

## Breast Pathway Group – EC x 4 – Accelerated Paclitaxel x 4: Epirubicin & Cyclophosphamide x 4 followed by Accelerated Paclitaxel x 4 in Early Breast Cancer

Indication: Neoadjuvant or adjuvant therapy for moderate to high risk node positive breast cancer

### **EC**

Regimen details:	Epirubicin	90 mg/m <sup>2</sup>	IV	Day 1
	Cyclophosphamide	600 mg/m <sup>2</sup>	IV	Day 1

Administration: Epirubicin IV bolus injection via a fast-running Sodium Chloride 0.9% infusion.  
Cyclophosphamide may be administered as IV bolus injection via a fast-running Sodium Chloride 0.9% infusion or as a short infusion e.g. in 100 - 250ml Sodium Chloride 0.9% over 30 minutes

Frequency: Day 1, every 21 days, for 4 cycles

Pre-medication: Not routinely required

Anti- emetics: High emetogenicity  
Follow Local Anti-emetic Policy

Supportive medication: Mouthcare as per Local Policy  
GCSF as per Local Policy

Extravasation: Epirubicin: Vesicant  
Cyclophosphamide: Non-vesicant

Epirubicin should be administered with appropriate precautions to prevent extravasation. If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016
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Regular investigations	Prior to cycle 1	
	FBC	Day 1 (within 14 days)
	LFTs	Day 1 (within 14 days)
	U&Es	Day 1 (within 14 days)
	MUGA scan/ECHO	see Comments
	Prior to Day 1 (all cycles)	
	FBC	Day 1 (within 72 hours)
	LFTs	Day 1 (within 72 hours)
	U&Es	Day 1 (within 72 hours)

Toxicities: Myelosuppression, nausea, vomiting, diarrhoea, mucositis, stomatitis, cardiotoxicity, alopecia, urine discoloration, haemorrhagic cystitis, alopecia, infertility, early menopause

## DOSE MODIFICATIONS

### Haematological Toxicity

Neutrophils (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Paclitaxel Dose
≥ 1.0	&	≥ 100	100%
< 1.0	& / or	< 100	Delay for 1 week. Repeat FBC - if recovered to above these levels, resume treatment with 100% dose

In neoadjuvant/adjuvant treatment, dose reduction and delays can compromise outcome.

- GCSF should be considered if more than one delay and/or before dose reduction. If in doubt, seek Consultant advice.
- If during the preceding cycle, the patient has experienced neutrophils < 0.5 x 10<sup>9</sup>/L or has febrile neutropenia diagnosed, GCSF should be considered.
- If despite GCSF treatment, febrile neutropenia occurs or a dose delay is required - seek Consultant advice and consider dose reduction by 25%
- If platelets persistently < 100 x 10<sup>9</sup>/L on Day 1 despite dose delay - seek Consultant advice and consider dose reduction by 25%

## Non-haematological Toxicities

### Renal Impairment

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### Epirubicin

Consider dose reduction in severe renal impairment (GFR <10ml/min) or serum creatinine >3.0 - 6.0 x ULN. Discuss with the Consultant and consider dose reduction.

### Cyclophosphamide

Creatinine Clearance (ml/min)	Cyclophosphamide Dose
> 20	100% dose
10 – 250	75% dose
< 10	Discuss with consultant and consider 50% dose

### Hepatic Impairment

#### Epirubicin

Bilirubin (µmol/L)	Epirubicin Dose
24 - 51	Give 50%
51 – 85	Give 25%
> 85	Omit

#### Cyclophosphamide

Not recommended in patients with a bilirubin > 17µmol/L or AST/ALT more than 2 – 3 x upper normal limit, however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision should be discussed with the Consultant

### Dose modifications for other toxicities as appropriate

#### Epirubicin

Mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and the sublingual mucosa. For grade III Painful erythema or ulcers requiring IV rehydration resolving to Grade I or less painless ulcers or mild soreness: give Epirubicin 85% dose and recommend regular mouth care

Location of regimen delivery:

Outpatient regimen

#### Comments:

#### Epirubicin

Maximum cumulative dose Epirubicin = 950mg/m<sup>2</sup>  
A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, diabetes, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy.

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MUGA scan or Echocardiogram should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum

Cyclophosphamide

Haematuria and haemorrhagic cystitis may rarely occur with cyclophosphamide administration (especially at doses above 1000mg). Patients should be monitored during therapy and encouraged to maintain adequate fluid intake whilst on therapy.

Pulmonary Fibrosis and Interstitial Pneumonitis is a rare complication of cyclophosphamide therapy and patients should be monitored for signs and symptoms of pulmonary dysfunction during treatment. Cyclophosphamide should be discontinued if fibrosis develops

Drug interactions:

Epirubicin

Use of Epirubicin with cardioactive compounds (e.g. calcium channel blockers) requires careful monitoring throughout treatment. Avoid commencing epirubicin based therapy for up to 25 weeks after stopping trastuzumab therapy

Cimetidine and Ciclosporin: can increase Epirubicin serum level

Verapamil: possibly increases Epirubicin bone marrow depressant effects

Epirubicin and Cyclophosphamide

Clozapine: increased risk of agranulocytosis, avoid concomitant use

Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)

