LONDON CANCER ALLIANCE
West and South

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

Indication:	Neoadjuvant therapy for high risk and fit breast cancer patients suitable for a taxane containing regimen			
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 docetaxel			
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.			

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

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.

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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

Followed by Docetaxel

Regimen details:	Docetaxel	100mg/m^2	IV	Day 1

Administration: Docetaxel in 250ml or 500ml Sodium Chloride 0.9% depending on final concentration IV over 1 hour

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 generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

Frequency: Day 1, every 21 days, for 4 cycles

Pre-medication: Oral dexamethasone 8mg BD for 3 days, starting the day before docetaxel administration to reduce the incidence and severity of fluid retention and hypersensitivity reactions.
If the patient has not taken the oral pre-medication, clinicians may prescribe dexamethasone IV 20mg, chlorphenamine IV 10mg and ranitidine IV 50mg to be administered 1 hour prior to chemotherapy. *(note: there is no data available to support the use of IV steroids in this setting, responsibility remains with the prescribing clinician).*

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: Primary Prophylactic Growth Factor support should be started at least 24 hours post chemotherapy given with each cycle of docetaxel chemotherapy, as per local policy

Mouthcare as per local policy

Extravasation: Vesicant
Docetaxel 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, nausea, vomiting, diarrhoea, stomatitis, asthenia, myalgia/arthralgia, fluid retention, peripheral neuropathy, hypersensitivity reactions; cutaneous reactions (reversible), nail disorder, ovarian failure, infertility

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 – treatment can be considered on medical advice. Or consider treatment delay for 1 week. Repeat FBC, if platelets recover to ≥ 100 x 10^9/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% dose for all subsequent cycles.

In neoadjuvant/adjuvant treatment, dose reduction and delays can compromise outcome.

- 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

Docetaxel: No dose adjustment required

Hepatic Impairment

ALP		AST / ALT		Bilirubin	Docetaxel Dose
≤ 2.5 X ULN	&	≤ 1.5 x ULN			100% dose
2.5 – 6 x ULN	&	1.6 – 3.5 x ULN			75% dose
> 6 ULN	&	> 3.5 x ULN	& / or	> 22µmol/L	Not recommended. Docetaxel should be administered with Consultant approval

Dose modifications for other toxicities as appropriate

NCI CTCAE Grade	Cutaneous Reactions	Dose
1	Erythema without associated symptoms	100% dose
2	Localised erythema of the palms of the hands and soles of the feet with oedema followed by desquamation	Consider dose reduction to 75% dose
3	Severe, generalised eruptions followed by desquamation	Delay until recovery to ≤ Grade 2, reduce to 75% dose For 2nd occurrence, discontinue docetaxel
4	Generalised exfoliative, ulcerative or bullous dermatitis	Discontinue docetaxel permanently

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	Consider dose reduction to 75mg/m^2
3	Paraesthesia interfering with activities of daily living	Delay until recovery to ≤ Grade 2, reduce to 75% dose For 2nd occurrence, discontinue

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		docetaxel
4	Disabling	Discontinue docetaxel permanently

Location of regimen delivery:	Outpatient setting Availability of resuscitation equipment must be ensured as a standard precaution.
Comments:	None
Drug interactions:	Concomitant administration of substrates, inducers or inhibitors of cytochrome P450-3A e.g. ciclosporin, terfenadine, ketoconazole, erythromycin etc, may alter the pharmacokinetics of docetaxel, presenting a theoretical interaction

References:

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