Doxorubicin

Indication
First-line treatment of patients with advanced soft tissue sarcoma. Can be considered second-line in some cases, for example after paclitaxel for angiosarcoma.

ICD-10 codes
Codes prefixed with C49.

Regimen details

Day	Drug	Dose	Route
1	Doxorubicin	*75mg/m^2	IV

*Consider starting dose of 60mg/m^2 in patients over 65 years of age.

Cycle frequency
21 days

Number of cycles
Maximum of 6 cycles

Administration
Doxorubicin is administered as a slow IV bolus via a fast running drip.

Pre-medication
Nil

Emetogenicity
This regimen has moderate emetic potential.

Additional supportive medication
Antiemetics as per local guidelines
Loperamide if required.
H2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy

Extravasation
Doxorubicin is a vesicant (Group 5)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Echocardiogram / MUGA	3 months

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours (and within 24 hours of day 8)
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram / MUGA	As clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9 /L
Platelets	≥ 100 x 10^9 /L
Creatinine Clearance (CrCl)	> 30 mL/min
Bilirubin	≤ 1.5 ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9 /L and/or platelets < 100 x 10^9 /L delay 1 week and recheck FBC. If within standard limits for go ahead, continue with full doses.

If > 1 week delay or febrile neutropenia, and other FBC parameters are satisfactory GCSF can be considered with subsequent cycles. Otherwise doxorubicin should be reduced to 80% dose. If further episode of grade 4 or febrile neutropenia doxorubicin should be further reduced to 66% dose.

- **Renal impairment**

If CrCl < 10mL/min, consider 75% dose of doxorubicin or omit, consultant decision.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**
< 1.5	And	≤ 2	100%
< 1.5	And	2-3	75%
1.5 – 3	Or	> 3	50%
3 – 5			25%
> 5			Omit

- **Other toxicities**

Doxorubicin:

Toxicity	Definition	Doxorubicin dose
Stomatitis/Mucositis	Grade 1	100%
	Grade 2	Omit until ≤ grade 1
	Grade 3	Omit until ≤ grade 1 then resume at 75% dose
	Grade 4	Discontinue
Other toxicities (except alopecia or nausea and vomiting)	≤Grade 2	100%(with or without treatment delay)
	≤Grade 3	Delay until recovery then consider dose reduction (consultant decision)

If cardiotoxicity (LVEF < 50% or 20% decrease) repeat echocardiogram after 7 days. If normal, continue, if not omit all further doxorubicin doses.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infusion-related reactions
Allergic reaction
Infertility
Cardiotoxicity
Hepatotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin or NOAC during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Doxorubicin is metabolised via cytochrome P450 and is a P-glycoprotein substrate. Concomitant administration of inhibitors of CYP450 and/or Pgp may lead to increased plasma concentrations of doxorubicin and thereby increased toxicity. Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, may decrease plasma concentrations of doxorubicin and reduce efficacy.

Digoxin: doxorubicin may reduce the oral bioavailability of digoxin.

Ciclosporin: can increase serum levels and toxicity of doxorubicin

Other cardiotoxic drugs: should be avoided

Antiepileptics (e.g. carbamazepine, phenytoin, valproate): absorption is decreased after concomitant use of doxorubicin.

Clozapine: increased risk of agranulocytosis – avoid concomitant use

Additional comments

Cardiotoxicity has been associated with anthracyclines, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2 (400mg/m^2 in patients with known cardiac dysfunction or previous mediastinal irradiation).

References

- Summary of Product Characteristics Doxorubicin (Pfizer) accessed 20 December 2017 via www.medicines.org.uk
- Tap W, Jones R, Van Tine B et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388: 488–97

Written/reviewed by: Dr A Dangoor (Consultant Oncologist UHBristol NHS Trust)

Checked by: Sarah Murdoch (Oncology/Haematology Pharmacist SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: December 2017