LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – Oral Cyclophosphamide & Methotrexate in Advanced Breast Cancer

Indication:	Pretreated metastatic breast cancer with ECOG performance status 0 - 2 Previously untreated metastatic breast cancer in patients unsuitable for other chemotherapy drugs due to excess toxicity risk			
Regimen details:	Cyclophosphamide	50mg ONCE a day	PO	Continuous therapy
	Methotrexate	2.5mg TWICE a day	PO	Day 1 & 2 each WEEK
Administration:	Orally, tablets to be swallowed whole, do not chew or crush. Take with a full glass of water. Cyclophosphamide available as 50mg tablets Methotrexate available as 2.5mg tablets			
Frequency:	Prescribed every 28 days - continue treatment according to response or unacceptable toxicity occurs			
Pre-medication:	Not routinely required			
Anti- emetics:	Low emetogenicity Follow Local Anti-emetic Policy			
Supportive medication:	Mouthcare as per local policy			
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)		
	CXR	Baseline, then as clinically indicated		

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
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

Prior to Day 1 (all cycles)	
FBC	Every 2 weeks until stabilised, then Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
U&Es	Day 1 (within 72 hours)

Toxicities: Myelosuppression, nausea, vomiting, anorexia, diarrhoea, skin reactions (rash, dry skin, pruritis, blisters, pigmentation), nail changes, alopecia, mucositis, taste change, anaemia, interstitial pneumonitis, elevation of liver enzymes and liver toxicity, renal toxicity, haematuria/haemorrhagic cystitis, blurred vision, azoospermia, secretion of anti-diuretic hormone (fluid retention and hyponatremia)

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.5	&	≥ 100	100% dose
1.0 – 1.49	& / or	75 - 99	Proceed at 50% dose reduction for both drugs
< 1.0	& / or	< 75	Delay 1 week. Repeat FBC, if recovered then restart treatment with 50% dose reduction for both drugs

Non-haematological Toxicities

Renal Impairment

Methotrexate

Creatinine Clearance (ml/min)	Methotrexate Dose
> 50	100% dose
10 – 50	2.5mg ONCE a day on Day 1 & 2 each week
< 10	Contra-indicated

Cyclophosphamide

Renal failure may lead to reduced excretion of metabolites and increased toxicity. Severe renally impaired patients (CrCl <10 ml/min) are at particular risk, consider 50% dose reduction

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Hepatic Impairment

Methotrexate

Bilirubin (µmol/L)		AST / ALT (Units)	Methotrexate Dose
< 50	&	< 180	100% dose
51 - 85	or	> 180	2.5mg ONCE a day on Day 1 & 2 each week
> 85			Contra-indicated

Cyclophosphamide

Consider dose reduction if transaminases or ALP > 2-3 x ULN. Clinical decision.

Dose modifications for other toxicities as appropriate

Withhold treatment for ≥ grade 2 non-haematological toxicity: anorexia, nausea, vomiting, diarrhoea, stomatitis, dry mouth, increased transaminases, epigastric pain, until resolved then consider dose reducing by 50%.

Location of regimen delivery: Outpatient setting

Comments: Patients able to tolerate oral dosage forms
To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Drug interactions: Avoid use of live vaccines – increased risk of infection

Methotrexate: Drugs with antifolate properties (e.g. co-trimoxazole, trimethoprim) – increased methotrexate toxicity
Aspirin / NSAIDS- reduced excretion of methotrexate, increased risk of toxicity
Phenytoin – reduced phenytoin effectiveness, increase risk of methotrexate toxicity
Warfarin – increases INR, risk of bleeding
Clozapine - increased risk of agranulocytosis, avoid concomitant use
Probenecid - increased effect of methotrexate
Retinoids – increases methotrexate levels, increase risk of hepatotoxicity

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	Vitamin products containing folic acid may alter response Increased risk of toxicity with haematotoxic/hepatotoxic drugs (eg. Leflunomide)
Cyclophosphamide	Effect of oral hypoglycaemic agents may be potentiated 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:

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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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