**Indication**
Adjuvant treatment for node positive or high risk node negative early breast cancer when an anthracycline is contra-indicated.

(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>Docetaxel</td>
<td>75mg/m²</td>
<td>IV infusion</td>
</tr>
<tr>
<td>1</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV slow bolus</td>
</tr>
</tbody>
</table>

**Cycle frequency**
21 days

**Number of cycles**
4 - 6 cycles

**Administration**
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.

Cyclophosphamide is 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**
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**
This regimen has mild - moderate emetic potential

**Additional supportive medication**
Mouthwashes as per local policy
H\_2 antagonist or proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.
GCSF is not usually required as primary prophylaxis but may be considered after occurrence of febrile neutropenia.

**Extravasation**
Docetaxel is an exfoliant (Group 4)
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>

**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>$\leq 1.5$ x ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>$\leq 2.5$ x ULN</td>
</tr>
</tbody>
</table>

**Dose modifications**

- **Haematological toxicity**
If neutrophils $<1.0 \times 10^9$/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 GCSF prophylaxis for all subsequent cycles. If a second occurrence reduce doses of docetaxel and cyclophosphamide 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 docetaxel in severe renal impairment. No modifications required.
**Hepatic impairment**

<table>
<thead>
<tr>
<th>AST/ALT (x ULN)</th>
<th>Alkaline phosphatase* (x ULN)</th>
<th>Docetaxel dose</th>
<th>Cyclophosphamide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5 and &lt; 2.5</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.5 or ≥ 2.5-6</td>
<td>75%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5 or ≥ 6</td>
<td>Discuss with consultant</td>
<td></td>
<td></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**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Grade 2</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Discuss with consultant</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Grade 3 or 4</td>
<td>1st occurrence – 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd occurrence – 60%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Grade 3 or 4</td>
<td>1st occurrence – 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd occurrence – 60%</td>
</tr>
</tbody>
</table>

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
  - 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
  - Deranged liver function
  - Phlebitis
  - Skin toxicity
  - Nail changes
  - Taste disturbances
  - Bladder irritation
**Significant drug interactions** – for full details consult product literature/ reference texts

**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.

**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.

**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
- **Phenytoin:** reduced absorption - may need to increase dose of phenytoin
- **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**
Nil

**References**
- Summary of Product Characteristics Taxotere® (Docetaxel) (Sanofi Aventis) 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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