Epirubicin and Cyclophosphamide) (breast)

Indication
Palliative treatment of advanced breast cancer.

(NICE CG81)

ICD-10 codes
Codes with a prefix C50

Regimen details

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epirubicin</td>
<td>75*mg/m²</td>
<td>IV bolus</td>
</tr>
<tr>
<td>1</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV bolus</td>
</tr>
</tbody>
</table>

*consider epirubicin 60mg/m² for patients with significant co-morbidity

Cycle frequency
21 days

Number of cycles
Maximum of 6 cycles

Administration
Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication
Nil

Emetogenicity
This regimen has moderate - high emetic potential

Additional supportive medication
Mouthwashes as per local policy
Antiemetics as per local policy
H₂ antagonist or proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.

Extravasation
Epirubicin is a vesicant (Group 5)
Cyclophosphamide is neutral (Group 1)
**Investigations – pre first cycle**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period (or as per local policy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>14 days</td>
</tr>
<tr>
<td>U+E (including creatinine)</td>
<td>14 days</td>
</tr>
<tr>
<td>LFTs</td>
<td>14 days</td>
</tr>
</tbody>
</table>

ECHO or MUGA if significant cardiac history or previous anthracycline treatment.

**Investigations - pre subsequent cycles**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period (or as per local policy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>96 hours</td>
</tr>
<tr>
<td>U+E (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
<td>LFTs</td>
<td>7 days</td>
</tr>
</tbody>
</table>

**Standard limits for administration to go ahead**

If blood results not within range, authorisation to administer must be given by prescriber/consultant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>≥ 1.0 x 10^9/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100 x 10^9/L</td>
</tr>
<tr>
<td>Creatinine Clearance (CrCl)</td>
<td>&gt; 20 mL/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≤ 1.5 ULN</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>≤ 2 x ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>≤ 2.5 x ULN</td>
</tr>
</tbody>
</table>

**Dose modifications**

- **Haematological toxicity**
  If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay 1 week or until recovery.

  If myelosuppression results in delays of subsequent cycles, consider reducing to 80% dose.

- **Renal impairment**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Cyclophosphamide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>100%</td>
</tr>
<tr>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

There is no data available on the use of epirubicin in severe renal impairment. Consider dose reduction if CrCl < 10 mL/min (consultant decision).

- **Hepatic impairment**

<table>
<thead>
<tr>
<th>Bilirubin (x ULN)</th>
<th>AST/ALT (x ULN)</th>
<th>Alkaline phosphatase (x ULN)</th>
<th>Epirubicin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>and</td>
<td>≤ 2.5</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 - &lt; 3</td>
<td>or</td>
<td>&gt; 2.0</td>
<td>50%</td>
</tr>
<tr>
<td>3 - &lt; 5</td>
<td>or</td>
<td>&gt; 3.5</td>
<td>25%</td>
</tr>
<tr>
<td>≥5</td>
<td>or</td>
<td>&gt; 10</td>
<td>Omit</td>
</tr>
</tbody>
</table>

*Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).*
• **Other toxicities**
For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reducing epirubicin to 80% dose.

Any other grade 3 or 4 toxicity - discuss with consultant.

**Adverse effects** - for full details consult product literature/ reference texts

• **Serious side effects**
Secondary malignancy
Myelosuppression
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity

• **Frequently occurring side effects**
Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Alopecia

• **Other side effects**
Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

**Significant drug interactions** – for full details consult product literature/ reference texts

*Warfarin/coumarin anticoagulants:* increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

*Phenytoin:* requires close monitoring if using concurrently.

*Co-trimoxazole/trimethoprim:* enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

*Cyclophosphamide:*

*Amiodarone:* increased risk of pulmonary fibrosis – avoid if possible

*Clozapine:* increased risk of agranulocytosis – avoid concomitant use

*Digoxin tablets:* reduced absorption – give as liquid form

*Indapamide:* prolonged leucopenia is possible - avoid

*Itraconazole:* may increase adverse effects of cyclophosphamide

*Grapefruit juice:* decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.
**Additional comments**
Cardiotoxicity has been associated with anthracyclines therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Epirubicin has a life time maximum cumulative dose of 900mg/m$^2$.

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**References**

- Summary of Product Characteristics Epirubicin (Hospira) accessed on 6 November 2014 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Summary of Product Characteristics Cyclophosphamide accessed on 6 November 2014 via [http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs](http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs)

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