TC: Docetaxel / Cyclophosphamide in Adjuvant Breast Cancer

Indication: Adjuvant alternative therapy to FEC100-Docetaxel for patients who can not tolerate anthracyclines in Early Breast Cancer.

Regimen details: Docetaxel 75mg/m² IV D1
Cyclophosphamide 600mg/m² IV D1

Administration: Docetaxel in 250mls Sodium Chloride 0.9% IV over 1 hour
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 250mls Sodium Chloride 0.9% over 30 minutes.

Premedication: Dexamethasone 8mg po bd for 3 days, starting the morning of the day prior to each Docetaxel administration, to reduce the incidence and severity of fluid retention and hypersensitivity reactions. If the patient has not taken the oral pre-med for any reason, Dexamethasone 20mg IV should be administered 1 hour prior chemotherapy.

Frequency: Every 21 days, for 4 cycles.

Extravasation: Docetaxel: Vesicant
Cyclophosphamide: Non-vesicant

Anti-emetics: Moderate emetogenic
Follow local Anti-emetic policy

Regular investigation: FBC D1
LFTs D1
U&Es D1

Comments: Hypersensitivity reactions may occur, during the first and second infusions, within a few minutes following the initiation of the infusion.

Degree of symptoms | Hypersensitivity reactions | Action
--- | --- | ---
Minor | Flushing
Localised cutaneous reaction | Do not require interruption of therapy. Administer prophylactic anti-anaphylactic medication before further cycles of Docetaxel

Severe | Severe hypotension
Bronchospasm
Generalised rash/erythema | Require immediate discontinuation of Docetaxel
Administer appropriate aggressive therapy

Reason for Update: Network Protocol Development
Version: 2
Supersedes: All other versions
Date: 14.12.09
Prepared by: M.T. Pacheca-Palomar Dec’09
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley
Date: 29/01/2010
DOSE MODIFICATIONS

In **adjuvant** treatment, dose reduction and delays can compromise outcome. G-CSF should be considered if more than one delay and / or before dose reduction. If in doubt, contact the relevant Consultant.

**Haematological Toxicity**

**Day1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &lt; 3.0 x 10⁹/L</td>
<td>Delay for 1 week. Repeat FBC - If within normal parameters, resume Docetaxel and Cyclophosphamide at 100% doses and give GCSF with subsequent cycles</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Neutrophils &lt; 1.0 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10⁹/ L</td>
<td></td>
</tr>
</tbody>
</table>

**Subsequent cycles:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils &lt; 0.5 x 10⁹/L for more than 7 days, OR</td>
<td>Delay for 1 week. Repeat FBC - If within normal parameters, resume Docetaxel and Cyclophosphamide at 100% doses and give GCSF with subsequent cycles</td>
</tr>
<tr>
<td>Febrile neutropenia is diagnosed, OR</td>
<td>Delay for 1 week. Repeat FBC - If within normal parameters, resume Docetaxel and Cyclophosphamide at 100% doses and give GCSF with subsequent cycles</td>
</tr>
<tr>
<td>Platelets &lt; 50 x 10⁹/L</td>
<td>Delay for 1 week. Repeat FBC - If within normal parameters, resume Docetaxel and Cyclophosphamide at 100% doses and give GCSF with subsequent cycles</td>
</tr>
</tbody>
</table>

If the blood counts are still low despite G-CSF support, seek Consultant advice about possible doses reduction

**Renal Impairment:**

Docetaxel: No dose adjustment required

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**

<table>
<thead>
<tr>
<th>ALP ≤ 2.5 x ULN</th>
<th>AST/ALT ≤ 1.5 x ULN</th>
<th>Bilirubin &gt; 22µmol/L</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 – 6 x ULN</td>
<td>1.6 – 3.5 x ULN</td>
<td>22µmol/L</td>
<td>Full dose</td>
</tr>
<tr>
<td>&gt; 6 x ULN</td>
<td>&gt; 3.5 x ULN</td>
<td>&gt; 22µmol/L</td>
<td>75% dose</td>
</tr>
</tbody>
</table>

**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
## DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

### CUTANEOUS REACTIONS / PERIPHERAL NEUROPATHY - DOCETAXEL

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cutaneous reactions</th>
<th>Neuropathy-sensory</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema without associated symptoms</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>100% dose</td>
</tr>
<tr>
<td>2</td>
<td>Localized erythema of the palms of the hands and soles of the feet with oedema followed by desquamation</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>May consider reduce Docetaxel dose to 60mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Severe, generalised eruptions followed by desquamation</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Delay Docetaxel until recovery to grade ≤ 2, thereafter, reduce Docetaxel dose to 60mg/m². If symptoms return, discontinue Docetaxel</td>
</tr>
<tr>
<td>4</td>
<td>Generalised exfoliative, ulcerative, or bullous dermatitis</td>
<td>Disabling</td>
<td>Discontinue Docetaxel, permanently</td>
</tr>
</tbody>
</table>

### Toxicities:
- Myelosuppression; nausea; vomiting; diarrhoea; stomatitis; asthenia; fluid retention; peripheral neuropathy; hypersensitivity reactions; cutaneous reactions (reversible); nail disorder; ovarian failure; infertility; fever; myalgia; arthralgia

### Drug interactions:
- **Docetaxel**
  - Concomitant administration of substrates, inducers or inhibitors of cytochrome P450-3A e.g. ciclosporin, terfenadine, ketoconazole, erythromycin etc, may alter the pharmacokinetics of Docetaxel, presenting a theoretical interaction

  - **Cyclophosphamide**
    - Allopurinol: can increase the incidence of serious bone marrow depression
    - Amiodarone: increased risk of pulmonary fibrosis; avoid combination if possible
    - Clozapine: increased risk of agranulocytosis, avoid concomitant use
    - Digoxin tablets: reduced absorption (resolved by giving the digoxin as liquid)
    - 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..
    - Phenytoin: reduced absorption of the antiepileptic
    - Warfarin: the anticoagulant effect is increase
References:

www.medicines.org.uk
BC Cancer Agency Protocol Summary UBRAJDC. June 2007
GSTT guidelines for treating nausea and vomiting in adult patients. Sept 2007
NLCN- Dosage Adjustment for Cytotoxics in Renal Impairment. Nov 2003
NLCN- Dosage Adjustment for Cytotoxics in Hepatic Impairment. Nov 2003
Stockley’s Drug Interactions. Interactions search: Docetaxel and Cyclophosphamide
February 2009
CTCAE v 3.0. August 2006