Systemic Anti Cancer Treatment Protocol

Paclitaxel with EC
Adjuvant or Neoadjuvant

PROTOCOL REF: MPHAPECBR
(Version No: 1.1)

Approved for use in:

ER positive, HER2 negative ("Luminal A/B"). Adjuvant or Neo-adjuvant.

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

Dosage:

Drug	Dosage	Route	Frequency
Paclitaxel	80mg/m^2	IV	Weekly
Followed by:			
Epirubicin	90mg/m^2	IV	3 weekly
Cyclophosphamide	600mg/m^2	IV	3 weekly

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 and consider stopping at week 3)

EC

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

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:

Paclitaxel: vesicant.

Epirubicin is a 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

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.

Administration:

Paclitaxel – cycles 1 to 4 (or cycles 1 to 3 dependent on clinician choice)

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	**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	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 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 – 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/m²**	**IV injection**	
1	**Cyclophosphamide**	**600mg/m²**	**IV injection**	Slow IV bolus over 30 minutes

Cycle is repeated every 21 days

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.
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:

Cycles 1 to 4

	Pre	C1	C1D8	C1D15	C2	C2D8	C2D15	Ongoing
Medical Assessment	X				X			Alternate cycles
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
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:

Cycles 1 to 4
Day 1, 8 and 15

Proceed with paclitaxel if:

Platelets $\geq$ 100 x 10^9/L	ANC $\geq$ 1.0 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:

Two consecutive omitted doses

Grade 2 peripheral neuropathy

Consider reducing dose or stopping weekly paclitaxel if severe febrile neutropenia

Cycle 5 commences 1 week after the final dose of paclitaxel

Cycles 5 to 8

Proceed with EC on day 1 if:

Platelets ≥ 100 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 severe febrile neutropenia occurs then dose reduce both agents by 25%

Non-Haematological Toxicity:

<table>
<tr><td>Hepatic</td><td>Epirubicin – excreted via hepatobilliary system – requires dose reduction if raised bilirubin levels;

<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>
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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>
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</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 (or persistent G2) peripheral neuropathy occurs, discontinue paclitaxel and proceed to EC part of regimen</td></tr>
<tr><td>Myalgia/Arthralgia</td><td>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</td></tr>
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References

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