LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – FEC 60 (Fluorouracil / Epirubicin / Cyclophosphamide) in Early Breast Cancer in Elderly / Frail

Indication:	Neoadjuvant or adjuvant therapy for elderly and frail patients with breast cancer			
Regimen details:	Epirubicin	60 mg/m^2	IV	Day 1
	Fluorouracil	600 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 Fluorouracil IV bolus injection via a fast-running Sodium Chloride 0.9% infusion Cyclophosphamide may be administered as a IV bolus injection via a fast-running Sodium Chloride 0.9% infusion or as a short infusion e.g. in 100-250 ml Sodium Chloride 0.9% over 30 minutes			
Frequency:	Day 1, every 21 days, for 6 cycles			
Pre-medication:	None required			
Anti- emetics:	High emetogenicity Follow local anti-emetic policy			
Supportive medication:	GCSF as per local policy Mouthcare as per local policy			
Extravasation:	Fluorouracil: Irritant Epirubicin: Vesicant Cyclophosphamide: Non-vesicant			

Reason for Update: LCA Protocol Development	Approved by LCA Consultant: Mark Harries
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: Isabel Munoz	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016

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

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:

Alopecia, nausea and vomiting, diarrhoea, mucositis and stomatitis, fatigue, menorrhagia and early menopause.
Discolouration of Urine – Epirubicin may colour the urine red
Fluorouracil: ECG Abnormalities – Isolated cases of angina, tachycardia, breathlessness and in rare occasions myocardial infarction have been reported with fluorouracil and monitoring is required during treatment with fluorouracil
Palmar Plantar Erythrodysesthesia (PPE) has been reported with high dose bolus therapy

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 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.

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- 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 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 10^9/L on Day 1 despite dose delay - seek Consultant advice and consider dose reduction by 25%

Non-haematological Toxicities

Renal Impairment

Creatinine Clearance (ml/ml)	Cyclophosphamide Dose	Fluorouracil Dose	Epirubicin Dose
> 20	100%	100%	100%
10-20	75%	100%	100%
<10	Discuss with consultant and consider 50% dose	Omit	Omit

Hepatic Impairment

Bilirubin (µmol/L)		AST / ALT (Units)	Cyclophosphamide Dose	Fluorouracil Dose	Epirubicin Dose
24-51	&/or	2-4 xULN	100%*	100%	50%
51-85	&/or	> 4 x ULN	Omit	Omit	25%
>85	&	Any	Omit	Omit	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 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: — Out-patient setting

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Comments:

Epirubicin

Maximum lifetime cumulative dose epirubicin = 950mg/m^2

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.

Fluorouracil

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of fluoruracil. Ensure patient is informed of action to take if signs of toxicity (e.g. severe mucositis, diarrhoea) develop within the first few days of treatment, as this is often an early indication of DPD deficiency.

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

Fluorouracil

Warfarin – INR raised when used concomitantly with fluorouracil. Switch to LMWH if anticoagulant therapy required.

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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:

Summary of Product Characteristics. Fluorouracil Hospira SPC updated 24/08/2011
Summary of Product Characteristics. Epirubicin. Hospira UK Ltd. SPC updated 28/06/2013
Summary of Product Characteristics. Cyclophosphamide. Pharmacia SPC updated 26/03/2012
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009
LCA Breast Cancer Clinical Guidelines October 2013

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