EC: Epirubicin / Cyclophosphamide in Advanced / Metastatic Breast Cancer

Indication: First line palliative therapy in locally Advanced / Metastatic Breast Cancer with no prior exposure to anthracyclines

Regimen details:
- Epirubicin 60 - 90mg/m²(*)  IV  D1
- Cyclophosphamide 600mg/m²  IV  D1

(*) May consider Epirubicin 60mg/m² if patient > 60

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: 21 days, 6 cycles

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

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

Regular investigation:
- FBC  D1
- LFTs  D1
- U&Es  D1
- CT scan  Every 3 cycles
- MUGA scan  see Comments (if necessary)

Comments: Maximum cumulative dose Epirubicin= 950mg/m²
- A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy.
- MUGA scan 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 10⁹/L  Delay for 1 week.
- or
Neutrophils < 1.5 x 10⁹/L  Repeat FBC - If within normal parameters, resume treatment with 100% doses
- or
Platelets < 100 x 10⁹/L
Subsequent cycles

If Neutrophils < 0.5 x 10⁹/L for 1 week, OR
Febrile neutropenia is diagnosed, OR
Platelets < 50 x 10⁹/L,
Epirubicin and Cyclophosphamide doses should be reduced to 80% from previous dose (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:** The 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

Mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and the sublingual mucosa. For grade III Painful erythema or ulcers requiring IV rehydration resolving to Grade I or less painless ulcers or mild soreness: give Epirubicin 80% dose and recommend regular mouth care

Toxicities:

Leucopenia; Myelosuppression; neutropenia; thrombocytopenia; cardiotoxicity; mucositis; Stomatitis; nausea; vomiting; diarrhoea; alopecia; lack of beard growth in males; urine discoloration; haemorrhagic cystitis; potential risk of 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

References:

www.medicines.org.uk
ASWCS Chemotherapy Handbook January 2005
SWSHCN- Approved Network Regimen for Breast Cancer. March 2008
HYCCN – Approved Network Regimen for Breast Cancer. April 2008
SWSHCN – Approved Network Regimen for Breast Cancer. March 2008
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
CTCAE v3.0. August 2006