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 status</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>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

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.

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>DOXOrubicin</td>
<td>60mg/m²</td>
<td>IV push</td>
<td>Slow IV push over 15min</td>
<td>Every 21 days for up to 4 cycles</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV infusion*</td>
<td>250ml 0.9% sodium chloride over 30min</td>
<td>Every 21 days for up to 4 cycles</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.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibly of the prescribing clinician. and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing. For any updates please check www.hse.ie/NCCPchemoprotocols
TESTS:

Baseline tests:
- FBC, renal and liver profile.
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated

Regular tests:
- FBC, renal and liver profile
- 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 1: Dose modifications for cycles of DOXOrubicin and cyclophosphamide

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^7/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 2: Dose modification of DOXOrubicin and Cyclophosphamide in 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</td>
<td>Serum Bilirubin</td>
</tr>
<tr>
<td></td>
<td>decision in severe impairment</td>
<td>(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>51-85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST 2-3 x normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If AST &gt; 3 x ULN</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CrCl (mL/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</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.

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:

2. Fisher B, Brown AM, Dimitrov NV et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors.
NCCP Chemotherapy Regimen


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29/04/2015</td>
<td></td>
<td>Dr Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>14/06/2017</td>
<td>Updated title, clarified administration order and dosing in renal and hepatic impairment, applied new NCCP regimen template</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>19/06/2019</td>
<td>Standardisation of treatment table for NCIS.</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>4</td>
<td>06/11/2019</td>
<td>Standardisation of treatment table</td>
<td>Prof Maccon Keane</td>
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</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfomedonc/cdmp/

2 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

NCCP Protocol: AC (60-600) Therapy-21 day Published: 29/04/2015
Review: 19/06/2021 Version number: 4
Tumour Group: Breast NCCP Protocol Code: 00252 ISMO Contributor: Prof Maccon Keane

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