LONDON CANCER ALLIANCE West and South

Breast Pathway Group – TCH (Docetaxel, Carboplatin & Trastuzumab) in Early Breast Cancer

Indication: Neoadjuvant or adjuvant therapy in high risk breast cancer (node negative or positive), HER2 positive, unsuitable for an anthracycline containing regimen

Regimen details:

Trastuzumab			Day 1
Docetaxel	75mg/m^2	IV	Day 1
Carboplatin	AUC 6*	IV	Day 1

* Carboplatin dose is calculated using the Calvert formula:
Dose = Target AUC x (25 + GFR)
Gold standard GFR is measured using EDTA wherever possible. If not available, Cockcroft & Gault equation may be used to estimate GFR; if the calculated GFR <60 or >120ml/min measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if >25% from baseline value re-calculate GFR using the Cockcroft & Gault equation.

Administration: In pivotal trials, docetaxel was administered the day following the first dose of trastuzumab, and immediately after the subsequent doses of trastuzumab if the preceding dose was well tolerated.

However, there is increasing worldwide experience that both trastuzumab and taxanes can be given on the same day:
Trastuzumab may be administered first, followed by docetaxel then carboplatin on Day 1.

For details of doses, administration, monitoring and on-going treatment with trastuzumab, see separate protocol for trastuzumab (IV or SC) in early breast cancer.
Docetaxel in 250ml or 500ml Sodium Chloride 0.9% depending on final concentration IV over 1 hour
Carboplatin in 500ml Glucose 5% IV over 1 hour

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: 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

	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 6 cycles, followed by trastuzumab alone for 12 cycles (i.e. 18 cycles of trastuzumab in total)
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:	High emetogenicity Follow Local Anti-emetic Policy
Supportive medication:	GCSF as per local Policy Mouthcare as per local Policy
Extravasation:	Docetaxel: vesicant Carboplatin: irritant 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)
	EDTA	Prior to cycle 1
	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

DOSE MODIFICATIONS

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% for docetaxel and reduce to AUC5 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 docetaxel and reduce to AUC5 for carboplatin

Non-haematological Toxicities

Renal Impairment

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Docetaxel: No dose adjustment required
Carboplatin: Contraindicated if creatinine clearance is < 20 ml/min

Hepatic Impairment

Carboplatin: No dose reduction necessary

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 for docetaxel as follows:

NCI CTCAE Grade	Cutaneous Reactions	Docetaxel 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	Docetaxel 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

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Location of regimen delivery:	Outpatient setting. Availability of resuscitation equipment must be ensured as a standard precaution.
Comments:	None
Drug interactions:	<u>Docetaxel</u> 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. <u>Carboplatin</u> concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, may increase / exacerbate toxicity due to carboplatin induced changes in renal clearance.

References:

Summary of product characteristics – docetaxel, carboplatin, trastuzumab. Available at www.medicines.org.uk

Slamon D, Wolfgang E, Robert N, et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med 2011;365:1273-83

Slamon D, Wolfgang E, Robert N, et al. BCIRG 006: Phase III randomised trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. San Antonio Breast Cancer Symposium 2009;Abstract 62

Coudert BP, Largillie R, Arnould L, et al. Multicenter Phase II Trial of Neoadjuvant Therapy With Trastuzumab, Docetaxel, and Carboplatin for Human Epidermal Growth Factor Receptor-2–Overexpressing Stage II or III Breast Cancer: Results of the GETN(A)-1 Trial. JCO 2007; 25 (19): 2678 - 2684

UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009

UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009

LCA Breast Cancer Clinical Guidelines October 2013

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