Cyclophosphamide, DOXOrubicin and CISplatin Therapy – 21 Day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of advanced salivary gland cancer	C08	00615a	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, cyclophosphamide and CISplatin are each administered on Day 1 of a 21 day cycle for up to 6 cycles until disease progression or unacceptable toxicity occurs.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	[a]DOXOrubicin	50mg/m^2	IV push	Slow IV push over 15 minutes	Every 21 days for up to 6 cycles
2	1	[b]CISplatin	50mg/m^2	IV infusion	in 1000 mL sodium chloride 0.9% over 120 minutes	Every 21 days for up to 6 cycles
3	1	Cyclophosphamide	500mg/m^2	IV infusion	250ml sodium chloride 0.9% over 30 mins	Every 21 days for up to 6 cycles

[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

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Adequate hematologic, hepatic, and renal function

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, CISplatin, cyclophosphamide any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Pre-existing neuropathies Grade 2 or greater
- Moderate/severe renal impairment (creatinine clearance less than 60 mL/min.)
- Significant hearing impairment/tinnitus.
- 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, liver profile

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 in haematological toxicity

ANC (x 10^9/L)	
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and reduce doxorubicin, cisplatin and cyclophosphamide by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and reduce doxorubicin, cisplatin and cyclophosphamide by 25% for subsequent cycles
Platelets (x 10^9/L)	
50 to <100	Delay treatment until recovery
<50	Delay treatment until recovery and reduce doxorubicin, cisplatin and cyclophosphamide by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td rowspan="5">DOXOrubicin</td><td colspan="2" rowspan="5">No dose reduction required.
Clinical decision in severe impairment</td><td>Serum Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>20-51</td><td>50%</td></tr>
<tr><td>51-85</td><td>25%</td></tr>
<tr><td>>85</td><td>Omit</td></tr>
<tr><td colspan="2">If AST 2-3 x normal give 75%
If AST > 3 x ULN give 50%</td></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="2" rowspan="4">No dose reduction necessary</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Clinical decision.
Consider carboplatin</td></tr>
<tr><td rowspan="4">Cyclophosphamide</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="2" rowspan="4">Severe impairment: Clinical decision</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>Clinical decision.</td></tr>
</table>

Management of adverse events:

Table 3: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Peripheral neuropathy Grade 2, grade 3, grade 4	 Omit CISplatin and consider alternative therapy
Mucositis and stomatitis Grade 2 Grade 3 or grade 4	 Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 25% 3rd occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 50% 4th occurrence: Withhold chemotherapy Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 50% 2nd occurrence: Withhold chemotherapy
Diarrhoea Grade 2 Grade 3 or grade 4	 Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: No dose reduction 2nd occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 25% 3rd occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 50% 4th occurrence: Withhold chemotherapy Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Reduce doxorubicin, cyclophosphamide and cisplatin by 50% 2nd occurrence: Withhold chemotherapy

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

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

OTHER SUPPORTIVE CARE:

- 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.

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
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-Fluorouracil, cyclophosphamide or paclitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- 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.

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1	02/12/2020		Prof Maccon Keane
2	12/10/2022	Reviewed.	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