

CHEMOTHERAPY PROTOCOL

DRUG REGIMEN

EOF (epirubicin, oxaliplatin, 5-fluorouracil)

Indication for use

1. Locally advanced or metastatic carcinoma of the stomach or oesophagus
2. Patients who are intolerant of or cannot swallow capecitabine.

Drug	Route	Fluid	Time
Epirubicin 50mg/m ²	IV		IV bolus
Oxaliplatin 130mg/m ²	IV	500mls 5% Glucose	IV 2 hours
5-Fluorouracil 200mg/m ² /day	IV		IV infuser over 21 days

Regimen

Day 8 and Day 15, 5-Fluorouracil pump changes,
Regimen to be repeated 3 weekly for 6 cycles

Investigation prior to initiating treatment

FBC, U&Es, LFTs

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 tests 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 levels for treatment to proceed (defer one week or contact consultant)

Neutrophils ≥ 1.0 and platelets ≥ 75

Creatinine Clearance ≥ 50 ml/min

Bilirubin $< 1.5 \times \text{ULN}$, ALT, AST $< 2.5 \text{ ULN}$, Alk Phos $< 2.5 \text{ ULN}$

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 (x10⁹/l)	Platelets (x10⁹/l)	Action
>1.0	> 75	Full Dose
0.5 - 0.9	50-74	Delay until recovery Restart 5-Fluorouracil at full dose Reduce Epirubicin by 25% Reduce Oxaliplatin 100mg/m ² on subsequent cycles
< 0.5	25-49	Delay until recovery Restart 5-Fluorouracil at full dose Reduce Epirubicin by 50% Reduce Oxaliplatin 100mg/m ² on subsequent cycles Discuss with consultant
	<25	Delay until recovery Restart 5-Fluorouracil 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.
5-Fluorouracil	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 inflation duration to 6 hrs.		

If grade 3/4 diarrhoea/stomatitis recurs despite appropriate dose reduction in 5-Fluorouracil, subsequent oxaliplatin should be reduced to 100mg/m².

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 5-Fluorouracil and administer appropriate symptomatic management. If toxicity is adequately controlled with symptomatic measures alone within 2 days, then 5-Fluorouracil 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		

Specific Information on Administration

Epirubicin is a vesicant and must be administered first.

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 erythrodysesthesia, chest pain or infection.

Day 8 and Day 15, 5-Fluorouracil pump changes, obtain FBC but continue with pump unless patient is clinically unwell.

References

D. Cunningham et 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

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