DOXOrubicin (25mg/m^2/day) and CISplatin (100mg/m^2) Therapy - 21 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant/Adjuvant therapy for osteosarcoma	C41	00420a	Hospital

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 patients 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).

Facilites to treat anaphylaxis MUST be present when the chemotherapy is administered

Order of Admin	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	1,2, 3	[a]DOXOrubicin	25mg/m^2	IV push	N/A
2	1	[b]CISplatin	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours

[a]Lifetime cumulative dose of doxorubicin is 450mg/m^2
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.

[b] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-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 to 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).

ELIGIBILTY:

- 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
- Lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal, liver profile
- 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, renal and liver profile 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

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

Renal and Hepatic Impairment:

Table 2: Dose modification for renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment		**Serum Bilirubin (micromol/L)**	**Dose**
			20-51	50%
			51-85	25%
			>85	Omit
			If AST 2-3 x normal give 75% If AST > 3 x ULN give 50%	
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary	
	≥60	100%		
	45-59	75%		
	<45	Clinical decision. Consider using carboplatin		

Non-haematological toxicity:

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

Drug	Adverse reaction	Recommended dose modification
DOXOrubicin	Grade ≥ 3 Mucositis	Reduce dose of DOXOrubicin to 80%
CISplatin	Grade ≥ 2 Peripheral neuropathy	Omit CISplatin and consider substituting CISplatin with carboplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOXOrubicin Moderate (**Refer to local policy).**
CISplatin 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:

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

REFERENCES:

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3. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis- and-prevention/184-nephrotoxicity-associated-with-CISplatin
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5. Doxorubicin HCl 50mg Powder for Solution for Injection. Summary of Product Characteristics. Accessed March 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-026-002_03032016152104.pdf
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Version	Date	Amendment	Approved By
1	08/05/2017		Prof Maccon Keane
2	06/12/2017	Updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane
3	08/01/2020	Reviewed. Standardised treatment table and emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[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