ECarboX – Epirubicin, Carboplatin and Capecitabine

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Fast Running / Line Flush</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral / Slow bolus / 15 min infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>50 mg/m²</td>
<td>IV Bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>AUC 3 to 5*</td>
<td>IV Infusion</td>
<td>500/250ml 5% Glucose over 30 to 60 Minutes</td>
</tr>
<tr>
<td>1 to 21</td>
<td>Capecitabine</td>
<td>625mg/m² TWICE Daily</td>
<td>Oral</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

DOSE FORM
Capecitabine is supplied as 150mg and 500mg tablets.

*CARBOPLATIN DOSAGE
Dose (mg) = AUC x (GFR + 25) standard dose is AUC=5 but this can be reduced depending on patients performance status

Where the GFR is the non-corrected EDTA clearance.
If estimated GFR is undertaken the Wright formula should be used with AUC 5. Avoid use of Cockcroft & Gault formulae as it is less accurate.

CYCLE LENGTH AND NUMBER OF DAYS
21 DAYS usually for 6-8 cycles

APPROVED INDICATIONS
Upper GI cancers including metastatic oesophago-gastric cancers

ELIGIBILITY CRITERIA
ECOG performance status 0-1, Karnofsky performance status >70% Adequate hepatic, renal, marrow and cardiac function

EXCLUSION CRITERIA
Inability to swallow Capecitabine tablets

PREMEDICATION
As above

RECOMMENDED TAKE HOME MEDICATION
Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10 mg three times daily as required
*Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

INVESTIGATIONS / MONITORING REQUIRED
FBC, U&Es and LFTs. Check renal function before commencing platinum.
Use EDTA or Wright formulae to calculate GFR
Prior to each cycle
FBC, U&Es, LFTs as required; GFR doubled checked using Wright formulae

ASSESSMENT OF RESPONSE
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN
To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

ADMINISTRATION NOTES
• Carboplatin is frequently substituted for cisplatin in chemotherapy protocols due to greater tolerability. However, in certain tumour groups, including oesophageal carcinoma, evidence from early trials suggested carboplatin is less active.
• Evidence from a published case series (Price et al 2002) suggests that the substitution of carboplatin ‘does not appear to be deleterious in the palliative treatment of advanced oesophageal carcinoma.’
• ECarboF and ECarboX may be used instead of ECF and ECX respectively however it must be noted there is more evidence of benefit for the EOX combination.
• Patient needs Glomerular Filtration Rate (GFR) prior to commencement of treatment for calculation of Carboplatin dosage. Subsequent measurement of GFR only needed if serum creatinine changes by >20% from initial measurement.

Counselling Points for Oral Capecitabine
How to take: Take tablets 12 hours apart, within 30 minutes after the end of meal (i.e. breakfast & evening meal.) Swallow whole with water

Side effects Common side effects to discuss with patient include; diarrhoea, nausea & vomiting, stomatitis (mouth ulcers), hand-foot syndrome (painful red swelling in hands and feet), fever or infection. If patients notice any of these advise them to stop taking treatment, contact doctor/chemotherapy day unit who will take steps to manage side effects and advise on continuing treatment.

Missed dose: If remember half an hour after they should have taken their tablets, then take the missed dose, otherwise only take the regular dose at next scheduled time. Do not double-up doses to make up for the missed doses or take extra doses at the end of the treatment cycle.

Post dose vomiting: In the case of vomiting within a few hours after drug intake, never repeat the administration of the dose.

Storage/ Disposal Tablets should be stored in cool dry place less than 30°C. Unused medicines must be returned to hospital pharmacy for disposal

Diarrhoea is common and may require intervention with fluids and electrolytes if severe. If diarrhoea is a problem, give loperamide 2 to 4 mg four times daily as required or codeine phosphate 30mg four times daily and stop taking Capecitabine if diarrhoea moderate/severe.

EXTRAVASATION See NCA/ Local Policy
Epirubicin is a vesicant drug. If extravasation occurs there is high risk of tissue damage.
TOXICITIES
- Risk of hypersensitivity and anaphylaxis, particularly on first and second cycle, start within a few minutes of administration
- Palmar/Plantar Erythrodysesthesia - Can be severe, patients must be forewarned
- Nausea and vomiting
- Cardiotoxicity. Maximum cumulative dose of epirubicin 900 mg/m².
- Hypotension and bradycardia
- Myelosuppression, particularly, thrombocytopenia, anaemia & neutropenia
- Nephrotoxicity
- Alopecia
- Peripheral neuropathy
- Otological impairment, especially at 8000 Hz
- Myalgia
- Back pain on administration
- Diarrhoea
- Stomatitis
- Hyperpigmentation
- Red urine for up to 24 hours with epirubicin

