PROTOCOL

Systemic Anti Cancer Therapy Protocol

Cisplatin and doxorubicin Sarcoma

PROTOCOL REF: MPHACISDO
(Version No. 1.2)

Approved for use in:

- Osteosarcoma- palliative/advanced disease
- Chordoma
- De –differentiated chrondrosarcoma
- High grade bone tumours

An alternative to PAM regimen in patients unsuitable for treatment with high dose methotrexate including those >40 years old or with creatinine clearance < 70ml/min.

Dosage:

Drug	Dose	Route	Frequency
Cisplatin	**100 mg/m^2**	IV infusion	Day 1
Doxorubicin	**37.5 mg/m^2**	Continuous IV infusion	Days 1 + 2
Repeated every 21 days for up to 6 cycles			

Consider doxorubicin at 80% dose in patients > 60 years old.

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

- Filgrastim SC ONCE daily for 7 days starting from Day 3
- Aprepitant 125mg capsule on Day 1 then 80mg on Day 2 + 3
- Dexamethasone 4mg tablets twice a day for three days starting day after last chemo
- Metoclopramide 10mg tablets up to three times a day if required

Extravasation risk:

Cisplatin-irritant

Doxorubicin- vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="2">Renal</td><td>Cisplatin</td><td><table><tr><th>Creatinine clearance (mL/min)</th><th>Cisplatin dose</th></tr><tr><td>> 60mL/min</td><td>100%</td></tr><tr><td>50-59 mL/min</td><td>75%</td></tr><tr><td>< 50mL/min</td><td>Not recommended</td></tr></table></td></tr>
<tr><td>Doxorubicin</td><td>No dose adjustments needed</td></tr>
<tr><td colspan="3">Consultants may request a nuclear medicine test can provide a more accurate measurement of renal function. For Cisplatin dosing the corrected result should be used.</td></tr>
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<table>
<tr><td rowspan="2">Hepatic</td><td>Cisplatin</td><td>No dose reduction necessary</td></tr>
<tr><td>Doxorubicin</td><td><table>
<tr><td>AST 2 to 3xs ULN</td><td>Consider 75% dose</td></tr>
<tr><td>AST > 3xs ULN
OR Bilirubin 21-50 µmol/L</td><td>Consider 50% dose</td></tr>
<tr><td>Bilirubin 51-85 µmol/L</td><td>Consider 25% dose</td></tr>
<tr><td>Bilirubin > 86 µmol/L</td><td>Omit</td></tr>
<tr><td colspan="2">Please liaise with consultant prior to dose reductions</td></tr>
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Interactions:

Cisplatin

- **Warfarin** - regularly to check the INR.
- **Anticonvulsive substances** - Serum concentrations of anticonvulsive medicines may remain at sub therapeutic levels during treatment with cisplatin. Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment.
- **Aminoglycosides e.g. gentamicin** - Increased risk of nephrotoxicity and ototoxicity
- **Weakened live vaccines:** Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available.

Doxorubicin

Significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g, verapamil), resulting in increased concentration and clinical effect of doxorubicin.

Inducers of CYP3A4 (e.g, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

The addition of ciclosporin to doxorubicin may result in increases in area under the concentration-time curve (AUC) for doxorubicin. Coma and seizures have also been described with concomitant administration of ciclosporin and doxorubicin. High dose ciclosporin increases the serum levels and myelotoxicity of doxorubicin.

For more detailed interactions please refer to the SPC and add a link to the appropriate SPC

Treatment schedule:

- Review patient's fluid intake over the previous 24 hours
- Review common toxicity criteria and performance status
- Calculate creatinine clearance using Cockcroft and Gault equation (see investigation section)
- Weigh the patient prior to commencing intravenous fluids
- Commence strict fluid balance (input and output)

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**12mg**	**PO**	30minutes before chemotherapy
	Ondansetron	**16mg**	**PO**	30 minutes before chemotherapy
	Doxorubicin	**37.5mg/m^2**	**IV**	Continuous infusion over 24 hours in 100mL sodium chloride 0.9%
	20mmol Potassium Chloride and 10mmol Magnesium sulphate In Sodium Chloride 0.9% 1000mL			**IV over 120 minutes**
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the urology team**			
	Cisplatin	**100 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 4 hours
	20mmol Potassium Chloride and 10mmol Magnesium sulphate In Sodium Chloride 0.9% 1000mL			**IV over 4 hours**
2	**Aprepitant**	**80mg**	**PO**	Give 24hours after day one dose
	Dexamethasone	**12mg**	**PO**	30 minutes before doxorubicin
	Ondansetron	**16mg**	**PO**	30 minutes before doxorubicin
	Doxorubicin	**37.5mg/m^2**	**IV**	Continuous infusion over 24hours in 100mL sodium chloride 0.9%
3	**Aprepitant**	**80mg**	**PO**	Give 48hours after day one dose

At the end of IV fluids:

- Weigh the patient and review fluid balance chart
- If there is a positive balance of 1.5L or 1.5kg in weight gained then consider furosemide 20mg orally and review output after 30 minutes. Any concerns then discuss with medical team prior to discharging the patient.

Ensure good oral fluid intake

- Confirm patient understanding of the importance of fluid intake
- Patient should ensure they have 2L of fluid in the 24 hours following chemotherapy

Hypersensitivity

As with all platinum based chemotherapy, patients may experience an allergic reaction during administration. The infusion should be stopped and the following should be administered.

