Chemotherapy Protocol

GASTROINTESTINAL (UPPER) CANCER

EPIRUBICIN, FLUOROURACIL and OXALIPLATIN

(EOF)

Regimen

- Gastrointestinal Cancer (upper) – Epirubicin-Fluorouracil-Oxaliplatin (EOF)

Indication

- First line therapy of advanced / metastatic eosophagogastric cancer
- Neoadjuvant therapy of potentially operable eosophagogastric cancer
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Epirubicin	Cardiac failure, urinary discolouration
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured, particularly in patients with a history of cardiac problems or in the elderly.
- FBC, LFT's and U&E's prior to each cycle
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following criteria must be met.

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion or the prescription of an erythropoietin produce according to NICE TA 323 if the patient is symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Neutrophils ($x10^9$/L)	Adjustment
1 or above	Full dose
0.5-0.9	Stop the fluorouracil, and delay treatment until recovery. Give oxaliplatin 100mg/m^2 and epirubicin 37.5mg/m^2. If counts recover re-start the fluorouracil (eg 7 days later)
less than 0.5	Stop the fluorouracil, and delay all treatment until recovery. Give oxaliplatin 100mg/m^2 and epirubicin 25mg/m^2. If counts recover re-start the fluorouracil (eg 7 days later) at the full dose

Platelets ($x10^9$/L)	Adjustment
75 or above	Full dose
50-74	Stop the fluorouracil, and delay treatment until recovery. Give oxaliplatin 100mg/m^2 and epirubicin 37.5mg/m^2. If counts recover re-start the fluorouracil (eg 7 days later)
25-49	Stop the fluorouracil and delay the oxaliplatin and epirubicin until recovery. Give oxaliplatin 100mg/m^2 and epirubicin 25mg/m^2.
less than 25	Stop all three agents until counts have recovered. Omit the epirubicin from subsequent cycles. Restart full dose fluorouracil and oxaliplatin 100mg/m^2.

Dose reductions should apply to all future cycles.

Hepatic Impairment

Drug	Dose (% of original dose)
Epirubicin	If the bilirubin concentration is between 24-51umol/L reduce the dose by 50%. If the bilirubin concentration is more than 51 then administer 25% of the dose
Fluorouracil	In moderate hepatic impairment reduce the initial dose by 33%. In severe hepatic impairment reduce the initial dose by 50%. The dose may be increased as tolerated. Fluorouracil is contra-indicated when the bilirubin is more than 85 or the AST/ALT are more than 180units
Oxaliplatin	Limited information available but there is probably little need to adjust the dose.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Epirubicin	Reduce doses in cases of severe impairment	
Fluorouracil	Consider dose adjustment in severe renal impairment	
Oxaliplatin	In moderate renal impairment, treat at normal dose, and monitor renal function. Dose adjust according to toxicity. If the CrCl is less than 20m/min then dose reduce	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis and palmar-plantar erythrodysesthesia among others.

Fluorouracil

	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	Consider mouthwashes	Stop fluorouracil and restart with a 50mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 100mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 150mg/m^2 dose reduction
Palmer-plantar	Consider topical emollients	Stop fluorouracil and restart with a 50mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 100mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 150mg/m^2 dose reduction
Diarrhoea	Consider anti-diarrheal	Stop fluorouracil until recovered and restart with a 50mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 100mg/m^2 dose reduction	Stop fluorouracil until recovered and restart with a 150mg/m^2 dose reduction

Oxaliplatin

If the neurosensory toxicity is NCI-CTC grade 1–2 and lasts less than 7 days administer full dose oxaliplatin. If the toxicity is NCI-CTC grade 2 and persists for more than 7 days reduce the oxaliplatin dose to 75mg/m^2. Oxaliplatin should be discontinued for neurosensory toxicities NCI-CTC grade 3 or above.

If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the fluorouracil dose the oxaliplatin dose should be reduced to 75mg/m^2.

There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptom occurs stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Regimen

21 day cycle for 8 cycles

Drug	Dose	Days	Route
Epirubicin	50mg/m^2	1	Intravenous bolus over 10 minutes
Fluorouracil	1400mg/m^2 over 7 days	1, 8, 15	Continuous intravenous infusion
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Dose Information

- Epirubicin will be dose banded in accordance with the national dose bands (2mg/ml PM)
- Fluorouracil will be dose banded in accordance with the national dose bands (50mg/ml)
- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Epirubicin – vesicant
- Fluorouracil – inflammitant
- Oxaliplatin - exfoliant

Other

- Central venous access and use of an ambulatory infusion pump is required.

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy
  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication;
  - dexamethasone 4mg twice a day for 3 days oral
  - metoclopramide 10mg three times a day when required
  - ondansetron 8mg twice a day for 3 days

- Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).
- Mouthwashes as per national or local guidelines for the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- A glucose 5% flush should be administered before and after the oxaliplatin

References
1. Cunningham D, Starling N, Rao S et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008: 358 (1): 36-46.

REGIMEN SUMMARY

EPIRUBICIN-FLUOROURACIL-OXALIPLATIN (EOF)

Day One

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Epirubicin 50mg/m^2 intravenous bolus over 10 minutes

4. Oxaliplatin 130mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

8. Fluorouracil 1400mg/m^2 (total dose) continuous infusion in an ambulatory pump over 7 days

Day Eight

9. Fluorouracil 1400mg/m^2 (total dose) continuous infusion in an ambulatory pump over 7 days

Day Fifteen

10. Fluorouracil 1400mg/m^2 (total dose) continuous infusion in an ambulatory pump over 7 days

Take Home Medicines (Day One Only)

9. Dexamethasone 4mg twice a day oral for 3 days starting on day 2 of the cycle

10. Metoclopramide 10mg three times a day when required oral

11. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day 1 of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	June 2015	None	Dr Deborah Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.