DOSE MODIFICATION / TREATMENT DELAYS
Haematological toxicity:

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>≥ 100</td>
<td>Full dose</td>
</tr>
<tr>
<td>1.0 – 1.5</td>
<td>75 – 100</td>
<td>Delay Carboplatin and Epirubicin until recovery. If patient well capecitabine can continue. Restart Carboplatin, Epirubicin at full dose unless delay &gt; 1 week</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>50 – 75</td>
<td>Interrupt Capecitabine, delay Carboplatin and Epirubicin until recovery. Restart Epirubicin with 25% dose reduction</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>&lt; 25</td>
<td>Interrupt Capecitabine and delay Carboplatin and Epirubicin until recovery. Restart Epirubicin with 50% dose reduction</td>
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</table>

Non-Haematological Toxicity for Oral Capecitabine
Any patient with CTC toxicity should be prescribed the therapeutic option for grade 1 toxicity in addition to dose modification.

Table of dose adjustments according to Common Toxicity Criteria (CTC)

<table>
<thead>
<tr>
<th>Grade</th>
<th>1st appearance</th>
<th>2nd appearance</th>
<th>3rd appearance</th>
<th>4th appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Interrupt until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible</td>
<td>Interrupt until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis where possible</td>
<td>Interrupt until resolved to grade 0/1, then continue at 50% of original dose</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Interrupt until resolved to grade 0/1, then continue at 75% of original dose</td>
<td>Interrupt until resolved to grade 0/1, then continue at 50% of original dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue treatment</td>
<td></td>
<td></td>
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</table>

Discontinue treatment
Table of hand/ foot toxicity grading for capecitabine only

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Numbness, dysesthesia/paraesthesia,</td>
<td>Discomfort but no interruption of normal activities</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema with swelling</td>
<td>Discomfort which affects activities of daily living</td>
</tr>
<tr>
<td>3</td>
<td>Moist desquamation, ulceration, blistering, severe pain</td>
<td>Severe discomfort, unable to work or perform activities of daily living</td>
</tr>
</tbody>
</table>

Table of Diarrhoea toxicity grading for capecitabine only

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Toxicity</th>
<th>% Capecitabine</th>
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<tbody>
<tr>
<td>1</td>
<td>Diarrhoea (watery stool 2-3 times/day)</td>
<td>Hold until recovery, then resume at 100% dose for remainder of course</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhoea (watery stool 4-6 times/day)</td>
<td>Hold until recovery, then resume at 75% dose for remainder of course</td>
</tr>
<tr>
<td>3/4</td>
<td>Diarrhoea (watery stool &gt;7 times/day)</td>
<td>Following grade 3 or 4 diarrhoea, subsequent doses of capecitabine should be decreased or treatment discontinued permanently (grade 4).</td>
</tr>
</tbody>
</table>

Renal dysfunction:
Capecitabine
- Capecitabine is renally excreted; therefore, patients with moderate renal impairment (CrCl < 50ml/min) require a 25% dose reduction.
- Contra-indicated in severe renal failure (CrCl < 30ml/min) (Wright equation or measured GFR)

Carboplatin
- Serum creatinine should be checked before each cycle of treatment. If there is a >20% increase compared to the baseline, then the EDTA must be repeated.
- If Wright formulae calculated clearance alters by > 20%, an EDTA clearance should be repeated and dose modification of the chemotherapy may be required, discuss with Oncologist
- If the GFR is 30 ml/min or less DO NOT GIVE and consult with prescriber before proceeding

Hepatic dysfunction:
- If bilirubin > 30µmol/L, then epirubicin should be omitted.
- No studies have been performed to examine safety of capecitabine in severe hepatic dysfunction.
- IF ALT >= 5ULN or ALP >= 5ULN, DO NOT GIVE and and consult with prescriber before proceeding

Infection
- Grade III infection associated with neutropenia requires a dose reduction of epirubicin by 25%
- Grade IV infection associated with neutropenia requires a dose reduction of epirubicin by 50%
TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REFERENCES:

Document Control

<table>
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<tr>
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<td>CRP09 UGI004</td>
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<tr>
<td>Reviewer(s):</td>
<td>Chris Beck – Chemo Pharmacist NCA</td>
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<tr>
<td>Date Approved:</td>
<td>09.03.2018</td>
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<tr>
<td>Approved by:</td>
<td>Steve Williamson Consultant Pharmacist NCA</td>
</tr>
<tr>
<td>Due for Review:</td>
<td>09.03.2021</td>
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Summary of Changes
1.1 Reformatted from old NCN/CCA versions
1.3 Protocol reviewed and reissued, Antiemetic advice updated
1.4 Updated with Chemocare parameters, updated capecitabine advice.