PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Doxorubicin Weekly Advanced Breast Cancer

PROTOCOL REF: MPHADOWEBR
(Version No. 1.1)

Approved for use in:

Locally advanced and/or metastatic breast cancer.

NOTE: NOT to be given concurrently with radiotherapy (please refer to 'Interactions' section for further information) OR if left ventricular ejection fraction (LVEF) < 50%.

Dosage:

Drug	Dose	Route	Frequency
Doxorubicin	**20mg/m^2**	IV	Every 7 days

Repeat weekly whilst clinically effective.

At 18 weeks review clinically and ensure maximum cumulative dose not reached. Continue if ongoing benefit from treatment.

NOTE: To avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of doxorubicin should not exceed 450-550mg/m² body surface area (BSA) and this should be reduced to 400 mg/m² should not be exceeded in cases of previous radiation of mediastinum, previous or concomitant treatment with potentially cardiotoxic agents. If the patient has had a related drug (eg epirubicin) the total dose of doxorubicin must also be reduced (taking into account the proportion of total anthracycline lifetime dose previously received).

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Dexamethasone 4mg oral, twice a day for 3 days

Metoclopramide 10mg oral tablets, up to 3 times a day or as required for nausea and vomiting for a maximum of 5 consecutive 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 Haemodialysis (HD): 75% of the original dose may be considered

	Bilirubin (µmol/L)	**Doxorubicin dose**
Hepatic	20 to 50	50%
	51 to 86	25%
	Above 86	Not recommended Discuss with clinical team

Interactions:

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines (e.g. epirubicin), or other potentially cardiotoxic drugs (e.g. 5-fluorouracil, cyclophosphamide or paclitaxel) or with products affecting cardiac function (like calcium antagonists). When doxorubicin is used together with the above mentioned agents, cardiac function must be followed carefully.

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically 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 (e.g. ciclosporin) . Inducers of CYP3A4 (e.g, rifampicin,

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

Doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug.

Doxorubicin is a **potent, radio sensitizing agent ("radio sensitizer")**, and recall phenomena induced by it may be life-threatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs.

For more detailed interactions please refer to the SmPC.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**16mg**	**PO**	30 minutes before chemotherapy
	Doxorubicin	**20mg/m^2**	**IV**	IV bolus over 10 to 15 minutes Concurrent administration, doxorubicin at 400mL/hr and sodium chloride 0.9% at 100mL/hr

Notes: Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2. Ensure all adjuvant anthracyclines and/or any anthracycline treatment for other tumours e.g. previous lymphoma is taken into account.

Perform baseline ejection function assessment (ECHO or MUGA) if patient is considered at risk of significantly impaired cardiac contractility. **450 mg/m² should not be exceeded in**

cases of previous radiation of mediastinum, previous or concomitant treatment with potentially cardiotoxic agents.

Main toxicities:

Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	Cardiomyopathy (e.g. decrease of LVEF. Shortness of breath or dyspnoea), arrhythmias Refer to NOTE in 'Dosage' section.
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis/stomatitis
Metabolism and Nutrition Disorders	Anorexia
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Skin and subcutaneous tissue disorders	Alopecia, Phlebitis Itching, local hypersensitivity reaction of the field of radiation (recall phenomenon- refer to 'Interactions' section')
General disorders and administration site conditions	Fatigue Infertility, early menopause

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X					
Clinical Assessment	X					As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	Every cycle
CT scan	X					Every 8 weeks and repeat as clinically indicated
ECG/MUGA/ECHO	X					Perform at baseline if suspected cardiac impairment* or if clinically Indicated (shortness of breath, chest pain, palpitations) If LVEF < 50% discuss with clinical team (consider an alternative regimen). Contraindicated in cases of severe arrhythmias, heart failure, previous myocardial infarction, acute inflammatory heart disease.
Full observations	X					Repeat if clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Height	X					

*Previous medical history of atrial fibrillation or ischaemic heart disease (IHD).

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 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

If bone marrow infiltration then these limits may be adjusted by the the clinical team.

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 MUGA in any patient with suspected cardiac impairment. If left ventricular ejection fraction (LVEF) < 50% discuss with clinical team (to consider an alternative regimen). Consider a lower maximum cumulative doxorubicin dose of 400mg/m^2 for any patient with cardiac dysfunction or that has been exposed to mediastinal radiation **NOTE:** that cardiomyopathy may be delayed – if 20% reduction in LVEF after total dose of 300mg/m^2 then STOP doxorubicin

References:

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Gundersen, S., Kvinnsland, S., Klepp, O., Lund, E., Høst, H. and Group, T.N.B.C., 1990. Weekly adriamycin® vs. 4-epidoxorubicin every second week in advanced breast cancer. A randomized trial. *European Journal of Cancer and Clinical Oncology*, 26(1), pp.45-48.

Supplement to: 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.

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Helen Flint **Consultant Pharmacist**	V1.0 New regimen protocol
		Gabriella Langton	V1.1

		Breast SRG Pharmacist	Routine protocol update