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

Indication: Third or fourth line treatment in advanced breast cancer

Regimen details:

**CMF ORAL**
- Cyclophosphamide 100mg/m\(^2\) PO once daily Days 1 – 14
  - OR
- Cyclophosphamide 200mg / 150mg alternate days PO Days 1 – 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.

OR
- 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.

Methotrexate IV and 5-Fluorouracil IV are given as 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

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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)

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
FBC Day 8 (within 48 hours)

Prior to Day 1 and Day 8 (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

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5</td>
<td>&amp;</td>
<td>≥ 100</td>
</tr>
<tr>
<td>&lt; 1.5</td>
<td>or</td>
<td>&lt; 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Non-haematological Toxicities

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/ml)</th>
<th>Cyclophosphamide Dose</th>
<th>Methotrexate Dose</th>
<th>Fluorouracil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>60-80</td>
<td>100%</td>
<td>65%</td>
<td>100%</td>
</tr>
<tr>
<td>30-60</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>20-30</td>
<td>100%</td>
<td>Omit</td>
<td>80%</td>
</tr>
<tr>
<td>10-20</td>
<td>75%</td>
<td>Omit</td>
<td>80%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Discuss with consultant and consider 50% dose</td>
<td>Omit</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Hepatic Impairment

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST / ALT (Units)</th>
<th>Cyclophosphamide Dose</th>
<th>Methotrexate Dose</th>
<th>Fluorouracil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-51</td>
<td>&lt;180</td>
<td>100%*</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>50-85</td>
<td>&gt;180</td>
<td>Omit</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>&gt;85</td>
<td>&gt;180</td>
<td>Omit</td>
<td>75%</td>
<td>Omit</td>
</tr>
</tbody>
</table>

*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

Comments:
Monitor for third-space fluid collections e.g. ascites, effusions, oedema. Methotrexate toxicity may be increased

Cardiotoxicity - 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.

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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: Wendy Ng
Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson

Second check by: Lisa Yuen
Date prepared: November 2014 Review Date: November 2016

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DPD deficiency - Fluorouracil
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.

Folinic acid rescue - 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 (make sure it is charted to start 24 hours after Methotrexate).

Interstitial pneumonitis - 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 - Methotrexate
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.

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- Probenecid: 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:
Fisher et al., (1990); JCO, Vol 8:pp 2483-96
Tancini et al., (1983); JCO, Vol 1:pp 2-10
Bonadonna et al., (1976); Vol 294:pp 405-10
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. Jan 2009
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. Jan 2009
LCA Breast Cancer Clinical Guidelines October 2013