PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

EC (Epirubicin Cyclophosphamide) Advanced Breast Cancer

PROTOCOL REF: MPHAECBR
(Version No. 1.1)

Approved for use in:

Locally advanced and/or metastatic breast cancer not previously treated with anthracycline based regimen

Dosage:

Drug	Dose	Route	Frequency
Epirubicin	**90mg/m^2**	IV	Every 21 days for 6 cycles
Cyclophosphamide	**600 mg/m^2**	IV	

For patients where clinical concern about potential for toxicity, then dose reduction to 60mg/m^2 or 75mg/m^2 are also acceptable starting doses.

Notes:

Maximum cumulative dose of epirubicin: 900 to 1000 mg/m$^{2.}$ Ensure all adjuvant treatment is included and any treatment for other tumours e.g. previous lymphoma

Perform baseline ejection function assessment (ECHO or MUGA) if patient is considered at risk of significantly impaired cardiac contractility. **Use alternative regimen if cardiac ejection fraction < 50%**

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or **concomitant radiotherapy to the mediastinal/pericardial area**, previous therapy with other anthracyclines or anthracenediones, concomitant use of other drugs with the ability to

suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) with an increased risk in the elderly.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Dexamethasone 4mg orally twice a day for three days

Ondansetron 8mg orally twice a day for three days

Metoclopramide 10mg oral tablets, up to 3 times a day or as required for a maximum of 5 consecutive days.

Filgrastim subcutaneous injection daily for 7 days from day 3 (dose of 300 micrograms for patients below 70kg, and 480 micrograms for those 70kg and above)

Extravasation risk:

- Epirubicin: VESICANT. Erythematous streaking along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.
- Cyclophosphamide – NEUTRAL

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

Dosing in renal and hepatic impairment:

Renal	**Epirubicin**	No dose adjustment needed	
	Cyclophosphamide	10-29ml/min	Consider 75% of original dose
		<10ml/min	Not recommended but if unavoidable consider 50% of original dose

Hepatic	**Epirubicin**	**Bilirubin (µmol/L)**		**AST**	**Epirubicin dose**

21 to 51	OR	2-4 x ULN	50%
52 to 86	OR	>4x ULN	25%
Above 86	OR	Child-Pugh C	omit

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

Child-Pugh Class
A (5-6 points)
B (7-9 points)
C (10 or more points)

INR: International Normalised Ratio.
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Cyclophosphamide	No dose adjustments needed for mild to moderate impairment. Not recommended in severe impairment

Interactions:

For detailed list of interactions please refer to the relevant SmPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**12mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**24mg**	**PO**	30 minutes before chemotherapy
	Epirubicin	**90 mg/m^2**	**IV**	IV bolus over 10 to 15 minutes Concurrent administration, doxorubicin at 400mL/hr and sodium chloride 0.9% at 100mL/hr
	Cyclophosphamide	**600 mg/m^2**	**IV**	IV bolus over 30 minutes

- Nasal stuffiness can occur immediately with administration of cyclophosphamide, if uncomfortable for the patient the drug can be slowed down
- Encourage an oral fluid intake of 2 litres per day to promote urinary output & prevent chemical cystitis with cyclophosphamide.

Main toxicities:

Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea, mucositis
Cardiotoxicity	Epirubicin - sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Congestive heart failure. Other cardiac events have been reported, included delayed toxicity.
Dermatological	Alopecia, normally reversible, although can be permanent following docetaxel.

Urological	Red colouration of urine for 1 to 2 days after administration following epirubicin Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Mesna can be given if required.
Ocular	Watery eyes, gritty and irritated
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	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	Every cycle
On treatment review					
FBC	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	x	x	x	x	Every Cycle
CrCl (Cockcroft and Gault)	x	x	x	X	Every cycle
CT scan	x				At the end of treatment and if clinically indicated
ECG/ECHO	x				At baseline if pre-existing cardiac risk factors
Full set of observations	x	x	x	x	Every cycle
Weight recorded	x	x	x	x	Every cycle
Height	x				

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

Second episode or severe febrile neutropenia: Defer by 7 days or until blood counts recovered if neutrophils ≤ 1.0 **or** platelets ≤ 100 x 10^9/L **and reduce** to 80% dose

Non- Haematological toxicity:

Cardiomyopathy	Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen. The risk of developing Congestive Heart Failure (CHF) increases rapidly with increasing total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m2; this cumulative dose should only be **exceeded with extreme caution.** Consider a lower maximum cumulative epirubicin dose ≤ 900mg/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 if LVEF after 600mg/m^2 then stop epirubicin

References:

1. Cyclophosphamide Injection 500 mg SmPC, Baxter Healthcare Ltd. accessed via https://www.medicines.org.uk/emc. Last updated 29 June 2016.

2. Epirubicin Hydrochloride 2 mg/ml solution for injection or infusion SmPC, Accord Healthcare Ltd accessed via https://www.medicines.org.uk/emc. Last updated 24 Apr 2019.
3. 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.
4. Blohmer J et al, Annals of Oncology 21(7):1430-143

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Helen Flint	New regimen protocol V1.0
		Gabriella Langton	Routine protocol update V1.1