LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – AC (Doxorubicin / Cyclophosphamide) in Early Breast Cancer

Indication:	Neoadjuvant or adjuvant treatment of breast cancer			
Regimen details:	Doxorubicin	60mg/m^2	IV	Day 1
	Cyclophosphamide	600mg/m^2	IV	Day 1

Administration: Doxorubicin 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 required

Anti- emetics: High emetogenicity
Follow local anti-emetic policy

Supportive medication: GCSF as per Local Policy
Mouthcare as per Local Policy

Extravasation: Doxorubicin: Vesicant
Cyclophosphamide: Non-vesicant
Doxorubicin 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

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Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016

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, cardiotoxicity, mucositis, stomatitis, nausea, vomiting, diarrhoea, alopecia, urine discolouration, potential risk of infertility / early menopause, fatigue, skin sensitivity to sun exposure

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.0	&	≥ 100	100%
< 1.0	or	< 100	Delay for 1 week. Repeat FBC - if recovered to above these levels, resume treatment with 100% doses

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%

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Non-haematological Toxicities

Renal Impairment

Creatinine Clearance (ml/ml)	Cyclophosphamide Dose	Doxorubicin Dose
> 20	100%	100%
10 - 20	75%	100%
< 10	Discuss with Consultant and consider 50% dose	Omit / Clinical decision

Hepatic Impairment

Bilirubin (µmol/L)		AST / ALT (Units)	Doxorubicin Dose
		2 - 3 x ULN	75% dose
20 - 50	&/or	> 3 x ULN	50% dose
51 - 85	&	Any	25% dose
> 85	&	Any	Omit

Cyclophosphamide is not recommended in patients with bilirubin > 17µmol/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

Doxorubicin: 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 1 or less painless ulcers or mild soreness: consider 25% dose reduction and recommend regular mouth care.

Location of regimen delivery: Outpatient regimen

Comments:

Doxorubicin dose doxorubicin = 450 - 550mg/m^2: Maximum cumulative lifetime

A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant

cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy.
MUGA scan 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:

Cyclophosphamide and Doxorubicin

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 -Warfarin : the anticoagulant effect is increased

Doxorubicin

Ciclosporin (high dose) increase Doxorubicin serum levels and myelotoxicity
Concomitant use of other cardioactive compounds e.g. calcium channel blockers require monitoring of cardiac function throughout treatment
Quinolones: antimicrobial effect of quinolones decreased

Cyclophosphamide

Allopurinol: can increase the incidence of serious bone marrow depression
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..

References:

Actavist UK Ltd. Summary of Product Characteristics: doxorubicin. 09/03/2012. Available at www.medicines.org.uk [accessed 04/02/2014]

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

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

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