**Indication**
Adjuvant or neo-adjuvant treatment for high risk early and locally advanced breast cancer.

(NICE CG80)

**ICD-10 codes**
Codes with a prefix C50

**Regimen details**

**Cycles 1-3**

<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>

*lower doses of 60mg/m² or 75mg/m² may be used for patients with significant co-morbidity

**Cycles 4-6**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Docetaxel</td>
<td>100mg/m²</td>
<td>IV infusion</td>
</tr>
</tbody>
</table>

**Cycle frequency**
21 days

**Number of cycles**
Maximum of 6 cycles (3 x FEC100 followed by 3 x docetaxel)

**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.

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.
Pre-medication
FEC cycles: none usually required

Docetaxel cycles: Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment). In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity
FEC cycles: moderate - high emetic potential

Docetaxel cycles: moderate emetic potential

Additional supportive medication
Primary GCSF prophylaxis as per local policy
Mouthwashes as per local policy
H$_2$ 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 inflammatant (Group 5)
Cyclophosphamide is neutral (Group 1)
Docetaxel is an exfollient

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>$\geq 1.0 \times 10^9$/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>$\geq 100 \times 10^9$/L</td>
</tr>
<tr>
<td>Creatinine Clearance (CrCl)</td>
<td>$&gt; 20$ mL/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>$\leq 1.0$ ULN</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>$\leq 1.5 \times$ ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>$\leq 2.5 \times$ 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 febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses of all drugs to 80% for future cycles.

- **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 <10mL/min (consultant decision).
  
  Docetaxel: consider dose reduction if CrCl <10mL/min (consultant decision).

- **Hepatic impairment**

  **FEC cycles:**

<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</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</td>
<td>50%</td>
<td>100%</td>
<td>100%*</td>
</tr>
<tr>
<td>≥ 3 - 5</td>
<td>or</td>
<td>&gt; 3.5</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).

  **Docetaxel cycles:**

<table>
<thead>
<tr>
<th>AST/ALT (x ULN)</th>
<th>Alkaline phosphatase* (x ULN)</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>and</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>or</td>
<td>75%</td>
</tr>
<tr>
<td>≥ 3.5</td>
<td>or</td>
<td>Discuss with consultant</td>
</tr>
</tbody>
</table>

  *unless due to bone metastases only.
  
  If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

- **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
  - Peripheral neuropathy

- **Frequently occurring side effects**
  - Diarrhoea
  - Constipation
  - Fatigue
  - Nausea and vomiting
  - Myelosuppression
  - Stomatitis and mucositis
  - 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.

**Docetaxel:**

**CYP3A4 Enzyme inducers/inhibitors:** in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.
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
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed 9 July 2014 via www.medicines.org.uk

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