Regimen Monograph

A - Regimen Name

ECX Regimen

EPIrubicin-CISplatin-XELODA ® (Capecitabine)

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

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

An alternative to ECF in the neoadjuvant (perioperative) / adjuvant settings for treating patients with potentially curable, surgically resectable (Stage 1B and above) gastric cancer. In Cunningham et al (2006), 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 - General Benefit (capecitabine)

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B - Drug Regimen

EPIrubicin	50 mg /m²	IV	Day 1
CISplatin	60 mg /m²	IV	Day 1
capecitabine	625 mg /m²	PO	BID* days 1 to 21

(*Total daily dose 1250 mg/m^2/day; outpatient prescription in 150mg and 500mg tablets)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

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
No routine prophylaxis for capecitabine

Febrile Neutropenia Risk: Moderate

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 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

<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 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

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	• Radiation recall reaction • Hypersensitivity • Seizures • Acute encephalopathy, ocular toxicity/neuritis • Thrombotic microangiopathy • Acute leukemia • Arterial and venous thromboembolism • SIADH

• Fatigue • ↑ LFTs • Myalgia, arthralgia • Rash (may be severe); photosensitivity • Reproductive risks	• 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, 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.

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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