NHS
North West Coast
Strategic Clinical Networks

Chemotherapy protocol

Drug regimen
EOX

Indications for use
Locally advanced or metastatic carcinoma of the stomach or oesophagus

Regimen

Drug	Route	Fluid	Time
Epirubicin 50mg/m^2	IV		IV bolus
Oxaliplatin 130mg/m^2	IV	500mls 5% Glucose	IV 2 hours

Capecitabine 1250mg/m^2 in 2 divided doses orally for 3 weeks

Regimen to be repeated 3 weekly for 6 cycles

Investigation prior to initiating treatment
FBC
Biochemical profile
MUGA scan for palliative patients with pre-existing cardiac disease only

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

Cautions
Caution if history of ischaemic heart disease.
Raised bilirubin or AST
Oxaliplatin should always be administered before fluoropyrimidines
Avoid cold drinks for 2-3 days after chemotherapy

Investigations and consultations prior to each cycle
FBC, U&Es, LFTs, calcium
The liver function test may be retrospectively looked at (i.e. after the chemotherapy treatment) **unless** they are known to be abnormal then they need to be repeated the day before so that the results are available pre-chemotherapy

Acceptable limits for treatment to proceed (if outside these delay one week or contact consultant)
Neutrophils ≥1.0 and platelets ≥75
Creatinine Clearance ≥50ml/min
Bilirubin <1.5 x ULN, ALT, AST < 2.5 ULN, Alk Phos < 2.5 ULN

Side Effects
Alopecia, Nephrotoxicity, Tiredness, diarrhoea and abdominal pain, nausea and vomiting, sore mouth, poor appetite, myelosuppression and thrombocytopenia, hand foot syndrome, cardiotoxicity (including coronary artery spasm, angina and tachycardia), ocular toxicity (excessive lacrimation, visual change, photophobia), peripheral neuropathy, cold related dysaesthesia (hands/feet or laryngopharyngeal), infusion reactions, pulmonary fibrosis, veno-occlusive disease, high tone and hearing loss, ovarian failure/infertility

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced

fluorouracil metabolism- avoid use in patients with known DPD deficiency

Dose Modification Criteria

Haematological Toxicity

Neutrophils ($x10^9$/l)	**Platelets ($x10^9$/l)**	**Action**
>1.0	> 75	Full Dose
0.5 - 0.9	50-74	Delay until recovery Restart capecitabine at full dose Reduce Epirubicin by 25% Reduce Oxaliplatin 100mg/m^2 on subsequent cycles
< 0.5	25-49	Delay until recovery Restart capecitabine at full dose Reduce Epirubicin by 50% Reduce Oxaliplatin 100mg/m^2 on subsequent cycles Discuss with consultant
	<25	Delay until recovery Restart capecitabine at full dose Omit Epirubicin from subsequent cycles Reduce Oxaliplatin 100mg/m^2 on subsequent cycles Discuss with consultant

Renal

Result	**GFR (ml/min)**	**Action**
Epirubicin		No dose reduction necessary
Oxaliplatin	<30	Contraindicated. Discuss with consultant consider risk benefit.
Capecitabine	30-50	Dose reduce by 25%
	<30	Omit

Neuropathy:

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity >7 days	Persistent between cycles
Cold-related dysaesthesia	No reduction	No reduction	Withhold oxaliplatin until recovery then restart at 100mg/m^2 Omit oxaliplatin if recurs
Paraesthesia without pain	No reduction	No reduction	Withhold oxaliplatin until recovery then restart at 100mg/m^2 Omit oxaliplatin if recurs
Paraesthesia with pain or functional impairment	No reduction	Reduce to 100mg/m^2 on subsequent cycles Omit oxaliplatin if recurs	Omit oxaliplatin Discuss with consultant Consideration may be given to substitution of carboplatin for oxaliplatin
Acute laryngopharyngeal dysaesthesia	Increase infusion duration to 6 hrs.		

If grade 3/4 diarrhoea/stomatitis recurs despite appropriate dose reduction in capecitabine, subsequent oxaliplatin should be reduced to 100mg/m^2.

Palmar-plantar erythema (PPE):

Palmar Plantar Erythrodysaesthesia	Grade	Action
	1	No dose reduction necessary
	2	Delay capecitabine until resolved to grade 0-1 then restart at 15% dose reduction
	3	Delay capecitabine until resolved to grade 0-1 then restart at 30% dose reduction

Liver function

If bilirubin increases to > 1.5 ULN, epirubicin should be omitted until bilirubin returns to acceptable levels

Non-haematological toxicity: stomatitis, diarrhoea, nausea & vomiting

(See separate section for palmar-plantar syndrome)

For grade 2-3 toxicity, stop capecitabine and administer appropriate symptomatic management. If toxicity is adequately controlled with symptomatic measures alone within 2 days, then capecitabine may be restarted at 100% full dose. If toxicity persists, the following dose reductions should be made:

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0-1 then continue at same dose. .	Interrupt treatment until resolved to grade 0-1 then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless consultant considers it to be in the best interest of the patient to continue at 50% of original dose once toxicity has resolved to grade 0-1.
2nd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1 then continue at 75% of original dose	Interrupt treatment until resolved to grade 0-1 then continue at 50% of original dose	
3rd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1 then continue at 50% of original dose	Discontinue treatment	
4th appearance of same toxicity	Discontinue treatment		

Consider EOF treatment (i.e. substituting 5FU for capecitabine) in patients with severe diarrhoea

Specific Information on Administration

Epirubicin is a vesicant and must be administered first.
Capecitabine tablets must be taken twice daily with food. Patients should be advised not to “double up” on missed doses and not to readminister any dose after vomiting
If the patient has difficulty swallowing, the capecitabine may be dispersed in water. Do not crush the tablets
Patients should be informed of the need to interrupt treatment immediately if they develop moderate or severe side effects particularly diarrhoea (not controlled by loperamide), palmar plantar erythrodyaesthesia, chest pain or infection.
Any unused tablets to be returned at the next appointment

References

D. Cunningham el al NCRI Upper GI Study Group Randomised multicentre phase III study comparing capecitabine with 5FU and oxaliplatin with cisplatin in patients with advanced oesophagogastric (OG) cancer: The REAL 2 trial N Engl J Med 2010; 362:858-859

THIS PROTOCOL HAS BEEN DIRECTED BY DR Mitchell DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER.

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

DATE **July 2017**

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VERSION **8**