SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Doxorubicin Sarcoma

PROTOCOL REF: MPHADOXOR
(Version No. 1.2)

Approved for use in:

- Soft tissue sarcoma
- Dedifferentiated chordoma
- Bone sarcoma

Dosage:

Drug	Dose	Route	Frequency
Doxorubicin	**75mg/m^2**	IV	Every 21 days

6 cycles

Administration:

- Maximum lifetime cumulative dose of doxorubicin to 450mg/m^2
- A higher lifetime cumulative dose of up to 550mg/m^2 can only be given when documented by a consultant
- See cardiomyopathy section for further details.

Emetogenic risk:

Moderately emetogenic.

Patient Counselling:

Counsel patients to report any symptoms of a decline cardiac function including worsening oedema, shortness of breath on exertion, chest pain, excessive heart rate or irregular heartbeat.

Supportive treatments:

Dexamethasone orals tablets 4mg twice a day for three days
Metoclopramide 10mg oral tablets three times a day or when required for five days

Extravasation risk:

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

Dosing in renal and hepatic impairment:

Renal	No dose adjustments needed	
Hepatic	AST 2 to 3xs ULN	Consider 75% dose
	AST > 3xs ULN **OR** Bilirubin 21-50 µmol/L	Consider 50% dose
	Bilirubin 51-85 µmol/L	Consider 25% dose
	Bilirubin > 86 µmol/L	Omit
	Please liaise with consultant prior to dose reductions	

Interactions:

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 cyclosporine 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 cyclosporine and doxorubicin. High dose cyclosporine increases the serum levels and myelotoxicity of doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), require monitoring of cardiac function throughout treatment. Changes in hepatic function

induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Please refer to the SPC for more information.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg**	**PO**	30 mins before chemotherapy
	Ondansetron	**16mg**	**PO**	30 mins before chemotherapy
	Doxorubicin	**75 mg/m^2**	**IV**	IV bolus over 10-15 minutes Concurrent administration doxorubicin 400mL/hr and sodium chloride at 0.9% at 100mL/hr

Main toxicities:

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 SPC for further 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	Every cycle
U&E & LFTs & Magnesium	X		X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X							
CT scan**	X							At the end of treatment and if clinically indicated
ECG								If clinically indicated
Main observations (blood pressure, resp 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:

Complete this guidance in line with SPC/ other protocols or trial protocols

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

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:

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.

<table>
<tr><td colspan="3">Repeat ECHO results</td></tr>
<tr><td>LVEF reduced >10% from baseline AND now <50%</td><td>Cardiotoxicity</td><td>Hold treatment. Refer to cardiology</td></tr>
<tr><td>>10% reduction in LVEH AND >15% fall in GLS (Global Longitudinal Strain)</td><td>Probable subclinical cardiotoxicity</td><td rowspan="3">Continue treatment.
Refer to cardiology.</td></tr>
<tr><td>LVEF reduced ≤10% from baseline AND now <50%</td><td rowspan="2">Possible subclinical cardiotoxicity</td></tr>
<tr><td>> 15% fall in GLS from baseline</td></tr>
<tr><td colspan="3">Adapted from: Dobson et al. Cardio-Oncology Echocardiograph Protocol for Anthracyclines and/or Herceptin. JAAC Cardiooncology March 2021.</td></tr>
</table>

References:

1. Electronic medicines compendium. Doxorubicin solution for injection. Available from :www.medicines.org.uk/emc/product/6184/smpc [accessed on 4/5/2023]
2. 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
3. Judson, Ian et al, Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial, The Lancet Oncology, Volume 15, No. 4, p415–423, April 2014 published online 4th March 2014.

4. Bramwell VH, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane database of systematic reviews (Online). 2003(3):CD003293

Circulation/Dissemination

Date added into Q-Pulse	8th November 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
1.2	12/07/23	**Rob Challoner (Pharmacist)**	**New regimen protocol.** **Following discussion with Dr Ali; summarized hepatic impairment dose modification. Added cardiomyopathy section and patient counselling.** **Regraded emetic risk as moderate.**