Systemic Anti Cancer Treatment Protocol

Paclitaxel/Carboplatin with Dose Dense EC
Neoadjuvant Regimen

PROTOCOL REF: MPHAPCECBR
(Version No: 1.1)

Approved for use in:

Neoadjuvant treatment of operable, previously untreated, clinical stage II to III invasive triple negative breast cancer (ER/PR must be ≤ 10% and HER2 negative by IHC or FISH)

Dosage:

Drug	Dosage	Route	Frequency
Paclitaxel	80mg/m²	IV	Weekly
Carboplatin	AUC5*	IV	3 weekly
Followed by:			
Epirubicin	90mg/m²	IV	2 weekly
Cyclophosphamide	600mg/m²	IV	2 weekly

***Notes: Meditech uses Wright formula to calculate estimated creatinine clearance**

For automated dose calculation this will be at AUC5

Calvert formula for Carboplatin dosage:

Carboplatin dose in mg = AUC x (creatinine clearance + 25)

There is the option to select carboplatin within the order set where Cockroft and Gault equation can be used manually to enter a calculated dose of carboplatin using AUC6, as undertaken in the clinical trial for this regimen.

If this option is selected a **prescription note must be written at time of prescribing** detailing the parameters used to calculate the dose. Pharmacy will then adjust to the national dose bands. Without a note the prescription will not be processed.

Maximum dose of carboplatin via either method = 890mg

Supportive Treatments:

Paclitaxel pre-medication:

Chlorphenamine 10mg IV bolus pre chemotherapy

Famotidine 20mg orally pre chemotherapy

Dexamethasone 8mg IV as a single dose 30mins before chemotherapy (reduce to 4mg from week 2)

Post carboplatin antiemetics:

Dexamethasone tablets 4mg twice daily for 3 days

Domperidone tablets 10mg three times a day as required

Post EC

Filgrastim prophylaxis – see administration details

Ondansetron tablets 8mg twice daily for 3 days

Dexamethasone tablets 4mg twice daily for 3 days

Domperidone tablets 10mg three times a day as required

Extravasation risk:

Paclitaxel: vesicants follow trust/network policy

Carboplatin: irritant

Cyclophosphamide: non 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.

Administration:

Paclitaxel and Carboplatin – cycles 1 to 4

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	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (can be discontinued after three cycles for those patients who do not experience a drug hypersensitivity reaction).
1	Ondansetron	16mg	Orally	30 minutes prior to paclitaxel
1	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**
1	**Carboplatin**	**AUC5**	**IV Infusion**	**500mL glucose 5% over 30 to 60 minutes**
8	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
8	Dexamethasone	4mg	IV Infusion	30 minutes prior to paclitaxel
8	Famotidine	20mg	Oral	At least 60 minutes prior to paclitaxel (see notes above)
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	Famotidine	20mg	Oral	At least 60 minutes prior to paclitaxel (see notes above)
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 12. EC part of regimen to commence 3 weeks after the final dose of carboplatin in this section

Epirubicin and Cyclophosphamide – cycles 5 to 8

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**	IV bolus over 10 to 15 minutes Concurrent administration, doxorubicin at 400mL/hr and sodium chloride 0.9% at 100mL/hr
1	**Cyclophosphamide**	**600mg/m^2**	**IV**	IV bolus over 30 minutes
3 to 9	Filgrastim	30 or 48MU	S/C	Daily for 7 days starting on day 3 of cycle

Cycle is repeated every 14 days

Filgrastim dose:

For patients under 70kg: 30 micrograms subcutaneous injection daily

For patients 70kg and above: 48 micrograms subcutaneous injection daily

Main Toxicities:

Comments: Premedication treatment of chlophenamine, dexamethasone and famotidine is 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 two cycles. Please note famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

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. Carboplatin is nephrotoxic
Ocular	Watery eyes, gritty and irritated Risk of cortical blindness with carboplatin (renal impairment may increase this risk)
Ototoxicity	Common when carboplatin used in high doses
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with paclitaxel or carboplatin 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 or carboplatin and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged.
General disorders	Carboplatin: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Renal function impairment Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol.
Nervous system	Carboplatin: Paraesthesia and decreased deep tendon reflexes. 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:

Cycles 1 to 4

	Pre	C1	C1D8	C1D15	C2	C2D8	C2D15	Ongoing
Medical Assessment	X				X			Every cycle
Nursing Assessment		X	X	X	X	X	X	Every treatment
FBC	X	X	X	X	X	X	X	Every treatment
U&E & LFT	X		X	X	X	X	X	Every treatment
Informed Consent	X							
PS recorded	X	X	X	X	X	X	X	Every treatment
Toxicities documented	X	X	X	X	X	X	X	Every treatment
Weight recorded	X	X	X	X	X	X	X	Every treatment

