

Breast Pathway Group – EC x 4: Epirubicin & Cyclophosphamide in Early Breast Cancer

Indication: Neoadjuvant or adjuvant treatment for moderate to high risk breast cancer

Regimen details:

Epirubicin	90 mg/m ²	IV	Day 1
Cyclophosphamide	600 mg/m ²	IV	Day 1

Administration: Epirubicin IV bolus injection via a fast-running Sodium Chloride 0.9% infusion.
Cyclophosphamide may be administered as an 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/Echocardiogram	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 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
≥ 1.0	&	≥ 100	100% dose
< 1.0	or	< 100	Delay for 1 week. Repeat FBC, if recovered to above these levels, resume treatment at 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 10⁹/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 10⁹/L on Day 1 despite dose delay - seek Consultant advice and consider dose reduction by 25%

Non-haematological Toxicities

Renal Impairment

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.

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Cyclophosphamide

Creatinine Clearance (ml/min)	Cyclophosphamide Dose
> 20	100% dose
10 – 20	75% dose
< 10	50% dose

Hepatic ImpairmentEpirubicin

Bilirubin ($\mu\text{mol/L}$)	Epirubicin Dose
24 – 51	Give 50%
51 – 85	Give 25%
> 85	Omit

Cyclophosphamide is not recommended in patients with a bilirubin > 17 $\mu\text{mol/L}$ 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. Decision should be discussed with the Consultant.

Dose modifications for other toxicities as appropriateEpirubicin

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 3 painful erythema or ulcers requiring IV rehydration resolving to Grade 1 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/m²
 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.
 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

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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

e.g.haemorrhagic cystitis, pigmentation of palms, nails and soles etc..

Warfarin: anticoagulant effect is increased

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

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LCA Breast Cancer Clinical Guidelines October 2013

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