LONDON CANCER ALLIANCE West and South

Breast Pathway Group – CMF (oral or IV): Cyclophosphamide / Methotrexate / Fluorouracil in Early Breast Cancer

Indication: Neoadjuvant or Adjuvant treatment for high risk breast cancer

Regimen details:

CMF ORAL

Cyclophosphamide	100mg/m^2 once daily PO		Days 1 to 14
	OR		
Cyclophosphamide	200mg / 150mg on alternate days PO		Days 1 to 14
5-Fluorouracil	600mg/m^2	IV	Day 1 & Day 8
Methotrexate	40mg/m^2	IV	Day 1 & Day 8

CMF IV

Cyclophosphamide	600 mg/m^2	IV	Day 1 & Day 8
Methotrexate	40 mg/m^2	IV	Day 1 & Day 8
5-Fluorouracil	600 mg/m^2	IV	Day 1 & Day 8

Administration: Cyclophosphamide tablets orally, swallow whole with water. Cyclophosphamide available as 50mg tablets.

Cyclophosphamide IV may be administered as an 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.

5-Fluorouracil IV bolus injection via a fast-running Sodium Chloride 0.9% infusion

Frequency: Every 28 days for up to 6 cycles

Pre-medication: Not routinely required

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

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

Supportive medication: Folinic acid rescue 15mg PO 6 hourly x 6 doses, starting 24 hours post methotrexate on Day 1 & Day 8 (only required for patients with toxicities such as mucositis, sore eyes, diarrhoea or severe renal impairment or "third-space" fluid collection – see Comments)

Diarrhoea can be managed with loperamide
GCSF as per local policy
Mouthcare as per local policy

Extravasation: Non-vesicants

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 8 (all cycles):

FBC	Day 8 (within 48 hours)

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)
CT scan	Every 3 cycles

Toxicities: Myelosuppression, risk of sepsis and thrombocytopenia, nausea, vomiting, diarrhoea (possibly constipation), mild alopecia, taste disturbance, fatigue, mucositis, long term risk of early menopause

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.

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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

Creatinine Clearance (ml/ml)	Cyclophosphamide Dose	Methotrexate Dose	Fluorouracil Dose
>80	100%	100%	100%
60-80	100%	65%	100%
30-60	100%	50%	100%
20-30	100%	Omit	80%
10-20	75%	Omit	80%
<10	Discuss with consultant and consider 50% dose	Omit	Omit

Hepatic Impairment

Bilirubin (µmol/L)		AST / ALT (Units)	Methotrexate Dose	Fluorouracil Dose
24-50	&	<180	100%	100%
51-85	&	Any	75%	100%
Any	&	> 180	75%	Omit
>85	&	Any	Omit	Omit

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

Location of regimen delivery: Outpatient setting

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Comments:

Fluorouracil

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

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.

Methotrexate

If the patient has a "third-space" fluid collection (ascites, effusion or extensive oedema) or significant renal impairment or toxicities such as mucositis, sore eyes or diarrhoea, the elimination of methotrexate may be prolonged, enhancing its toxicity. Seek Consultant advice and consider folinic acid rescue in such cases (ensure it is charted to start 24 hours after methotrexate)

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur with methotrexate and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit.

Hepatotoxicity, including hepatitis and cirrhosis, has been associated with methotrexate. It is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy.

Drug interactions:

Significant interactions below. For full details consult product literature/reference texts.

- Warfarin/coumarin anticoagulants: elevations in INR have been reported in patients taking warfarin and receiving fluorouracil. Patients should be switched to low molecular weight heparin for the duration of therapy.
- Folinates: Folinic acid enhances the toxicity of fluorouracil and reduces the maximum tolerated dose. It is possible that folic acid has the same effect. Avoid concomitant use.

- NSAIDS: may reduce renal excretion of methotrexate (increased risk in those with renal impairment). Monitor renal function & FBC if used concomitantly.
- Probenicid: Increases methotrexate toxicity. Avoid.
- Antibacterials: Penicillins, doxycycline, tetracyclines, sulphonamides & ciprofloxacin may reduce methotrexate clearance. Monitor FBC.
- Co-trimoxazole/trimethoprim: Increases antifolate effect. Avoid if possible. If must be used, monitor FBC.
- Retinoids: Increased risk of hepatotoxicity. Avoid.

References:

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