Phenytoin: reduced absorption of the antiepileptic

Cyclophosphamide

Allopurinol: can increase the incidence of serious bone marrow depression

Amiodarone: increased risk of pulmonary fibrosis ; avoid combination if possible

Grapefruit juice: decreased or delayed activation of cyclophosphamide. Avoid grapefruit juice for 48 hours before and on day of cyclophosphamide

Indapamide: prolonged leucopenia is possible

Itraconazole: might increase Cyclophosphamide side effects

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e.g. haemorrhagic cystitis, pigmentation of palms, nails and soles etc..  
 Warfarin: anticoagulant effect is increased

**Followed by Paclitaxel (Accelerated)**

Regimen details: Paclitaxel 175mg/m<sup>2</sup> IV Day 1

Administration: Paclitaxel in 500ml Sodium Chloride 0.9% or Glucose 5% over 3 hours  
 Paclitaxel to be given via non-PVC infusion bag, with a 0.22 micron in-line filter. Paclitaxel must be diluted to a concentration of 0.3-1.2mg/ml to maintain stability in clinical practice

Frequency: Day 1, every 14 days, for 4 cycles

Premedication: Dexamethasone 20mg IV 30 – 60 minutes prior to paclitaxel administration  
 OR  
 Dexamethasone 20mg PO 6 hours and 12 hours prior to paclitaxel administration  
 Chlorphenamine 10mg IV 30 – 60 minutes prior to paclitaxel administration over at least 1 minute  
 Ranitidine 50mg IV 30 – 60 minutes prior to paclitaxel administration over at least 2 minutes

Paracetamol / Chlorphenamine / Hydrocortisone can be given for administration-related reactions such as chills / fever.

Anti- emetics: Low emetogenicity  
 Follow local anti-emetic policy

Supportive medication: GCSF as per Local Policy  
 Mouthcare as per Local Policy

Extravasation: Vesicant  
 Paclitaxel should be administered with appropriate precautions to prevent extravasation.  
 If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation

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Regular investigations:	Prior to Day 1 (all cycles):	
	FBC	Day 1 (within 72 hours)
	LFTs	Day 1 (within 72 hours)
	U&Es	Day 1 (within 72 hours)

Toxicities: Myelosuppression, anaemia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting, mucositis, diarrhoea, dysgeusia, hypersensitivity reactions (mainly flushing, rash and hypotension); infection; peripheral neuropathy, arthralgia, myalgia, alopecia

## DOSE MODIFICATIONS

### Haematological Toxicity

Neutrophils (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Paclitaxel Dose
≥ 1.0	&	≥ 100	100%
< 1.0	& / or	< 100	Delay for 1 week. Repeat FBC - if recovered to above these levels, resume treatment with 100% dose

In neoadjuvant/adjuvant treatment, dose reduction and delays can compromise outcome.

- GCSF should be considered if more than one delay and/or before dose reduction. If in doubt, seek Consultant advice.
- If during the preceding cycle, the patient has experienced neutrophils < 0.5 x 10<sup>9</sup>/L or has febrile neutropenia diagnosed, GCSF should be considered.
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- If platelets persistently < 100 x 10<sup>9</sup>/L on Day 1 despite dose delay - seek Consultant advice and consider dose reduction by 25%

### Non-haematological Toxicities

#### **Renal Impairment**

No dose adjustment required. Assess renal function when clinically indicated

#### **Hepatic Impairment**

Bilirubin (µmol/L)	Paclitaxel Dose (mg/m <sup>2</sup> )
22 - 26	135mg/m <sup>2</sup>
27 – 51	75mg/m <sup>2</sup>
> 51	50mg/m <sup>2</sup>

#### **Dose modifications for other toxicities as appropriate**

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PERIPHERAL NEUROPATHY

NCI CTCAE Grade	Sensory Neuropathy	Dose
1	Paraesthesia (including tingling), but not interfering with function	100% dose
2	Paraesthesia interfering with function, but not interfering with activities of daily living	80% dose
3	Paraesthesia interfering with activities of daily living	Omit paclitaxel
4	Disabling	Discontinue paclitaxel permanently

ARTHRALGIA / MYALGIA

NCI CTCAE Grade	Arthralgia/Myalgia	Action
1	Joint and muscle pain, not interfering with function	Consider use of NSAIDs
2	Joint and muscle pain, interfering with function, but not interfering with activities of daily living	Consider use of NSAIDs

Location of regimen delivery:                      Outpatient setting  
 Availability of resuscitation equipment must be ensured as a standard precaution.

Comments:    None

Drug interactions:                                  Concomitant administration of inducers or inhibitors of cytochrome P450 Isoenzymes (CYP2C8 and 3A4) may alter the pharmacokinetics of Paclitaxel, presenting a theoretical interaction  
 Clozapine: avoid concomitant use, increased risk of agranulocytosis

References:

Hospira UK Ltd. Summary of Product Characteristics: epirubicin 28/06/2013 Available at <http://www.medicines.org.uk/emc/> [Accessed 19/11/13]

Accord Healthcare Ltd. Summary of Product Characteristics: paclitaxel 07/11/2012 Available at <http://www.medicines.org.uk/emc/> [Accessed 19/11/13]

UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. Jan 2009

UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. Jan 2009

LCA Breast Cancer Clinical Guidelines October 2013

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