EC-Docetaxel: Epirubicin / Cyclophosphamide followed by Docetaxel in Breast Cancer

Indication: Neoadjuvant therapy for high risk and fit Breast Cancer patients, suitable for a taxane containing regimen

EC

Regimen details:
- Epirubicin 90mg/m² IV D1
- Cyclophosphamide 600mg/m² IV D1

Administration: Epirubicin IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion
Cyclophosphamide may be administered as IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion or as a short infusion e.g. in 250ml Sodium Chloride 0.9% over 30 minutes

Frequency: Every 21 days, for 4 cycles, followed by 4 cycles Docetaxel (see Docetaxel, page 3)

Extravasation:
- Epirubicin: Vesicant
- Cyclophosphamide: Non-vesicant

Anti- emetics: Highly emetogenic. Follow Local Anti-emetic Policy

Regular investigations:
- FBC D1
- LFTs D1
- U&Es D1
- MUGA scan/Echocardiogram Prior to 1st cycle (see Comments)

Comments:
- Maximum cumulative dose Epirubicin = 950mg/m²
- A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, diabetes, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or Echocardiogram should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum

DOSE MODIFICATIONS

Haematological Toxicity

Day 1

WBC < 3.0 x 10^9/L Delay for 1 week.
or Neutrophils < 1.0 x 10^9/L Repeat FBC - If within normal parameters, resume
or Platelets < 100 x 10^9/L all drugs with 100% doses
In adjuvant treatment, dose reduction and delays can compromise outcome. G-CSF should be considered if more than one delay and/or before dose reduction. If in doubt, contact the relevant Consultant.

**Subsequent cycles**
If Neutrophils < 0.5 x 10^9/L for ≥7 days OR
Febrile neutropenia is diagnosed OR
Platelets < 50 x 10^9/L,

Seek Consultant advice and consider a longer course of G-CSF or a dose reduction to 85% from previous doses in all drugs (do not escalate for subsequent cycles). If the patient continues to experience these side effects at the lower dose, treatment should be discontinued.

**Renal Impairment:**
Epirubicin:
If patients have Creatinine > 3.0 – 6.0 x ULN OR higher creatinine levels OR,
GFR < 10ml/min, contact the relevant Consultant and consider dose reduction.

Full Cyclophosphamide dose is not recommended in patients with a plasma creatinine above the upper limit of the normal range at the institution. Dose adjustments for Cyclophosphamide should be made using Cockcroft and Gault following the guidelines below. EDTA should be requested so that the dose can be adjusted if necessary, according to EDTA result, on all subsequent cycles.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cyclophosphamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Give 100%</td>
</tr>
<tr>
<td>10 – 50</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

**Hepatic Impairment:**
Cyclophosphamide is not recommended in patients with a bilirubin > 17 µmol/L or AST/ALT more than 2 – 3 x upper normal limit, however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Decision should be discussed with the Consultant.

Epirubicin dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Epirubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>51 – 85</td>
<td>Give 25%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

**DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis, grade 2 or higher</td>
<td>Delay for a maximum of 2 weeks</td>
</tr>
<tr>
<td>Mucositis recovered to at least grade 2</td>
<td>Give Epirubicin 75mg/m² and Cyclophosphamide 500mg/m²</td>
</tr>
<tr>
<td>Mucositis greater than grade 2 persisted</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Neuropathy, grade 3</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

Reason for Update: Network Protocol Development

| Version: 1 | Approved by Breast Consultant: Anne Rigg |
| Supersedes: All other versions | Date: 15/04/09 |
| Prepared by: Maria Teresa Pacheca-Palomar March '09 | Checked by (Network Pharmacist): Jacky Turner |
| Approved by SELCN DTAC Chair: Nic Ketley | Date: 23/07/09 |

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Toxicities: Myelosuppression; nausea; vomiting; diarrhoea; mucositis; stomatitis; cardiotoxicity; alopecia; urine discoloration; haemorrhagic cystitis; alopecia; infertility; early menopause

Drug interactions: Epirubicin and Cyclophosphamide
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Phenytoin: reduced absorption of the antiepileptic

Epirubicin
- Cimetidine and Ciclosporin: can increase Epirubicin serum levels
- Verapamil: possibly increases Epirubicin bone marrow depressant effects

Cyclophosphamide
- Allopurinol: can increase the incidence of serious bone marrow depression
- Amiodarone: increased risk of pulmonary fibrosis; avoid combination if possible
- Grapefruit juice: decreased or delayed activation of Cyclophosphamide
  Avoid grapefruit juice for 48 hours before and on day of dose
- Indapamide: prolonged leucopenia is possible
- Itraconazole: might increase Cyclophosphamide side effects e.g. haemorrhagic Cystitis, pigmentation of palms, nails and soles etc..
- Warfarin: the anticoagulant effect is increased