Cycles 5 to 8

	C5	C6	C7	C8
Medical Assessment		X		X
Nursing Assessment	X	X	X	X
ECHO/ECG	X			
FBC	X	X	X	X
U&E & LFT	X	X	X	X
PS recorded	X	X	X	X
Toxicities documented	X	X	X	X
Weight recorded	X	X	X	X

Dose Modifications and Toxicity Management:

Cycles 1 to 4

Day 1

Proceed with **carboplatin and paclitaxel** if:

Platelets ≥ 75 x 10^9/L **AND**	ANC ≥ 0.8 x 10^9/L

Administer **paclitaxel only** if:

Platelets 50 to 75 x 10^9/L **AND**	ANC ≥ 0.8 x 10^9/L

Defer both agents for one week if:

Platelets < 50 x 10^9/L **OR**	ANC < 0.8 x 10^9/L

Days 8 and 15

Proceed with paclitaxel if:

Platelets ≥ 50 x 10^9/L **AND**	ANC ≥ 0.8 x 10^9/L

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

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

Grade 2 peripheral neuropathy

Reduce carboplatin dose permanently by 25% following:

Two week delay for thrombocytopenia

Or a single occurrence of platelets < 25 x 10^9/L

Consider reducing or stopping carboplatin if severe febrile neutropenia or two consecutive omitted doses of paclitaxel

Cycle 5 commences 3 weeks after the fourth dose of carboplatin (i.e. usually one week after week 12 of paclitaxel)

Cycles 5 to 8

Proceed with EC on day 1 if:

Platelets ≥ 75 x 10^9/L	ANC ≥ 1.0 x 10^9/L

If parameters below these limits then defer for one week.

If delayed by two consecutive weeks or febrile neutropenia occurs then dose reduce both agents by 25%

Non-Haematological Toxicity:

<table>
<tr><td>Renal</td><td>Carboplatin: review serum creatinine result at each cycle, if this has changed then recalculate clearance using Wright formula and amend the carboplatin dose if there will be a 10% difference</td></tr>
<tr><td>Hepatic</td><td>Epirubicin – excreted via hepatobilliary system

<table>
<tr><td></td><td>Epirubicin</td><td>Cyclophosphamide</td></tr>
<tr><td>Bilirubin µmol/L</td><td>Dose</td><td>Dose</td></tr>
<tr><td>24 to 50</td><td>50%</td><td>100%</td></tr>
<tr><td>51 to 85</td><td>25%</td><td>75%</td></tr>
<tr><td>Above 85</td><td>Omit</td><td>Omit</td></tr>
</table>

Paclitaxel
<table>
<tr><td>Bilirubin less than 1.25 times ULN and AST < 10 x ULN</td><td>Give 100% dose</td></tr>
<tr><td>Bilirubin greater than 1.25 times ULN</td><td>Consider dose reduction</td></tr>
<tr><td>Alk Phos more than 3 times ULN</td><td>Consider dose reduction</td></tr>
</table></td></tr>
<tr><td>Peripheral Neuropathy</td><td>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 peripheral neuropathy occurs, discontinue paclitaxel and proceed to EC part of regimen</td></tr>
<tr><td>Myalgia/Arthralgia</td><td>Often co-exist, usually grade 1 or 2. Manage with reassurance that the condition is self-limiting. NSAIDs may be considered but they may be ineffective</td></tr>
</table>

References:

Summary of Product characteristics for Epirubicin hydrochloride 2mg/ml solution for injection, medac GmbH, available via the electronic medicines compendium on https://www.medicines.org.uk/

https://www.medicines.org.uk/emc/medicine/15842/SPC/Paclitaxel+6+mg+ml+concentrate+for+solution+for+infusion/

Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast conserving surgery and breast conservation rates
Golshan, M et al
Ann Surg 2015 262(3):434-439

Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once per week paclitaxel followed by dose dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple negative breast cancer: CALGB 40603
Sikov WM et al
JCO 2014

Creatinine Clearance

Wright Creatinine Clearance Formula

Male patients $\frac{(6580 - (38.8 \times age)) \times bsa}{creatinine}$

Female patients $\frac{(6580 - (38.8 \times age)) \times bsa \times 0.832}{creatinine}$

Cockroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

NB Weight in kg

Creatinine in micromol/L