SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Paclitaxel with Dose Dense EC Neoadjuvant / Adjuvant Breast Cancer

PROTOCOL REF: MPHAPAECBR
(Version No. 1.3)

Approved for use in:

ER positive, HER2 negative. Adjuvant or Neo-adjuvant use

For less fit patients or if ≥60years of age.

Triple negative breast cancer - neo-adjuvant use, in lower risk and/or less fit patients. For this group duration of paclitaxel may be 9 or 12 weekly doses at consultant's discretion

Triple negative breast cancer - adjuvant use, the duration of the paclitaxel may be 9 or 12 weeks at the consultant's discretion.

Dosage:

Drug	Dose	Route	Frequency
Paclitaxel	80mg/m²	IV	Weekly For 9 – 12 cycles at consultants discretion and to be documented on Meditech
Followed by			
Epirubicin	**90mg/m²**	IV infusion	2 weekly for 4 cycles
Cyclophosphamide	**600 mg/m²**	IV infusion	

Administration Counselling Points:

- 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.
- Review IV access, PICC line insertion is recommended

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Supportive Treatments: Paclitaxel

Metoclopramide 10mg three times a day as required
Ondansetron 8mg orally pre chemotherapy can be considered if struggling with nausea
Loperamide 4mg stat followed by 2mg after each loose stool if develops diarrhoea

EC

Ondansetron tablets 8mg twice daily for 3 days
Dexamethasone tablets 4mg twice daily for 3 days
Filgrastim subcutaneous injection daily for 7 days from day 3

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

Extravasation risk:

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

Paclitaxel: vesicant

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

Dosing in renal and hepatic impairment:

NB If adjuvant zoledronate treatment is given in combination and renal function has dropped below 60ml/min then do not administer the zoledronate until the patient's clinical team have reviewed the results and confirmed it is appropriate to continue.

Renal	**Epirubicin and paclitaxel**	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

Paclitaxel

Bilirubin	**Percentage dose**
>1.25 – 2 x ULN	80%
2-5 x ULN	50%
>5 x ULN or transaminase ≥10 x ULN	Contraindicated
<10 x ULN and bilirubin ≤1.25 x ULN	Dose at 100%

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

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

The metabolism of paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Use with caution when administering paclitaxel concomitantly with medicines known

to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

For detailed list of interactions please refer to the relevant SmPC

Treatment schedule:

Paclitaxel

Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.

Day	Drug	Dose	Route	Diluent and rate
1	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
1	Dexamethasone	8mg	IV Infusion	30 minutes prior to paclitaxel
1	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**
8	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
8	Dexamethasone	4mg	IV Infusion	30 minutes prior to paclitaxel
8	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**
15	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
15	Dexamethasone	4mg	IV Infusion	30 minutes prior to paclitaxel
15	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**

Cycle is repeated every 21 days

Paclitaxel doses are omitted not delayed, with the intention of completing treatment on schedule at week 9 or 12 as per initial plan. EC part of regimen to commence 1 week after the final dose of paclitaxel in this section

Epirubicin and Cyclophosphamide

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	12mg	Orally	30 minutes prior to chemotherapy
1	Ondansetron	24mg	Orally	30 minutes prior to chemotherapy
1	**Epirubicin**	**90mg/m^2**	**IV injection**	
1	**Cyclophosphamide**	**600mg/m^2**	**IV injection**	Slow IV bolus over 30 minutes

Cycle is repeated every 14 days (Or every 21 days at consultant discretion)

Main toxicities:

Comments: Premedication treatment of chlophenamine and dexamethasone are given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first three cycles.

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 Paclitaxel: Brittle, chipped and ridged nails
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
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with paclitaxel, 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 paclitaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel.
Nervous system	Paclitaxel: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with paclitaxel
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D8	Cycle 1 Day 15	Cycle 2	Cycle 2 Day 8	Cycle 2 Day 15	Ongoing
Informed Consent	X							
Clinical Assessment * All patients on SACT should have **at least one F2F review during treatment.**	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	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	Every cycle
ECHO	X*							*Echo for all patients should be documented before starting anthracycline, unless stated by medical team that this is not required
ECG	X**							**ECG for all patients should be documented before starting anthracycline, unless stated by medical team that this is not required
CT scan	X***							***If clinically indicated based on the stage of cancer and clinical history
Blood pressure measurement	X							Repeat if clinically indicated
Weight recorded	X	X	X	X	X	X	X	Every cycle
Height recorded	X							

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed with paclitaxel or EC if:

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

If parameters are outside above limits then paclitaxel is **omitted** (not deferred) and EC is deferred.

Reduce paclitaxel dose permanently by 10mg/m^2 following:

- Two consecutive omitted doses
- Grade 2 peripheral neuropathy

Consider reducing dose or stopping weekly paclitaxel if severe febrile neutropenia

Reduce epirubicin and cyclophosphamide by 25% if delayed two consecutive weeks or severe febrile neutropenia occurs

Non- Haematological toxicity:

Peripheral Neuropathy	NCI-CTC grade 2 peripheral neuropathy withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce by 10mg/m^2 If NCI-CTC grade 3 (or persistent G2) peripheral neuropathy occurs, discontinue paclitaxel and proceed to EC part of regimen
Myalgia/Arthralgia	Often co-exist, if grade 1 or 2 manage with reassurance that the condition is self-limiting. NSAIDs may be considered but they may be ineffective

Taxanes- 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 taxane and appropriate treatment.

Patients who have developed severe hypersensitivity reactions should not be re-challenged.

Should an infusion reaction occur the infusion should be discontinued. The symptoms should be managed as per Hypersensitivity- Management Prevention Policy

References:

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6. Seidman AD et al, JCO 2008 26(10):1642-1649. Randomized phase III trial of weekly compared to 3 weekly paclitaxel CALGB-9840
7. Tolaney SM et al, NEJM 2015 372:134-141. Adjuvant paclitaxel and trastuzumab for node negative, HER2 positive breast cancer
8. Sparano JA et al, NEJM 2008 358:1663-1671 Weekly paclitaxel in the adjuvant treatment of breast cancer

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
28 Apr 2023	1.1	**Gabriella Langton**	
	1.2	**Gabriella Langton**	V1.2 Routine update, new policy layout, updated hepatic/renal information, supportive medication switched from domperidone to metoclopramide
	1.3	**Gabriella Langton**	**V1. 3 Removal of famotidine as per SRG/Trust approval, updated renal information if addition of AZS, updated investigations tablet with info regarding ECG/ECHOs. Added line that all patients need at least 1 face to face review during treatment**