ECX Regimen

EPIrubicin-CISplatin-XELODA ® (Capecitabine)

Disease Site

Gastrointestinal - Gastric/Stomach

Intent

Palliative
Adjuvant
Neoadjuvant

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 treatment of advanced (non-resectable; either locally advanced or metastatic) gastric, esophageal or gastroesophageal cancer, but not for squamous cell carcinomas. In the phase 3 clinical trial by Cunningham, approximately 10% of patients in the ECX arm had squamous cell carcinoma.

An alternative to ECF in the neoadjuvant (perioperative) / adjuvant settings for treating patients with potentially curable, surgically resectable (Stage 1B and above) gastric cancer (ECX has not been studied in prospective peri-operative clinical trials). In the clinical trial, ECF was used in patients with adenocarcinoma of the stomach or lower third of the esophagus, stage II or higher with no evidence of distant metastases, or locally advanced inoperable disease, with WHO performance status 0 or 1 and who had no previous chemotherapy or radiotherapy.

Supplementary Public Funding	**capecitabine** ODB Limited Use (In combination with a platinum-containing product and epirubicin for the treatment of advanced (non-resectable; either locally advanced or metastatic) gastric or gastro-esophageal junction cancer) (ODB Formulary) (criteria do not include use in perioperative/resectable disease)

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B - Drug Regimen

EPIrubicin (Round to nearest 1mg)	50 mg /m²	IV	Day 1
CISplatin (Round to nearest 1mg)	60 mg /m²	IV	Day 1
capecitabine (*Total daily dose 1250 mg/m^2/day; outpatient prescription in 150mg and 500mg tablets)	625 mg /m²	PO	BID* for 21 days (starting Day 1)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Advanced disease: For a usual total of up to 8 cycles unless disease progression or unacceptable toxicity occurs

Perioperative: For 6 cycles (3 prior to and 3 after surgery) in the absence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen:	High (epirubicin and cisplatin) Low (capecitabine)
Febrile Neutropenia	Moderate

Risk:

Other Supportive Care:

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

• 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 Summary

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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.

Use capecitabine with extreme caution in patients with partial DPD deficiency; reduce the initial dose substantially, monitor frequently and adjust the dose for toxicity as recommended in the dosage with toxicity section. In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; discontinue if acute grade 2-4 toxicity develops.

Dosage with toxicity

<table>
<tr><th>Worst Toxicity Grade/ Counts (x 10^9/L) in Prior Cycle</th><th>Epirubicin (% previous dose)</th><th>Cisplatin Dose (% previous dose)</th><th>Capecitabine</th></tr>
<tr><td>Febrile Neutropenia
Thrombocytopenic bleeding
Grade 4 ANC ≥ 7 d</td><td colspan="2">Hold, then ↓ 75%*</td><td rowspan="4">Refer to table below.</td></tr>
<tr><td>Cardiotoxicity**</td><td>Discontinue</td><td>No change</td></tr>
<tr><td>Grade 3 related non-hematologic/organ</td><td colspan="2">Hold, then ↓ 75%* for suspect drug</td></tr>
<tr><td>Grade 4 related non-hematologic/organ</td><td colspan="2">Discontinue</td></tr>
</table>

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

Capecitabine:

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 2nd appearance 3rd appearance 4th appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 100% 75% 50% --
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/TEN, OR cardiotoxicity OR acute renal failure	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 or 50%
2nd appearance	Discontinue permanently	--

Hepatic Impairment

Bilirubin		AST	Epirubicin	Cisplatin	Capecitabine
1-2 x ULN	Or	2-4 x ULN	↓ to 50% dose	No change	Refer to the dose modification table for Capecitabine
2-4 x ULN	Or	> 4 x ULN	↓ to 25% dose		
> 4 x ULN			OMIT		

Renal Impairment

Creatinine clearance (mL/min)	Epirubicin	Cisplatin	Capecitabine
> 50	No change	No change	No change (monitor closely)
30-50		50%	↓ to 75% dose (use with caution)
10-<30	Consider ↓ dose	Discontinue or ↓ 50%	Omit
< 10	↓ dose	Discontinue	

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F - Adverse Effects

Refer to EPIrubicin, 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 • Cardiotoxicity, hypertension • Stomatitis,diarrhea, anorexia • Hand foot syndrome • Vesicant • Fatigue • ↑ LFTs • Myalgia, arthralgia • Rash (may be severe); photosensitivity • Reproductive risks	• Radiation recall reaction • Hypersensitivity • Seizures • Acute encephalopathy, ocular toxicity/neuritis • Thrombotic microangiopathy • Acute leukemia • Arterial and venous thromboembolism • SIADH • Raynauds • Arrhythmia • Cardiotoxicity

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G - Interactions

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

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H - Drug Administration and Special Precautions

Refer to EPIrubicin, CISplatin, capecitabine 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 at each visit

- Liver and renal function tests (including electrolytes and magnesium); baseline and regular
- INR if on anticoagulants; baseline and regular
- Cardiac examination especially with risk factors (including prior therapy with doxorubicin, mitoxantrone or other cardiac drug), or a cumulative epirubicin dose of > 650 mg/m^2
- Clinical toxicity assessment (including diarrhea, infection, stomatitis, hand-foot-syndrome, ototoxicity, local toxicity, neurotoxicity); at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Audiogram; periodic

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J - Administrative Information

Approximate Patient Visit	Day 1: 4 hours
Pharmacy Workload (average time per visit)	41.231 minutes
Nursing Workload (average time per visit)	61.667 minutes

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K - References

Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36-46.

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.

Epirubicin, cisplatin, capecitabine drug monographs, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric Cancer

July 2016 updated dosage section with details re: DPD deficiency with capecitabine

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L - Other Notes

CCO Practice Guidelines: Systemic Therapy for Advanced Gastric Cancer: ECX is the preferred regimen over the prior standard, epirubicin, cisplatin, and 5FU (ECF). This recommendation is based on results of a meta-analysis of two randomized controlled trials which indicated a significant survival benefit for chemotherapy including capecitabine compared with chemotherapy including 5FU.

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M - Disclaimer

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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