LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – Epirubicin & Cyclophosphamide x 4 followed by Carboplatin & Paclitaxel x 4 for Early Breast Cancer

Indication:	Neoadjuvant therapy for patients with BRCA1/2 mutations			
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, followed by 4 cycles of carboplatin and paclitaxel

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.

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Reason for Update:	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla and Rebecca Johl 21/01/2016
Prepared by: Melanie Dalby	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jatinder Harchowal 21/01/2016
Second check by: Lisa Yuen 08/12/15	Date prepared: December 2015 Review Date: December 2017

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 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 resume 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 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 – 20	75% dose
< 10	50% dose

Hepatic Impairment

Epirubicin

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

Cyclophosphamide is 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

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 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 increase

Followed by Carboplatin and Weekly Paclitaxel

Regimen details:	Paclitaxel	80 - 90mg/m^2	IV	Day 1, 8 and 15
	Carboplatin	AUC 6	IV	Day 1

Administration: Paclitaxel in 250ml Sodium Chloride 0.9% or Glucose 5% over 60 minutes. Paclitaxel to be given via a 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.

Carboplatin in 500mls Glucose 5% IV over 30 – 60 minutes

Aluminium containing equipment should not be used during preparation and administration of carboplatin

Hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills, usually during the first and second infusions and within a few minutes following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered.
Severe reactions such as hypotension and/or bronchospasm or g eneralised rash/erythema requires immediate discontinuation.
Availability of resuscitation equipment must be ensured as a standard precaution.

Frequency: Day 1, 8 and 15, every 21 days for 4 cycles

Pre-medication:	Dexamethasone	*8mg	IV	30 – 60 minutes 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

*To minimise steroid side effects, the dose of dexamethasone may be reduced to 4mg if there has been no evidence of hypersensitivity. Paracetamol / Chlorphenamine / Hydrocortisone can be given for administration-related reactions such as chills / fever.

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

Supportive medication: Mouthcare as per local policy
GCSF as per local policy

Extravasation: Paclitaxel: Vesicant
Carboplatin: Non- 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 investigation: Prior to Cycle 1:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
EDTA	See comments

Comments:
Carboplatin dose should be calculated using the Calvert formula: Dose = Target AUC x (25 + GFR).
GFR should be calculated using EDTA clearance before prescribing. (If EDTA not available prior to cycle 1, initiate treatment using the Cockcroft & Gault formula to calculate GFR, and ensure EDTA prior to cycle 2).
Monitor trends in serum creatinine between treatments, if >25% from baseline value re-calculate GFR using the Cockcroft & Gault formula or EDTA.

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)

Prior to Day 8 and 15 (all cycles):

	FBC	Day 1 (within 48 hours)

Toxicities: Infection, myelosuppression, anaemia, nausea, vomiting, diarrhoea, stomatitis, asthenia, peripheral neuropathy, hypersensitivity reactions, hypotension, alopecia, arthralgia, myalgia.

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets x (x 10^9/L)	Dose
≥ 1.0	&	≥ 100	100% dose
≥ 1.0	&	75 - 99	Discuss with Consultant – treatment can be considered on medical advice. Or consider treatment delay for 1 week. Repeat FBC, if platelets recover to ≥ 100 x 109/L, resume treatment at 100% dose.
< 1.0	or	< 75	Delay for 1 week. Repeat FBC, if recovered to above these levels, resume treatment with 75% paclitaxel dose for all subsequent cycles and consider reducing to AUC 5 for carboplatin.

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.
- 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% for paclitaxel and reduce to AUC 5 for carboplatin.
- If platelets persistently < 100 x 10^9/L on Day 1 despite dose delay - seek Consultant advice and consider dose reduction by 25% for paclitaxel and reduce to AUC 5 for carboplatin.

Non-haematological Toxicities

Renal Impairment

Creatinine Clearance	Paclitaxel Dose	Carboplatin Dose
≥ 20ml/min	100% dose	100% dose
< 20ml/min	No dose adjustment required	Carboplatin is contraindicated

Hepatic Impairment

Bilirubin	Paclitaxel Dose	Carboplatin Dose
22 - 26	Give 75 – 80% dose	No dose adjustment necessary
27 – 51	Give 40 – 45% dose	
> 51	Give 30% dose	

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% doses
2	Paraesthesia interfering with function, but not interfering with activities of daily living	75% dose paclitaxel
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:	Day case setting Availability of resuscitation equipment must be ensured as a standard precaution.

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Comments:	Cumulative lifetime doses anthracyclines
Drug interactions:	Paclitaxel Concomitant administration of inducers or inhibitors of cytochrome P450 Isoenzymes (CYP2C8 and 3A4) e.g. erythromycin, fluoxetine, gemfibrozil, rifampicin,carbamazepine, phenytoin, phenobabrbital etc, may alter the pharmacokinetics of Paclitaxel, presenting a theoretical interaction Carboplatin Clozapine - increased risk of agranulocytosis, avoid concomitant use Diuretics - increased risk of nephrotoxicity and ototoxicity Nephrotoxic drugs - increased nephrotoxicity; not recommended
References:	Accord Healthcare Ltd. Summary of product characteristics – paclitaxel. 26/11/2015. Available at www.medicines.org.uk Hospira UK Ltd. Summary of product characteristics – carboplatin. 26/11/2015. Available at www.medicines.org.uk LCA GSTT Systemic Therapy for Breast Cancer 2015 Sikov, W. et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). Journal of Clinical Oncology (2015) vol. 33 no. 1 13-21.

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