LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – EC (Epirubicin/Cyclophosphamide) in Advanced Breast Cancer

Indication:	First line for advanced breast cancer with no prior exposure to anthracyclines			
Regimen details:	Epirubicin	*60-90mg/m^2	IV	Day 1
	Cyclophosphamide	600mg/m^2	IV	Day 1
	* Consider Epirubicin 60mg/m^2 if patient > 60 years			
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 6 cycles			
Premedication:	Not routinely required			
Anti- emetics:	Highly emetogenic Follow local anti-emetic policy			
Supportive medication:	Mouthcare 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 to reduce the risk of permanent tissue damage			

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Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Laura Cameron	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

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, cardiotoxicity, mucositis, stomatitis, nausea, vomiting, diarrhoea, alopecia, urine discolouration, potential risk of infertility / early menopause, fatigue, skin sensitivity to sun exposure

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.5	&	≥ 100	100% dose
< 1.5	or	< 100	Delay for 1 week. Repeat FBC, if recovered resume at 100% dose. Consider dose reduction for >1 delay.

- Dose reduction and / or delay is more appropriate in the advanced setting
- If during the preceding cycle, the patient has experienced neutrophils <0.5 x 10^9/L or has febrile neutropenia diagnosed, GCSF should be considered
- If platelets persistently < 100 x 10^9/L on Day 1 despite dose delay – see 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.

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

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Hepatic Impairment

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

Cyclophosphamide is not recommended in patients with bilirubin >17 µmol/L or AST/ALT more than 2-3ULN, however, exposure to active metabolites may not be increased, therefore a dose reduction may not be necessary. Decision should be discussed with the Consultant.

Dose modifications for other toxicities

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 setting
Comments:	
Epirubicin	Maximum cumulative dose epirubicin = 950mg/m^2 A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan 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 e.g.haemorrhagic cystitis, pigmentation of palms, nails and soles etc.
Warfarin: anticoagulant effect is increased

References:

Hospira UK Ltd, 2013. Summary of Product Characteristics: Epirubicin. Available at www.medicines.org.uk [Accessed 15/11/13]
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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