LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – EC x 4 – Paclitaxel x 4 (3-weekly): Epirubicin & Cyclophosphamide x 4 followed by Paclitaxel x 4 (3-weekly) 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^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 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			

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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

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 10^9/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 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 10^9/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

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^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

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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Followed by Paclitaxel

Regimen details:	Paclitaxel	175mg/m^2	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 21 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:	Mouthcare as per local policy GCSF 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			

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 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.0	&	≥ 100	100% dose
≥ 1.0	&	75 - 99	Discuss with Consultant. Consider a treatment delay for 1 week. Repeat FBC, if platelets recover to ≥ 100, resume treatment with 100% dose.
< 0.5	or	<75	Delay for 1 week. FBC, if neutrophils recover to ≥ 1.0 and platelets recover to ≥ 100, resume treatment with 75% dose for all subsequent cycles.

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 10^9/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

No dose adjustment required. Assess renal function when clinically indicated

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Hepatic Impairment

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

Dose modifications for other toxicities as appropriate

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
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