DOXOrubicin (25mg/m²/day) and CISplatin (100mg/m²) Therapy - 21 day cycle

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>Neoadjuvant/Adjuvant therapy for osteosarcoma</td>
<td>C41</td>
<td>00420a</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 been 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 is administered on days 1-3 and CISplatin on Day 1 of a 21 day cycle for six cycles (THREE cycles usually given pre-operatively and THREE cycles given post-operatively following review of pathology).

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

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,2, 3</td>
<td>DOXOrubicin</td>
<td>25mg/m²²</td>
<td>IV push</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>CISplatin</td>
<td>100mg/m²²</td>
<td>IV infusion</td>
<td>500ml-1000ml 0.9% NaCl over 2 hours</td>
</tr>
</tbody>
</table>

*Pre and post hydration therapy required for CISplatin.
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
1. Administer 10mmol magnesium sulphate (MgSO₄) (±/− KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.
Administer CISplatin as described above.
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins.
Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3,4).

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate organ function

EXCLUSIONS:

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

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NCCP Chemotherapy Regimen

- Lactation

**PRESCRIPTIVE AUTHORITY:**
The treatment plan must be initiated by a Consultant Medical Oncologist.

**TESTS:**

**Baseline tests:**
- FBC, U&E, LFTs
- ECG
- MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated.
- Audiology and creatinine clearance if clinically indicated

**Regular tests:**
- FBC, U&E, LFTs before each cycle
- 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 modification for haematological toxicity**

<table>
<thead>
<tr>
<th>ANC (x 10^9/L) (on day of chemotherapy)</th>
<th>Platelets (x 10^9/L) (at any stage during cycle)</th>
<th>Dose Modification of DOXorubicin and CISplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5</td>
<td>&gt;100</td>
<td>100% Dose</td>
</tr>
<tr>
<td>1.0 - 1.5</td>
<td>70-100</td>
<td>80%</td>
</tr>
<tr>
<td>&lt;1</td>
<td>&lt;70</td>
<td>Delay 1 week</td>
</tr>
<tr>
<td>Febrile neutropenia and ANC &lt;0.5</td>
<td></td>
<td>On recovery reduce dose of DOXorubicin to 80% and continue with this dose for future cycles (CISplatin remains at 100%)</td>
</tr>
</tbody>
</table>

**Renal and Hepatic Impairment:**

**Table 2: Dose modification for 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) Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-51 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51-85 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85 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>CISplatin</td>
<td>GFR (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>45-59</td>
<td>75%</td>
</tr>
</tbody>
</table>

No dose reduction necessary

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Non-haematological toxicity:

Table 3: Dose modification schedule for DOXOrubicin and CISplatin based on adverse events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse reaction</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOXOrubicin</td>
<td>Grade ≥ 3 Mucositis</td>
<td></td>
<td>Reduce dose of DOXOrubicin to 80%</td>
</tr>
<tr>
<td>CISplatin</td>
<td>Grade ≥ 2 Peripheral neuropathy</td>
<td></td>
<td>Omit CISplatin and consider substituting CISplatin with carboplatin</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (Refer to local policy).

PREMEDICATIONS:

- Hydration prior and post CISplatin administration (Reference local policy or see recommendations above).

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions 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.

DOXOrubicin

- 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.

CISplatin

- Renal toxicity: Renal toxicity is common with CISplatin. Encourage oral hydration.
- Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of doxorubicin
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

- DOXOrubicin - L01DB01
- CISplatin - L01XA01

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REFERENCES:

3. Nephrotoxicity Associated with Cisplatin EviQ ID: 184 v.3.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>08/05/2017</td>
<td>Updated with revised Cisplatin hydration regimen recommendations</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>06/12/2017</td>
<td>Updated with revised Cisplatin hydration regimen recommendations</td>
<td>Prof Maccon Keane</td>
</tr>
</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/profinfo/medonc/cdmp/

ii 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 Regimen: DOXOrubicin 25 and CISplatin 100 Therapy
Published: 11/05/2017
Review: 06/12/2019
Version number: 2

Tumour Group: Sarcoma
NCCP Regimen Code: 00420

ISM0 Contributor: Prof Maccon Keane

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