**Indication**

Neoadjuvant or adjuvant treatment of early or locally advanced triple negative breast cancer where anthracyclines are not appropriate.

Palliative treatment for advanced breast cancer.

**ICD-10 codes**

Codes pre-fixed with C50.

**Regimen details**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 8 and 15</td>
<td>Paclitaxel</td>
<td>80mg/m²</td>
<td>IV infusion</td>
</tr>
<tr>
<td>1</td>
<td>Carboplatin</td>
<td>AUC 5</td>
<td>IV infusion</td>
</tr>
</tbody>
</table>

* Carboplatin dose calculated using the Calvert equation:  
\[
\text{Carboplatin dose (mg)} = \text{AUC} \times (\text{CrCl} + 25)
\]

Measured GFR (such as 24-hour urine or 51Cr-EDTA) is preferred whenever feasible, particularly in circumstances of co-morbidity that could affect renal function such as dehydration or extremes of weight. Alternatively the Cockcroft and Gault Method can also be used to estimate a patient’s CrCl. CrCl should be capped at 125mL/min.

**Cycle frequency**

28 days

**Number of cycles**

6 cycles

**Administration**

Paclitaxel should be administered first.

Paclitaxel is administered in a 250-500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 1 hour.

Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 500mL glucose 5% over 30-60 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 paclitaxel or carboplatin. 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 restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy should be initiated.
Pre-medication
30 minutes prior to each paclitaxel infusion:

Ranitidine 50mg IV slow bolus
Chlorphenamine 10mg IV slow bolus
Dexamethasone 8mg IV slow bolus

Emetogenicity
This regimen has high emetic potential.

Additional supportive medication
H₂ antagonist or proton pump inhibitor if required.
Loperamide if required.
Mouthwashes as per local policy

Extravasation
Paclitaxel – vesicant (Group 5)
Carboplatin – irritant (Group 3)

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>
<tr>
<td>Calcium</td>
<td>14 days</td>
</tr>
<tr>
<td>Magnesium</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Baseline EDTA if suspected or significant renal dysfunction.

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>
<tr>
<td>Calcium</td>
<td>7 days</td>
</tr>
<tr>
<td>Magnesium</td>
<td>7 days</td>
</tr>
</tbody>
</table>

*Additional FBC within 24 hours of day 8 and 15 doses.

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>≥ 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100 x 10⁹/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; 1.5 x ULN</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>&lt; 5 x ULN</td>
</tr>
<tr>
<td>Creatinine Clearance (CrCl)</td>
<td>&gt; 30 mL/min (and &lt; 10% change)</td>
</tr>
</tbody>
</table>
Dose modifications

- **Haematological toxicity**

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Carboplatin dose</th>
<th>Paclitaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 and ≥ 100</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 or &lt; 100</td>
<td>Delay 1 week (or until recovery) then reduce dose by 1 x AUC</td>
<td>Delay 1 week (or until recovery)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 and &lt; 100</td>
<td>Delay 1 week (or until recovery) then reduce dose by 1 x AUC</td>
<td>Delay 1 week (or until recovery) then reduce dose to 70mg/m^2.</td>
<td></td>
</tr>
</tbody>
</table>

In the case of febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m² and carboplatin by 1 x AUC for all subsequent doses.

- **Renal impairment**

If calculated CrCl falls by >10% from previous dose, consider EDTA and/or dose recalculation.

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Carboplatin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>100%</td>
</tr>
<tr>
<td>20-30</td>
<td>EDTA then 100% dose (or consider changing to non-nephrotoxic regimen)</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>

No dose modification required for paclitaxel.

- **Hepatic impairment**

**Paclitaxel:**

Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant’s decision, at a reduced dose with weekly monitoring of LFTs.

**Carboplatin:**

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

- **Other toxicities**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Carboplatin dose</th>
<th>Paclitaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Grade 3</td>
<td>100%</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence – reduce to 70mg/m² for all subsequent doses or omit.</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Grade 2</td>
<td>100%</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence – reduce to 70mg/m² for all subsequent doses or omit.</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td></td>
<td>Discuss with the consultant.</td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>Grade ≥ 2</td>
<td>100%</td>
<td>Consider diclofenac +/- co-codamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 70mg/m².</td>
</tr>
</tbody>
</table>

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with dose reduction of paclitaxel to 60mg/m² and carboplatin by 1 x AUC. If further toxicity discuss with consultant.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.
**Adverse effects** - for full details consult product literature/ reference texts

- **Rare or serious side effects**
  - Myelosuppression
  - Infertility
  - Teratogenicity
  - Hypersensitivity reactions
  - Pulmonary fibrosis
  - Nephrotoxicity
  - Electrolyte disturbances
  - Arrhythmias
  - Cardiac failure

- **Frequently occurring side effects**
  - Nausea and vomiting
  - Mucositis, stomatitis
  - Myelosuppression
  - Diarrhoea, constipation
  - Peripheral neuropathy
  - Oedema
  - Phlebitis
  - Myalgia, arthralgia
  - Alopecia
  - Fatigue

- **Other side effects**
  - Flu-like symptoms
  - Taste changes
  - Headache
  - Abdominal pain
  - Deranged liver function
  - Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

**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.

**Clozapine:** increased risk of agranulocytosis

**Paclitaxel** is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

**Carboplatin only:**
- **Aminoglycoside antibiotics:** increased risk of nephrotoxicity and ototoxicity.
- **Clozapine:** increased risk of agranulocytosis, avoid concomitant use.
- **Diuretics:** increased risk of nephrotoxicity and ototoxicity.
- **Nephrotoxic drugs:** increased nephrotoxicity; not recommended.
- **Phenytoin:** carboplatin reduces absorption and efficacy of phenytoin.
References

- Summary of Product Characteristics Carboplatin (Hospira) accessed 7 December 2016 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 7 December 2016 via www.medicines.org.uk

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