- Hydrocortisone 100 to 200mg IV
- Chlorphenamine 10 mg IV

It should be strongly noted that patients who have severe reactions should not be re-challenged.

Alternatively, doxorubicin can be administered as IV bolus over 60 minutes, 37.5mg/m^2 on days 1, and at 24 hour intervals. Patients will require double lumen PICC line (or equivalent) Hydration for cisplatin to commence at same time as doxorubicin infusion

Main toxicities:

Cisplatin	
Cardiac disorders	Arrhythmia, bradycardia, tachycardia can occur with cisplatin
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis.
General disorders and administration site conditions	Pyrexia (very common), asthenia, malaise, injection site extravasation Dehydration, hypokalaemia, hypophosphataemia, hypocalcaemia, hypomagnesaemia, tetany, muscle spasms
Haematological	Neutropenia, anaemia, thrombocytopenia
Hepatobiliary	Hepatic enzymes and blood bilirubin increased
Musculoskeletal	Muscle spasms
Nervous system	Cisplatin can cause peripheral neuropathy (see below). Neurologic examination must be carried out at regular intervals.
Ototoxicity	Ototoxicity is common with cisplatin and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally.
Skin and subcutaneous tissue disorders	Alopecia, rash

Doxorubicin	
Cardiac Disorders	Cardiac failure congestive, Sinus tachycardia
Eye Disorders	Lacrimation, conjunctivitus
Gastrointestinal and Nutritional Disorders	Constipation, diarrhoea, nausea, vomiting, stomatitis
General disorders and administration site conditions	Asthenia, fatigue, mucositis, weakness, fever, Paresthesia, somnolence, headache, dizziness, neuropathy, hypertonia. Back pain, myalgia
Haematological	Neutropenia, anaemia, thrombocytopenia
Hypersensitivity reactions	Flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia (Hand-foot syndrome), alopecia, rash. Dry skin, skin discolouration, pigmentation abnormal, erythema

Please refer to product SPC for more information.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Informed Consent	X							
Clinical Assessment	X					X		As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	Every cycle
CT scan**	X							At the end of treatment and if clinically indicated
ECG								If clinically indicated
Main observations (Blood pressure measurement and respiratory rate)	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle
Height recorded	X							
Blood glucose	X							Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay and repeat FBC in 2 to 3 days -

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

If platelets or ANC still below required levels for treatment despite a 1 week deferral a dose reduction may be required in laison with the patient's consultant.

If patient suffers an episode of Grade 3 febrile neutropenia, discuss with Oncologist.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% or AUC 4 of original dose with prophylaxis where possible	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 4	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose or AUC 3.5	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose or AUC 3.5	Discontinue treatment	
4Th appearance	Discontinue treatment		

Peripheral neuropathy

Severe cases of neuropathies have been reported. These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a sensation of vibrations. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals. Cumulative dose related peripheral sensory neuropathy: Usually occurs after a cumulative dose. It can occur after treatment with cisplatin is completed, and is usually reversible, taking approximately 3-5 months to recovery.

Neurotoxicity / Ototoxicity

If patient develops Grade 2 neuropathy or ototoxicity, discuss with Consultant. Patients with functional hearing loss should have cisplatin omitted; carboplatin is a potential alternative

Cardiomyopathy

Perform baseline ECHO to access LVEH (Left Ventricular Ejection Fraction) in all patients with either known or suspected cardiac impairment or a history of previous anthracycline treatment.

Patients who have received mediastinal radiation are at increased risk of cardiomyopathy

Should new or increased symptoms of cardiac dysfunction occur during treatment a repeat ECHO is required.

Doxorubicin is only to be used in patients with baseline LVEH < 50% when documented by a consultant following liaison with cardiology.

Repeat ECHO results		
LVEF reduced >10% from baseline **AND** now <50%	Cardiotoxicity	Hold treatment. Refer to cardiology
>10% reduction in LVEH **AND** >15% fall in GLS (Global Longitudinal Strain)	Probable subclinical cardiotoxicity	Continue treatment. Refer to cardiology.
LVEF reduced ≤10% from baseline **AND** now <50%	Possible subclinical cardiotoxicity	
> 15% fall in GLS from baseline		

References:

1. Summary of product characteristics. *Cisplatin.* Available from*:* https://www.medicines.org.uk/emc/product/3788 [accessed on 3/2/2023]
2. Electronic medicines compendium. Doxorubicin solution for injection. Available from :www.medicines.org.uk/emc/product/6184/smpc [accessed on 4/5/2023]
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08
4. Souhami, Robert et al, Randomised trial of two regimens of chemotherapy in operable osteosarcoma.The lancet volume 350, iss 9082,p911-917 September 1997.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
1.1	04/05/23	**Anna Burke (Pharmacist)**	Format Supportive med Interactions Toxicities Treatment plan Renal and hepatic impairment Non-haematological toxicities

1.2	12/07/23	**Rob Challoner (Pharmacist)**	**Following review with Dr Ali** **Switch to Doxorubicin over 2 days (from 3)** **Formatting changes to hepatic impairment** **Cardiomyopathy section to match SA doxorubicin**