SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

EC-D
Epirubicin, Cyclophosphamide followed by Docetaxel
Adjuvant / Neo-adjuvant Breast Cancer

PROTOCOL REF: MPHAECDBR
(Version No. 1.1)

Approved for use in:

Adjuvant or Neo-adjuvant Breast: ER positive, HER2 negative. Fit, moderate to high risk patients.

NB: paclitaxel EC may be more appropriate for patients aged 60 years and over or if surgical wound healing is prolonged

Dosage:

Drug	Dose	Route	Frequency
Epirubicin	**90 mg/m^2**	IV infusion	Cycles 1 to 3 Day 1 only of a 14 day cycle*
Cyclophosphamide	**600 mg/m^2**	IV infusion	
Followed by			
Docetaxel	**100 mg/m^2**	IV infusion	Cycles 4 to 6 Day 1 only of a 21 day cycle

***EC can be given at the same doses every 3 weeks for 3 cycles at consultants' discretion. Docetaxel part of regimen commences 2 weeks after cycle 3 EC if having dose dense**

Administration Counselling Points:

Consider IV access, PICC line insertion is recommended for this regimen

- 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.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Ondansetron 8mg orally twice a day for three days

Metoclopramide 10mg tablets, three times a day as required

Filgrastim subcutaneous injection daily for 7 days from day 3

- 300 micrograms for patients below 70kg
- 480 micrograms for those 70kg and above

Additional item EC – cycles one to three

Dexamethasone 4mg orally twice a day for three days

Additional item Docetaxel – cycles four to six

Premedication of dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration

Extravasation risk:

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

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

Docetaxel: exfoliant

Dosing in renal and hepatic impairment:

Renal	**Epirubicin and docetaxel**	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)

<table>
<tr><td></td><td></td><td>INR: International Normalised Ratio.
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.</td></tr>
<tr><td></td><td>Cyclophosphamide</td><td>No dose adjustments needed for mild to moderate impairment. Not recommended in severe impairment</td></tr>
<tr><td></td><td>Docetaxel</td><td>
<table>
<tr><th colspan="2">Docetaxel</th></tr>
<tr><td>AST and/or ALT > 1.5- 5 x ULN concomitant with ALP > 2.5 –5.0 x ULN and normal bilirubin</td><td>Consider 75% of the original dose</td></tr>
<tr><td>AST or ALT >1.5-5 x ULN concomitant with ALP ≤ 2.5-6 x ULN
and/or
bilirubin ≤ 1-1.5 x ULN</td><td>Consider 50% of the original dose</td></tr>
<tr><td>Bilirubin > 1.5 x ULN
or
AST/ALT > 10 x ULN
or
ALP > 6 x ULN</td><td>Not recommended</td></tr>
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Interactions:

For detailed list of interactions please refer to the relevant SmPC

Treatment schedule:

EC Cycles 1 to 3

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**12mg**	**PO**	30 mins before chemotherapy
	Ondansetron	**24mg**	**PO**	30 mins before chemotherapy
	Epirubicin	**90 mg/m^2**	**IV bolus**	IV bolus over 10 to 15 minutes
	Cyclophosphamide	**600 mg/m^2**	**IV bolus**	IV bolus over 30 minutes

Repeat every 14 days for 3 cycles (or every 21 days at consultant discretion) **– at cycle 3 ensure patient has dexamethasone for prior to docetaxel**

Docetaxel Cycles 4 to 6

Day	Drug	Dose	Route	Diluent and rate
Premedication: Dexamethasone 8mg twice daily for 3 days starting 1 day prior to docetaxel administration				
1	**Ondansetron**	**8mg**	**PO**	30 mins before chemotherapy
	Docetaxel	**100 mg/m^2**	**IV infusion**	250ml 0.9% sodium chloride over 60 minutes

Repeat every 21 days for 3 cycles

The infusion volume for docetaxel may increase to 500mL depending on the dose to be administered

If oral dexamethasone has not been taken then an intravenous dose of 8mg can be administered on the day of treatment, in addition to the oral dose of 8mg

Switch to paclitaxel

If severe toxicity from docetaxel then consider switch to weekly paclitaxel with 3 weeks of weekly paclitaxel for each docetaxel dose.

If surgical healing is delayed, then weekly paclitaxel can be administered as the first part of the regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Famotidine**	**20mg**	**PO**	60 mins before chemotherapy for first 3 doses
	Dexamethasone	**6.6mg (reduce to 3.3mg for week 2)**	**IV bolus**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV bolus**	30 mins before chemotherapy
	Paclitaxel	**80 mg/m^2**	**IV infusion**	IV infusion over 60 minutes

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.
Respiratory	Acute respiratory distress syndrome, pneumonitis
Dermatological	Alopecia, normally reversible, although can be permanent following docetaxel. Docetaxel: Brittle, chipped and ridged nails
Urological	Red colouration of urine for 1 to 2 days after administration following epribucin 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
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with docetaxel, facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised rash with or without pruritus do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.
Nervous system	Docetaxel: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with docetaxel
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			X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
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				ECHO/ECG at baseline if pre-existing cardiac risk factors. If clinically indicated
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle
Height recorded	X				

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

Second episode or severe neutropenic sepsis: Defer by 7 days or until blood counts recovered if neutrophils $\leq$ 1.0 **or** platelets $\leq$ 100 x 10^9/L **and reduce** to 80% dose

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.

Peripheral Neuropathy

NCI-CTC grade 2 peripheral neuropathy: withhold docetaxel until neuropathy recovers to grade 1 then dose reduce by 20%

If NCI-CTC grade 3 (or persistent grade 2) peripheral neuropathy occurs, discontinue docetaxel and consider completing course with further EC cycles

References:

1. https://www.medicines.org.uk/emc
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. BNF available via: https://bnf.nice.org.uk/

Circulation/Dissemination

Date added into Q-Pulse	28th April 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
March 2023	V1.1	**Gabriella Langton**	Routine protocol update with new form, updated renal/hepatic information and supportive medication domperidone switched to metoclopramide