

Systemic Anti Cancer Treatment Protocol

**Epirubicin Oxaliplatin Capecitabine
(EOX gastric)**

**PROTOCOL REF: MPHAUGIEOX
(Version No: 1.0)**

Approved for use in:

Gastric / gastro-oesophageal junction adenocarcinoma

Neoadjuvant / Adjuvant – when specific cisplatin toxicities

Locally advanced / metastatic disease – as an alternative to ECX

Consider omitting epirubicin in patients with PS2 or over 75 years

Dosage:

Drug	Dosage	Route	Frequency
Epirubicin	50mg/m ²	IV	Every 21 days
Oxaliplatin	130mg/m ²	IV	Every 21 days
Capecitabine	625mg/m ² BD	PO	Continuous

Supportive treatments:

Dexamethasone 4mg orally twice a day for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Loperamide 2mg after each loose stool

Extravasation risk:

Epirubicin – vesicant – follow trust / network extravasation policy. Specific treatment available

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Oxaliplatin – Irritant, Follow trust / network extravasation policy. No specific antidote needed but use WARM compression if symptoms warrant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone 30 mins prior to chemotherapy	8mg	PO	
1	Ondansetron 30 mins prior to chemotherapy	16mg	PO	
1	Epirubicin	50mg/m²	IV	IV bolus with concurrent sodium chloride 0.9%
1	Oxaliplatin	130mg/m²	IV	500mL Glucose 5% over 2 hours
1 to 21	Capecitabine	625mg/m² BD	PO	Morning and evening continuously

Neoadjuvant – 3 cycles

Adjuvant – 3 cycles

Advanced – up to 6 cycles

Capecitabine

Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants

Counselling points:

Tablets should be taken 12 hours apart

Swallow whole with water within 30 minutes of a meal

Do not add doses missed onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.

Take missed doses if remembered within 2 hours of the normal scheduled time.

Otherwise continue with the next scheduled dose. Do not double up missed doses

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In case of swallowing difficulties the tablets may be dissolved in 200mL warm water (boiled and cooled). Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only.

If capecitabine cannot be administered then alternative regimen infusional fluorouracil is an alternative (EOF regimen)

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone 30 mins prior to chemotherapy	8mg	PO	
1	Ondansetron 30 mins prior to chemotherapy	16mg	PO	
1	Epirubicin	50mg/m²	IV	IV bolus with concurrent sodium chloride 0.9%
1	Oxaliplatin	130mg/m²	IV	500mL Glucose 5% over 2 hours
1 to 7	Fluorouracil	200mg/m²/24hours	IV	Continuous via infusor device over 7 days
8 to 14	Fluorouracil	200mg/m²/24hours	IV	Continuous via infusor device over 7 days
15 to 21	Fluorouracil	200mg/m²/24hours	IV	Continuous via infusor device over 7 days

Main Toxicities:

Myelosuppression, alopecia, nausea and vomiting, stomatitis, ovarian failure/infertility, cardiotoxicity

Oxaliplatin: infusion reactions, neuropathy

Capecitabine / Fluorouracil: - diarrhoea, PPE

DPD deficiency – leads to severe early 5FU toxicity, affects approximately 3% of population, may be life threatening

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Drug Interactions

Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully

Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH

Sorivudine and analogues – Potentially fatal interaction – avoid completely

Allopurinol – reduced efficacy of capecitabine – avoid

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X	X	X	At end of treatment
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, LFT, Mg2+	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)	X	X	X	X	X	Every cycle
CT scan	X				X	As clinically indicated
Informed Consent	X					
ECG	X					If clinically indicated
Blood pressure measurement	X					Repeat if clinically indicated
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

For EOF regimen blood tests are not required on day 8 and day 15

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Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC $\geq 1.0 \times 10^9/L$	Platelets $> 75 \times 10^9/L$
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Delay 1 week on day 1 and dose reduce as per table below, if:-

ANC $\leq 0.9 \times 10^9/L$	Platelets $\leq 74 \times 10^9/L$
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	Epirubicin dose	Oxaliplatin dose
ANC 0.5 to $0.9 \times 10^9/L$ OR Platelets 50 to $74 \times 10^9/L$	75%	100mg /m ²
ANC less than $0.5 \times 10^9/L$ OR Platelets 25 to $49 \times 10^9/L$	50%	100mg /m ²
Platelets less than $25 \times 10^9/L$	Omit	100mg /m ²

Capecitabine dose adjustment guidelines

Common Toxicity Criteria / Haematological Parameter	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose(% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
-1st appearance	Interrupt until resolved to grade 0-1	100% (for PPE give 85% dose)*
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75% (for PPE give 70% dose)*
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4		

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-1st appearance	Discontinue permanently Or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50% (consultant approval only)
-2nd appearance	Discontinue permanently	Not applicable

Non-haematological toxicity

Renal	Calculate CrCl using Cockroft and Gault formula at baseline and before each cycle and adjust dose according to table.		
	Creatinine Clearance (mL/min)	Capecitabine Dose	Oxaliplatin Dose
	Above 50	Give 100%	Give 100%
	30 to 50	Give 75%	Give 100%
	Below 30	Omit	Omit
If moderate impairment monitor closely and adjust oxaliplatin dose if deterioration or toxicity appears.			

Hepatic	Bilirubin (mmol/L)		Epirubicin dose
	24 to 51		50%
	52 to 85		25%
	Above 85		Omit
	Capecitabine – If ALT/AST > 2 x ULN or Bilirubin > 3 x ULN – omit until recovery Oxaliplatin – dose reduction probably not necessary but discuss with consultant and consider 50% dose if severe impairment		

Oxaliplatin

Neurotoxicity	Grade 1 any duration or grade 2 > 7 days but resolving before next cycle	Full dose
	Grade 2 persisting to next cycle or Grade 3 resolved by next cycle	Delay until recovered to grade 1 then reduce to 100mg/m ²
	Grade 3 persisting to next cycle or any grade 4	Stop oxaliplatin
Laryngopharyngeal dysaesthesia	Symptoms are exacerbated by cold, advise patients on suitable precautions eg avoid cold drinks. And increase infusion time for oxaliplatin to 4 to 6 hours.	

	If symptoms are troublesome, eg dropping items or persist until the next cycle then omit oxaliplatin until symptoms resolve to grade 1.
Acute cold related dysaesthesia (CRD)	Transient paraesthesia of hands and feet is common, and may present as dropping items that are cold. If remains transient then dose reduction not required.
Cumulative dose related sensory neuropathy	Usually occurs after a cumulative dose of 800mg/m ² . It can occur after treatment is completed, is usually reversible taking up to 6 months to recover
Allergic reactions during infusion	Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine. There is no need to stop the capecitabine. Discuss re-challenge with consultant

Capecitabine

Diarrhoea	Treat symptomatically with Loperamide at standard doses, codeine may be added. If persistent or grade 3 or 4 stop capecitabine until resolved to grade 0 or 1. Restart as per CTC table above for dose reductions
Stomatitis	Regular mouthwashes (water, saline or non alcoholic proprietary brand), brush gently with a soft brush, adequate pain relief, nutritional support in severe cases – see above for dose reductions.
PPE	Manage as per trust policy, withhold treatment until resolved to grade 1, dose reductions as per CTC table above.
Conjunctivitis	Eye drops for symptomatic treatment
Chest Pain / coronary artery spasm	Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently

References:

Cunningham, D et al; NEJM 2008; 358: 36-46 (REAL-2)

Cunningham, D et al; NEJM 2006; 355: 11-20 (peri-operative ECF)

Wagner, A et al; JCO 2006; 24 (18) 2903 - 2909

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