Regimen Monograph

A - Regimen Name

ECARBOX Regimen

Epirubicin-Carboplatin-Capecitabine (XELODA)®

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 or gastroesophageal cancer (ECARBOX has not been studied in prospective perioperative clinical trials). In the clinical trial with ECF, it 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)

back to top

B - Drug Regimen

EPIrubicin	50 mg /m²	IV	Day 1
CARBOplatin	AUC 5	IV	Day 1
capecitabine	625 mg /m²	PO	BID* days 1 to 21

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

back to top

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

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)
No routine prophylaxis for capecitabine

Febrile Neutropenia Risk: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

- 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.

back to top

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

Worst Toxicity Grade/ Counts (x 10^9/L) in Prior Cycle	Epirubicin (% previous dose)	Carboplatin Dose (% previous dose)	Capecitabine
Febrile Neutropenia Thrombocytopenic bleeding Grade 4 ANC ≥ 7 d	Hold, then ↓ 75%*	Hold, then ↓ 1 AUC*/#	Refer to table below.
Cardiotoxicity**	Discontinue	No change	
Grade 3 related non-hematologic/organ	Hold, then ↓ 75%* for suspect drug	Hold, then ↓ 1 AUC* for suspect drug	
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 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%.
- # Use Egorin formula if isolated thrombocytopenia (See "Other Notes" section).

Capecitabine: Dose Modification:

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. Supportive care should be provided, including loperamide for diarrhea. 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 or 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% Not applicable

Hepatic Impairment

Epirubicin is contraindicated in patients with severe hepatic impairment, especially with elevated bilirubin. Consideration should be given to dose modification for patients with severe increases in transaminases.

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

Bilirubin (µmol/L)		AST/ALT	Epirubicin (% usual dose)	Carboplatin	Capecitabine
1-2 x ULN	or	2-4 x ULN	50%	No change	Use capecitabine dose modification table above
2-4 x ULN	or	> 4 x ULN	25%		
> 4 x ULN		omit	Omit		

Renal Impairment

Creatinine Clearance (ml/min)	Epirubicin (% previous dose)	Carboplatin (% previous dose)	Capecitabine (% previous dose)
51 - 80	No change	No change	100 % with close monitoring
30 - 50		Use Calvert or Chatelut formula	75% (use with caution)
21 - 29			CONTRAINDICATED
< 20	Adjust dose with severe renal impairment (creatinine > 440 µmol/L)	Discontinue	

back to top

F - Adverse Effects

Refer to EPIrubicin, CARBOplatin, capecitabine drug monograph(s) for additional details of adverse effects

Most common adverse effects	Less common adverse effects, but may be severe or life-threatening
• Alopecia • Hand-foot syndrome (may be severe) • Mucositis • Diarrhea (may be severe), abdominal pain • Nausea, vomiting • Myelosuppression +/- bleeding, infection • Fatigue • ↑ LFTs (may be severe) • Ototoxicity • Nephrotoxicity • Electrolyte abnormalities	• Cardiotoxicity • Hypersensitivity • Arterial thromboembolism • Venous thromboembolism • Rash • Radiation recall reaction • Neuropathy • GI obstruction, perforation • Hemolytic uremic syndrome, ITP • Pneumonitis • Secondary malignancy

back to top

G - Interactions

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

back to top

H - Drug Administration and Special Precautions

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

back to top

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
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular including electrolytes
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors or cumulative epirubicin doses > 650mg/m^2; baseline and periodic
- INR and/or PT; Baseline and regular if on anticoagulants
- Clinical toxicity assessment for neurotoxicity, ototoxicity, hypersensitivity, bleeding, infection, GI, cardiac and skin effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Approximate Patient Visit	1 hour
Pharmacy Workload (average time per visit)	27.365 minutes
Nursing Workload (average time per visit)	65.833 minutes

back to top

K - References

Capecitabine, epirubicin, carboplatin drug monographs, Cancer Care Ontario.

Cunningham D , Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008 Jan 3;358(1):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: 11-20.

April 2023 Removed PEBC guideline link; Updated DPD deficiency information in the Dose Modifications section

back to top

L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

back to top

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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back to top