Followed by Docetaxel

Regimen details: Docetaxel 100mg/m² IV D1

Administration: Docetaxel in 250mls Sodium Chloride 0.9% IV over 1 hour

Premedication: Dexamethasone 8mg po bd for 3 days, starting the morning of the day prior to each Docetaxel administration, to reduce the incidence and severity of fluid retention and hypersensitivity reactions. If the patient has not taken the oral pre-med for any reason, Dexamethasone 20mg IV should be administered 1 hour prior chemotherapy

Frequency: Every 21 days, for 4 cycles, starting 21 days after final cycle of EC

Extravasation: Vesicant

Anti- emetics: Low emetogenic

Supportive medication: Primary Prophylactic Growth Factor support should be used starting at least 24 hours post chemotherapy given with each cycle of chemotherapy, following the local Guidelines for the Use of Colony Stimulating Factors to Manage Neutropenia

Regular investigation: FBC D1
  LFTs D1
  U&Es D1
Comments: Hypersensitivity reactions may occur, during the first and second infusions, within a few minutes following the initiation of the infusion

<table>
<thead>
<tr>
<th>Degree of symptoms</th>
<th>Hypersensitivity reactions</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Flushing</td>
<td>Do not require interruption of therapy. Administer prophylactic anti-anaphylactic medication before further cycles of Docetaxel.</td>
</tr>
<tr>
<td></td>
<td>Localised cutaneous reaction</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Severe hypotension</td>
<td>Require immediate discontinuation of Docetaxel.</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>Administer appropriate aggressive therapy.</td>
</tr>
<tr>
<td></td>
<td>Generalised rash/erythema</td>
<td></td>
</tr>
</tbody>
</table>

**DOSE MODIFICATIONS**

**Haematological Toxicity**

**Day 1**

- WBC < 3.0 x 10^9/L
- Neutrophils < 1.0 x 10^9/L
- Platelets < 100 x 10^9/L

**Subsequent cycles:**

- Neutrophils < 0.5 x 10^9/L for more than 7 days, OR
- Febrile neutropenia is diagnosed, OR
- Platelets < 50 x 10^9/L,

If still these low counts despite Docetaxel dose reduction and G-CSF support, seek Consultant advice about further Docetaxel dose reduction.

**Renal Impairment:** Docetaxel: No dose adjustment required

**Hepatic Impairment**

<table>
<thead>
<tr>
<th>ALP</th>
<th>and</th>
<th>AST/ALT</th>
<th>and/or</th>
<th>Bilirubin</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.5 x ULN</td>
<td>≤ 1.5 x ULN</td>
<td>Full dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 – 6 x ULN</td>
<td>1.6 – 3.5 x ULN</td>
<td>75% dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 x ULN</td>
<td>&gt; 3.5 x ULN</td>
<td>Not recommended. Docetaxel should be administered with Consultant approval</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

CUTANEOUS REACTIONS / PERIPHERAL NEUROPATHY - DOCETAXEL

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cutaneous reactions</th>
<th>Neuropathy-sensory</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema without associated symptoms</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>100% dose</td>
</tr>
<tr>
<td>2</td>
<td>Localized erythema of the palms of the hands and soles of the feet with oedema followed by desquamation</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>May consider reduce Docetaxel dose to 75mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Severe, generalised eruptions followed by desquamation</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Delay Docetaxel until recovery to grade ≤ 2, thereafter, reduce Docetaxel dose to 75mg/m². If symptoms return, discontinue Docetaxel</td>
</tr>
<tr>
<td>4</td>
<td>Generalised exfoliative, ulcerative, or bullous dermatitis</td>
<td>Disabling</td>
<td>Discontinue Docetaxel, permanently</td>
</tr>
</tbody>
</table>

Toxicities: Myelosuppression; nausea; vomiting; diarrhoea; stomatitis; asthenia; fluid retention; peripheral neuropathy; hypersensitivity reactions; cutaneous reactions (reversible); nail disorder; ovarian failure; infertility

Drug interactions: Concomitant administration of substrates, inducers or inhibitors of cytochrome P450-3A e.g. ciclosporin, terfenadine, ketoconazole, erythromycin etc, may alter the pharmacokinetics of docetaxel, presenting a theoretical interaction

References:
- www.medicines.org.uk
- GSTT guidelines for treating nausea and vomiting in adult patients. Sept 2007
- UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. Nov 2003
- Stockley’s Drug Interactions. Interactions search: Cyclophosphamide, Epirubicin and Docetaxel. March 2009
- CTCAE v 3.0. August 2006