**Systemic Anti Cancer Treatment Protocol**

# Epirubicin, Cisplatin & Capecitabine (ECX gastric)

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

## Approved for use in:

Gastric / gastro-oesophageal junction adenocarcinoma

Neoadjuvant

Adjuvant

Locally advanced / metastatic disease

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Epirubicin | 50mg/m$^2$ | IV | Every 21 days |
| Cisplatin | 60mg/m$^2$ | IV | Every 21 days |
| Capecitabine | 625mg/m$^2$ BD | PO | Continuous |

**Supportive treatments:**

**Antiemetic risk**

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

**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

## Extravasation risk:

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

Cisplatin – Irritant - Follow trust / network extravasation guidelines, no specific treatment needed

## Administration:

Review patient's fluid intake over the previous 24 hours

Calculate creatinine clearance using Cockroft and Gault equation

| Day | Drug | Dosage | Route | Diluent and Rate |
|---|---|---|---|---|
| 1 | **Aprepitant** 30 minutes prior to chemotherapy | 125mg | PO | With 80mg on days 2 and 3 |
| 1 | **Dexamethasone** 30 minutes prior to chemotherapy | 12mg | PO | |
| 1 | **Ondansetron** 30 minutes prior to chemotherapy | 24mg | PO | |
| 1 | Furosemide | 20mg | PO | |
| 1 | **Epirubicin** | **50mg/m$^2$** | IV | IV bolus with concurrent sodium chloride 0.9% |
| 1 | Sodium Chloride 0.9% with 20mmol potassium chloride | 1000mL | IV | Over 90 minutes |
| 1 | Monitor urine output – see notes below | | | |
| 1 | **Cisplatin** | **60mg/m$^2$** | IV | 1000mL Sodium Chloride 0.9% over 90 minutes |
| | Sodium Chloride 0.9% with 20mmol potassium chloride | 1000mL | IV | Over 90 minutes |
| 1 to 21 | **Capecitabine** | **625mg/m$^2$ BD** | PO | Morning and evening continuously |

**Neo adjuvant**: Give 3 cycles

**Adjuvant** – Give 3 cycles post operatively

**Advanced** – Give 3 cycles and reassess, may continue to 6 cycles subject to patient choice, tolerability and response

**Notes**

Ensure adequate hydration pre and post cisplatin

Do not start Cisplatin infusion unless urine output is at least 100mL/hour estimated from the previous 3 hours

If necessary administer further 500mL 0.9% sodium chloride and furosemide 20mg orally.

The patient should be asked to drink 2 litres of fluid over 24 hours after the infusion and should contact the unit immediately if unable to do so for any reason.

**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, morning and evening

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 (ECF regimen)**

| Day | Drug | Dosage | Route | Diluent and Rate |
|---|---|---|---|---|
| 1 | **Aprepitant** Immediately prior to hydration | 125mg | PO | With 80mg on days 2 and 3 |
| 1 | **Dexamethasone** Immediately prior to hydration | 12mg | PO | |
| 1 | **Ondansetron** Immediately prior to hydation | 24mg | PO | |
| 1 | Furosemide | 20mg | PO | |
| 1 | **Epirubicin** | **50mg/m$^2$** | IV | IV bolus with concurrent sodium chloride 0.9% |
| 1 | 20mmol potassium chloride | Sodium Chloride 0.9% 1000mL | IV | Over 90minutes |
| 1 | Monitor urine output – see notes below | | | |
| 1 | **Cisplatin** | **60mg/m$^2$** | IV | 1000mL Sodium Chloride 0.9% over 90 minutes |
| | 20mmol potassium chloride | Sodium Chloride 0.9% 1000mL | IV | Over 90 minutes |
| 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, renal impairment, nausea and vomiting, stomatitis, ovarian failure/infertility, cardiotoxicity

Cisplatin: Neuropathy, ototoxicity, nephrotoxicity

Capecitabine / Fluorouracil: Diarrhoea, PPE

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

## 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 |
| CT scan | X | | | | | Surgical arrangement if neoadjuvant intent |
| 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. |
| 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 ECF regimen blood tests are not required on day 8 and day 15.**

## Dose Modifications and Toxicity Management:

For patients with specific cisplatin related toxicities who are still fit to continue treatment e.g. tinnitus, consider switch to EOX.

### 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 |

| Day 1 of cycle | **Epirubicin dose** | **Cisplatin dose** | **Capecitabine dose** |
|---|---|---|---|
| ANC 0.5 to 0.9 x $10^9$/L OR Platelets 50 to 74 x $10^9$/L | 75% | Full | Full |
| ANC < 0.5 x $10^9$/L OR Platelets 25 to 49 x $10^9$/L | 50% | Full | Full |
| Platelets < 25 x $10^9$/L | Omit | Full | Full |

### Non-haematological toxicity

**Renal**

Cisplatin is eliminated primarily (>90%) in the urine and is itself nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Recalculate CrCl using Cockroft and Gault every cycle

| **GFR (mL/min)** | **Cisplatin dose** | **Capecitabine dose** |
|---|---|---|
| ≥ 60 | 100% dose | 100% dose |
| 50 to 59 | 50% dose | 100% dose |
| 40 to 49 | 50% dose | 75% dose |
| <40 | Consider carboplatin | 75% dose |

**Hepatic**

If bilirubin increases to 1.5 times ULN epirubicin should be omitted until it returns to normal level.

If bilirubin increases to 3 times ULN or ALT/AST to 2.5 times ULN, omit capecitabine until liver function recovers

No modifications needed with cisplatin

## Capecitabine dose adjustment guidelines for non haematological toxicities, including diarrhoea, vomiting, stomatitis, and PPE

| Common Toxicity Criteria | 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% |
| -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% |
| -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 |

### 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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