

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

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

### **Docetaxel**

Regimen details: Docetaxel 100mg/m<sup>2</sup> 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 followed by 4 cycles of EC

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).*

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Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
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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 used starting at least 24 hours post chemotherapy given with each cycle of 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 investigation: Prior to cycle 1  
FBC Day 1 (within 14 days)  
LFTs Day 1 (within 14 days)  
U&Es Day 1 (within 14 days)
- 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 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Dose
≥ 1.0	&	≥ 100	100% dose
≥ 1.0	&	75 - 99	Discuss with Consultant – treatment can be considered on medical advice.

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			Or consider treatment delay for 1 week. Repeat FBC, if platelets recover to $\geq 100 \times 10^9/L$ , 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 a dose reduction by 25%
- If platelets persistently  $< 100 \times 10^9/L$  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
$\leq 2.5 \times \text{ULN}$	&	$\leq 1.5 \times \text{ULN}$			Full dose
$2.5 - 6 \times \text{ULN}$	&	$1.6 - 3.5 \times \text{ULN}$			75% dose
$> 6 \text{ ULN}$	&	$> 3.5 \times \text{ULN}$	& / or	$> 22 \mu\text{mol/L}$	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 $\leq$ Grade 2, reduce to 75% dose For 2 <sup>nd</sup> occurrence, discontinue docetaxel
4	Generalised exfoliative, ulcerative or bullous dermatitis	Discontinue docetaxel permanently

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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 75% dose
3	Paraesthesia interfering with activities of daily living	Delay until recovery to ≤ Grade 2, reduce to 75% dose For 2 <sup>nd</sup> occurrence, discontinue 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

### **Followed by EC**

Regimen details:

Epirubicin	90 mg/m <sup>2</sup>	IV	Day 1
Cyclophosphamide	600 mg/m <sup>2</sup>	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

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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

Regular investigation: 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)  
MUGA scan/ECHO Prior to 1<sup>st</sup> cycle (see comments)

Toxicities: Myelosuppression, nausea, vomiting, diarrhoea, mucositis, stomatitis, cardiotoxicity, alopecia, urine discoloration, haemorrhagic cystitis, alopecia, infertility, early menopause

## DOSE MODIFICATIONS

### Haematological Toxicity

Neutrophils (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /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.
- If during the preceding cycle, the patient has experienced neutrophils < 0.5 x 10<sup>9</sup>/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%

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- If platelets persistently  $< 100 \times 10^9/L$  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  $< 10\text{ml/min}$ ) or serum creatinine  $> 3.0 - 6.0 \times \text{ULN}$  - discuss with the Consultant

##### Cyclophosphamide

<b>Creatinine Clearance (ml/min)</b>	<b>Cyclophosphamide Dose</b>
$> 20$	100%
10 – 20	75% dose
$< 10$	Discuss with consultant and consider 50% dose

#### **Hepatic Impairment**

<b>Bilirubin (<math>\mu\text{mol/L}</math>)</b>	<b>Epirubicin Dose</b>
24 – 51	Give 50%
51 – 85	Give 25%
$> 85$	Omit

**Cyclophosphamide** is not recommended in patients with a bilirubin  $> 17\mu\text{mol/L}$  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:                      Outpatient regimen  
delivery

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Comments:

Epirubicin

Maximum cumulative dose Epirubicin = 950mg/m<sup>2</sup>

A baseline MUGA scan or ECHO 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 ECHO 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

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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:

Accord. Summary of Product Characteristics: docetaxel 04/10/2013 Available at <http://www.medicines.org.uk/emc/> [Accessed 19/11/13]  
Hospira UK Ltd. Summary of Product Characteristics: epirubicin 28/06/2013 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  
LCA Breast Cancer Clinical Guidelines October 2013

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