LONDON CANCER ALLIANCE West and South

Breast Pathway Group– TC (Docetaxel / Cyclophosphamide) in Early Breast Cancer

Indication:	Neoadjuvant or adjuvant treatment for patients in whom anthracyclines are contraindicated or inappropriate			
Regimen details:	Docetaxel	75 mg/m^2	IV	Day 1
	Cyclophosphamide	600 mg/m^2	IV	Day 1
Administration:	Docetaxel in 250ml or 500ml Sodium Chloride 0.9% depending on final concentration IV over 1 hour Cyclophosphamide may be administered as IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion or a short infusion e.g. in 100 - 250ml Sodium Chloride 0.9% over 30 minutes 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 and should not be re-challenged. Availability of resuscitation equipment must be ensured as a standard precaution.			
Frequency:	Day 1, every 21 days, for 4 to 6 cycles			
Pre-medication:	Oral dexamethasone 8mg BD for 3 days, starting the morning of the day before docetaxel administration to reduce the incidence and severity of fluid retention and hypersensitivity reactions.			

Reason for Update: LCA Protocol Development	Approved by LCA Consultant: Mark Harries
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: Isabel Munoz	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016

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:

Moderate emetogenicity
Follow Local Anti-emetic Policy

Supportive medication:

GCSF as per local policy
Mouthcare as per local policy

Extravasation:

Docetaxel: vesicant
Cyclophosphamide: non-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 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, alopecia, nausea, vomiting, diarrhoea, mucositis asthenia, myalgia/arthralgia, fatigue, 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	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.

- 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

CrCl (ml/min)	Docetaxel Dose	Cyclophosphamide Dose
> 20	100%	100%
10 - 20	100%	75%
< 10	Discuss with consultant, consider a dose reduction	Discuss with consultant, consider 50%

Hepatic Impairment

Bilirubin		AST / ALT		ALK Phos	Docetaxel Dose	Cyclophosphamide dose
Any	&	≤ 1.5	&	≤ 2.5 x ULN	100%	100%
Any	&	1.6 - 3.5 x ULN	&	2.5 – 6 x ULN	75% dose	100%
> ULN	&	> 3.5	&	> 6 x ULN	Do not give	Consider dose reduction*

* Cyclophosphamide is not recommended in patients with a bilirubin >17µmol/L or AST/ALT more than 2-3 UNL, however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be needed. Discuss with Consultant.

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Dose modifications for other toxicities as appropriate

Docetaxel

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

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.

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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:

Docetaxel

Concomitant administration of substrates, inducers or inhibitors of cytochrome P450-3A e.g. ciclosporin, terfenadine, ketoconazole, erythromycin, rifampicin, barbiturates etc, may alter the pharmacokinetics of docetaxel

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

References:

Summary of Product Characteristics. Docetaxel Accord, updated 04/10/2013
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009
Jones SW, Savin MA, Holmes FA, *et al.* Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide With Docetaxel Plus Cyclophosphamide As Adjuvant Therapy for Operable Breast Cancer. J Clin Oncol 2009; 27(8): 1177-1183
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