**FEC 100 (Fluorouracil, Epirubicin and Cyclophosphamide) (breast)**

**Indication**
Adjuvant or neo-adjuvant treatment for high risk lymph node negative and node positive early breast cancer.

(NICE CG80)

**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>*100mg/m²</td>
<td>IV bolus</td>
</tr>
<tr>
<td>1</td>
<td>Fluorouracil</td>
<td>500mg/m²</td>
<td>IV bolus</td>
</tr>
<tr>
<td>1</td>
<td>Cyclophosphamide</td>
<td>500mg/m²</td>
<td>IV bolus</td>
</tr>
</tbody>
</table>

*FEC75 (Epirubicin 75mg/m²) is used for patients with significant comorbidities*

**Cycle frequency**
21 days

**Number of cycles**
Maximum of 6 cycles

**Administration**

Epirubicin, fluorouracil 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-medications**
None usually required

**Emetogenicity**
This regimen has moderate - high emetic potential

**Additional supportive medication**

GCSF prophylaxis as per local policy
Mouthwashes as per local policy
Antiemetetics 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)
Fluorouracil is an inflammatory (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>$\geq 1 \times 10^9/L$</td>
</tr>
<tr>
<td>Platelets</td>
<td>$\geq 100 \times 10^9/L$</td>
</tr>
<tr>
<td>Creatinine Clearance (CrCl)</td>
<td>$&gt; 20 \text{ mL/min}$</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>$\leq 1.5 \text{ ULN}$</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>$\leq 2 \times \text{ ULN}$</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>$\leq 2.5 \times \text{ ULN}$</td>
</tr>
</tbody>
</table>

Dose modifications

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

  If febrile neutropenia or neutrophils $<0.5 \times 10^9/L$ for more than 1 week consider reducing doses of all drugs to 80% for future cycles.

  In adjuvant treatment dose reduction and delays can compromise outcome. GCSF should be considered if more than one delay and/or dose reduction.

- **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 or fluorouracil in severe renal impairment. Consider dose reduction if CrCl $<10\text{mL/min}$ (consultant decision).
**Hepatic impairment**

<table>
<thead>
<tr>
<th>Bilirubin (x ULN)</th>
<th>AST/ALT (x ULN)</th>
<th>Alkaline phosphatase (xULN)</th>
<th>Epirubicin dose</th>
<th>Fluorouracil dose</th>
<th>Cyclophosphamide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>and</td>
<td>≤ 2.0 and 2.5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 - &lt; 3</td>
<td>or</td>
<td>&gt; 2.0 – 3.5 or 2.5 - &lt;5</td>
<td>50%</td>
<td>100%</td>
<td>100%*</td>
</tr>
<tr>
<td>≥3 - 5</td>
<td>or</td>
<td>&gt; 3.5 and 5-10</td>
<td>25%</td>
<td>Consider dose reduction (discuss with consultant)</td>
<td>Consider dose reduction (discuss with consultant)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>or</td>
<td>&gt; 10</td>
<td>Omit</td>
<td>Omit</td>
<td>Contraindicated</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 reduce dose of fluorouracil and 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
  - Infusion related reactions
  - Anaphylaxis
  - Teratogenicity
  - Infertility/Early menopause
  - Cardiotoxicity

- **Frequently occurring side effects**
  - Diarrhoea
  - Constipation
  - Fatigue
  - Nausea and vomiting
  - Myelosuppression
  - Stomatitis and mucositis
  - Peripheral neuropathy
  - Arthralgia and myalgia
  - 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 and fluoropyrimidine 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.

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism – avoid use in patients with known DPD deficiency.

Epirubicin has a life time maximum cumulative dose of 900mg/m²

**References**
- Bonneterre, J., et al. JSC. 2005. 23 (12) 2686-2693

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