DOXOrubicin, and Cyclophosphamide (AC 60/600)
Therapy - 21 day

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.</td>
<td>C50</td>
<td>00252a</td>
<td></td>
</tr>
</tbody>
</table>

*If a reimbursement indicator (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

DOXOrubicin and cyclophosphamide are administered once every 21 days for four cycles (one cycle = 21 days).

If radiation therapy is required, it is given following completion of chemotherapy.

Order of Admin  Day  Drug  Dose  Route  Diluent & Rate  Cycle
<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>DOXOrubicin</td>
<td>60mg/ m²</td>
<td>IV push</td>
<td>N/A</td>
<td>1-4</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV infusion*</td>
<td>100 to 250ml 0.9% sodium chloride over 20min to 1 hr</td>
<td>1-4</td>
</tr>
</tbody>
</table>

* Cyclophosphamide may also be administered as an IV bolus over 5-10mins

Lifetime cumulative dose of doxorubicin is 450mg/m². In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below* and to the age of the patient.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

ELIGIBILITY:

- Indications as above.
- ECOG status 0-2.

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cyclophosphamide or any of the excipients.
- Congestive heart failure (LVEF < 50%) or other significant heart disease.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, U&Es, LFTs.
- ECG
- MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated

NCCP Protocol: AC (60-600) Therapy-21 day
Published: 29/04/2015
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Version number: 2

Tumour Group: Breast
NCCP Protocol Code: 00252
ISON Contributor: Prof Maccon Keane

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NCCP Chemotherapy Regimen

Regular tests:
- FBC, U&Es, LFTs
- If clinically indicated creatinine, MUGA scan or echocardiogram.

Disease monitoring:
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant

Haematological:

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (Both Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>&gt; 90</td>
<td>100%</td>
</tr>
<tr>
<td>1 - 1.49</td>
<td>70 to 90</td>
<td>*75%</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>&lt; 70</td>
<td>Delay</td>
</tr>
</tbody>
</table>

*May consider using G-CSF for neutrophil support rather than dose reduction

Renal and Hepatic Impairment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOXOrubicin</td>
<td>No dose reduction required. Clinical decision in severe impairment</td>
<td>Serum Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51-85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Omit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST 2-3 x normal give 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST &gt; 3 x ULN give 50%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CrCl (mL/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
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<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
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</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (Refer to local policy).

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:
Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Extravasation**: DOXOrubicin may cause pain and tissue necrosis if extravasated. *(Refer to local extravasation guidelines).*
- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

DRUG INTERACTIONS:

- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Concurrent administration of calcium channel blockers with doxorubicin should be avoided as they may decrease the clearance of doxorubicin.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Doxorubicin  L01DB01  
Cyclophosphamide  L01AA01

REFERENCES:

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.