**Systemic Anti Cancer Treatment Protocol**

# Epirubicin, Oxaliplatin & Capecitabine (EOX gastric)

**PROTOCOL REF: MPHAUGIEOX**
**(Version No: 1.1)**

## 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

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/m$^2$** | IV | IV bolus with concurrent sodium chloride 0.9% |
| 1 | **Oxaliplatin** | **130mg/m$^2$** | IV | 500mL Glucose 5% over 2 hours |
| 1 to 21 | **Capecitabine** | **625mg/m$^2$ 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

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/m$^2$** | IV | IV bolus with concurrent sodium chloride 0.9% |
| 1 | **Oxaliplatin** | **130mg/m$^2$** | IV | 500mL Glucose 5%over 2 hours |
| 1 to 7 | **Fluorouracil** | **200mg/m$^2$/24hours** | IV | Continuous via infusor device over 7 days |
| 8 to 14 | **Fluorouracil** | **200mg/m$^2$/24hours** | IV | Continuous via infusor device over 7 days |
| 15 to 21 | **Fluorouracil** | **200mg/m$^2$/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

## 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 |
| Dihydropyrimidine dehydrogenase (DPD) deficiency test | X | | | | | This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency. |
| 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**

## Dose Modifications and Toxicity Management:

### Haematological toxicity

Proceed on day 1 if:-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Platelets > 75 x $10^9$/L |

Delay 1 week on day 1 and dose reduce as per table below, if:-

| | |
|---|---|
| ANC ≤ 0.9 x $10^9$/L | Platelets ≤ 74 x $10^9$/L |

| | **Epirubicin dose** | **Oxaliplatin dose** |
|---|---|---|
| ANC 0.5 to 0.9 x $10^9$/L **OR** Platelets 50 to 74 x $10^9$/L | 75% | 100mg /$m^2$ |
| ANC less than 0.5 x $10^9$/L **OR** Platelets 25 to 49 x $10^9$/L | 50% | 100mg /$m^2$ |
| Platelets less than 25 x $10^9$/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 | | |

| | | |
|---|---|---|
| -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.**<br><br>If symptoms are troublesome, e.g. 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