Capecitabine plus Docetaxel in Advanced Breast Cancer

Indication: Palliative therapy in Anthracycline-Pretreated Patients with Advanced Breast Cancer

Regimen details: Docetaxel 75mg/m² IV D1
Capecitabine* 1250mg/m² PO (BD) D1-D14 followed by a 7-day rest period

* Patients ≥ 60 years of age, Capecitabine starting dose 950 mg/m² BD is recommended
If no toxicity is observed in patients ≥ 60 years of age treated with a reduced Capecitabine starting dose in combination with Docetaxel, the dose of Capecitabine may be cautiously escalated to 1250 mg/m² BD

Administration: Docetaxel in 250mls Sodium Chloride 0.9% IV over 1 hour (PVC-free)
Capecitabine po bd, available as 500mg and 150mg tablets, should be swallowed whole with water within 30 minutes after a meal. Capecitabine tablets are not scored or divisible therefore they must NOT be crushed. See also Appendix 1, on page 5

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 21days, for 6 cycles

Extravasation: Docetaxel : Vesicant
Capecitabine : N/A

Anti- emetics: Moderate emetogenic. Follow local Anti-emetic policy
If the patient vomits after taking Capecitabine tablets, report to doctor as soon as possible

Regular investigation: FBC D1
LFTs D1
U&Es D1
CrCl Prior to 1st cycle, if clinically indicated
Disease evaluation Every 3 cycles

Comments: Missed dose – Capecitabine
Patient should not double-up doses or take extra doses at the end of the treatment cycle to make up for the missed doses. If remember 30 to 90 minutes after they should have taken their tablets, then patient should take the missed dose. However, if it is near to the time when their next dose is due, patient should NOT take the missed dose. Patient should inform doctor/chemotherapy unit and keep to normal dosing schedule

Hypersensitivity reactions - Docetaxel
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

**DOSE MODIFICATIONS**

**Haematological Toxicity**

**Day 1**

WBC < 3.0 x 10⁹/L  
or  
Neutrophils < 1.5 x 10⁹/L  
or  
Platelets < 100 x 10⁹/L

Delay both drugs for 1 week.

Repeat FBC - If within normal parameters, resume Docetaxel and Capecitabine at full doses

**Subsequent cycles:**

**Docetaxel** dose should be reduced to 55mg/m² if:

- Neutrophils < 0.5 x 10⁹/L for more than 7 days, OR
- Febrile neutropenia is diagnosed, OR
- Platelets < 50 x 10⁹/L

If the patient continues to experience these side effects at the lower dose, Docetaxel should be discontinued. Do not escalate for subsequent cycles

**Capecitabine** is not expected to worsen or prolong Grade 3 or 4 neutropenia, therefore Capecitabine should be continued throughout Grade 3 or 4 neutropenic episodes. However, Capecitabine needs to be discontinued if any Grade 2 clinical adverse event coincided with the neutropenic phase and the patient was to be hospitalized and closely monitored

**Renal Impairment:**

**Docetaxel** : No dose adjustment required

**Capecitabine** is contraindicated in patients with severe renal impairment. Please, follow table below:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Capecitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Give 100%</td>
</tr>
<tr>
<td>30 – 50</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Omit</td>
</tr>
</tbody>
</table>

---

**Reason for Update:** Network Protocol Development

**Version:** 1  
**Supersedes:** All other versions  
**Prepared by:** Maria Teresa Pacheca-Palomar  
**Approved by Breast Consultant:** Anne Rigg  
**Date:** 25.01.10  
**Approved by SELCN DTAC Chair:** Nic Ketley  
**Date:** 29/01/2010
**Hepatic Impairment**

Capecitabine: In the absence of safety and efficacy data in patients with hepatic impairment, Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis

