

Breast Pathway Group – FEC(100)-Docetaxel: Fluorouracil / Epirubicin / Cyclophosphamide followed by Docetaxel in Early Breast Cancer

Indication: Neoadjuvant or adjuvant therapy in node positive patients. Also considered in high risk node negative patients e.g. triple negative or HER2 positive.

FEC100

Regimen details:	Epirubicin	100mg/m ²	IV	Day 1
	Fluorouracil	500mg/m ²	IV	Day 1
	Cyclophosphamide	500mg/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 IV bolus injection via a fast-running Sodium Chloride 0.9% infusion or as a short infusion e.g. in 100-250mls Sodium Chloride 0.9% over 30 minutes

Frequency: Day 1, every 21 days, for 3 cycles followed by 3 cycles of Docetaxel

Pre-medication: Not routinely required

Anti- emetics: High emetogenicity
Follow Local Anti-emetic Policy

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

Extravasation: Epirubicin: Vesicant
Fluorouracil: Irritant

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: Anabel Rodriguez Marina	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
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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 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: Myelosuppression, nausea, vomiting, diarrhoea, mucositis, stomatitis, cardiotoxicity, alopecia, fever, fatigue, urine discoloration, haemorrhagic cystitis, taste disturbances, early menopause

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

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- 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 $< 0.5 \times 10^9/L$ 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 $< 100 \times 10^9/L$ 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 / Clinical decision	Omit / Clinical decision

Hepatic Impairment

Bilirubin ($\mu\text{mol/L}$)		AST / ALT (Units)	Cyclophosphamide Dose	Fluorouracil Dose	Epirubicin Dose
24 - 51	&/or	2 - 4 x ULN	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 $>17 \mu\text{mol/L}$ or AST/ALT more than 2 – 3 x ULN, 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 3 painful erythema or ulcers requiring IV rehydration resolving to Grade I or less painful ulcers or mild soreness: give epirubicin 85% dose and recommend regular mouth care.

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Location of regimen delivery: Outpatient setting
 Comments:

Epirubicin

Maximum lifetime cumulative dose epirubicin = 950mg/m²
 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

Haemorrhagic cystitis & 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 and regular voiding of urine

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

Fluorouracil

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of fluorouracil. 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.

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

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Warfarin: INR raised when used concomitantly with fluorouracil.

Switch to LMWH if anticoagulant therapy required

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/m² 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 3 cycles

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- 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 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 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

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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 10⁹/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			Full 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

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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 nd 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 75% dose
3	Paraesthesia interfering with activities of daily living	Delay until recovery to \leq Grade 2, reduce to 75% dose For 2 nd 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

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