Administration of Capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur

<table>
<thead>
<tr>
<th>ALP</th>
<th>AST/ALT and/or Bilirubin</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.5 x ULN</td>
<td>≤ 1.5 x ULN</td>
<td>Full dose</td>
</tr>
<tr>
<td>2.5 – 6 x ULN</td>
<td>1.6 – 3.5 x ULN</td>
<td>75% dose</td>
</tr>
<tr>
<td>&gt; 6 x ULN</td>
<td>&gt; 3.5 x ULN</td>
<td>Not recommended. Docetaxel should be administered with Consultant approval</td>
</tr>
<tr>
<td>≥ 6 x ULN</td>
<td>≥ 22µmol/L</td>
<td></td>
</tr>
</tbody>
</table>

**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>

**NAUSEA / VOMITING / DIARRHOEA / STOMATITIS / PALMAR-PLANTAR ERYTHRODYSESTHESIA – CAPECITABINE**

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>1st Appearance</th>
<th>2nd Appearance</th>
<th>3rd Appearance</th>
<th>4th Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capecitabine dose</td>
<td>Capecitabine dose</td>
<td>Capecitabine dose</td>
<td>Capecitabine dose</td>
</tr>
<tr>
<td>0 - 1</td>
<td>Give 100%</td>
<td>Give 100%</td>
<td>Give 100%</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Delay**, then give 100%</td>
<td>Delay**, then give 75%</td>
<td>Delay**, then give 50%</td>
<td>Discontinue</td>
</tr>
<tr>
<td>3</td>
<td>Delay**, then give 75%</td>
<td>Delay**, then give 50%</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue or delay**, then give 50%</td>
<td>Discontinue</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**stop treatment immediately and delay until toxicity resolved to Grade 0-1**
Toxicities: Myelosuppression; nausea; vomiting; diarrhoea; stomatitis; asthenia; fluid retention; peripheral neuropathy; hypersensitivity reactions; cutaneous reactions (reversible); palmar-plantar erythrodysesthesias; nail disorder

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

Capecitabine:
- Allopurinol: reduced efficacy of Capecitabine. Avoid concomitant use
- Folinates: toxicity of Capecitabine enhanced. Avoid concomitant use
- Phenytoin: increased Phenytoin plasma concentrations, leading to Phenytoin intoxication. Patients taking Phenytoin concomitantly with Capecitabine should have regular monitoring of Phenytoin plasma concentrations
- Warfarin / coumarin anticoagulants: altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin. Patients should be switched to low molecular weight Heparin for the duration of therapy

References:
- www.medicines.org.uk
- GSTT guidelines for treating nausea and vomiting in adult patients. Sept 2007
- UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. Nov 2003
- CTCAE v 3.0. August 2006
## Appendix 1: Capecitabine dose calculations

Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine of 1250 mg/m²

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>Dose per administration (mg)</th>
<th>150 mg</th>
<th>500 mg</th>
<th>Dose per administration (mg)</th>
<th>Dose per administration (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.26</td>
<td>1500</td>
<td>-</td>
<td>3</td>
<td>1150</td>
<td>800</td>
</tr>
<tr>
<td>1.27 - 1.38</td>
<td>1650</td>
<td>1</td>
<td>3</td>
<td>1300</td>
<td>800</td>
</tr>
<tr>
<td>1.39 - 1.52</td>
<td>1800</td>
<td>2</td>
<td>3</td>
<td>1450</td>
<td>950</td>
</tr>
<tr>
<td>1.53 - 1.66</td>
<td>2000</td>
<td>-</td>
<td>4</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>1.67 - 1.78</td>
<td>2150</td>
<td>1</td>
<td>4</td>
<td>1650</td>
<td>1000</td>
</tr>
<tr>
<td>1.79 - 1.92</td>
<td>2300</td>
<td>2</td>
<td>4</td>
<td>1800</td>
<td>1150</td>
</tr>
<tr>
<td>1.93 - 2.06</td>
<td>2500</td>
<td>-</td>
<td>5</td>
<td>1950</td>
<td>1300</td>
</tr>
<tr>
<td>2.07 - 2.18</td>
<td>2650</td>
<td>1</td>
<td>5</td>
<td>2000</td>
<td>1300</td>
</tr>
<tr>
<td>≥ 2.19</td>
<td>2800</td>
<td>2</td>
<td>5</td>
<td>2150</td>
<td>1450</td>
</tr>
</tbody>
</table>