Epirubicin – CMF: Epirubicin followed by Cyclophosphamide/ Methotrexate/ Fluorouracil in Early Breast Cancer

Indication: First line adjuvant therapy in moderate to high risk Breast Cancer patients unsuitable for a taxane containing regimen

**Epirubicin**

Regimen details: Epirubicin 100mg/m² IV D1

Administration: Epirubicin IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion

Frequency: Every 21 days, for 4 cycles, followed by 4 cycles CMF (oral). See below

Extravasation: Epirubicin: Vesicant

Anti-emetics: Moderate emetogenic. Follow local Anti-emetic Policy

Regular investigations: FBC D1, LFTs D1, U&Es D1, MUGA scan/Echocardiogram See Comments (if necessary)

Comments: Maximum cumulative dose Epirubicin=950mg/m²

A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, diabetes, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or Echocardiogram should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum

**Followed by CMF (oral)**

See Administration below for CMF (IV)

Regimen details: Cyclophosphamide 100mg/m² PO once daily (round dose to nearest 50mg) D1 – D14

OR

Cyclophosphamide 200mg / 150mg PO alternate days D1 – D14

5-Fluorouracil (5-FU) 600mg/m² IV D1 and D8

Methotrexate 40mg/m² IV D1 and D8

Administration: Methotrexate and 5-Fluorouracil are given as IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion

Cyclophosphamide is available as 50mg tablets, which are not scored or divisible.

*(SELCN Oral Chemotherapy Guidelines must be followed)*

The daily dose should be taken once daily with a large glass of water.

Patients unable to swallow cyclophosphamide tablets may be given intravenous therapy (Cyclophosphamide 600mg/m² IV D1 and D8)
*The “classical” oral CMF should be the regimen of choice as in some studies, it has shown a survival benefit. The intravenous regimen should be considered for patients with uncontrolled nausea (who may not absorb Cyclophosphamide) and those with concerns about compliance.*

Premedication: Not usually required

Frequency: Every 28 days, for 4 cycles, starting 21 days after final cycle of Epirubicin

Extravasation: Methotrexate and 5-Fluorouracil are non-vesicants

Anti-emetics: Moderate emetic potential
Specific individual drugs are stated in the Trust anti-emetic policy

Supportive medication: Mouthwashes (as per local policy) for mucositis

Folinic acid rescue 15mg po 6 hourly x 6 doses, starting 24 hours post Methotrexate (D1 & D8) (only required for patients with toxicities such as mucositis, sore eyes, diarrhea or severe renal impairment or “third –space” fluid collection). See Comments on page 4

Loperamide 4mg po stat then 2mg prn for diarrhea

Regular investigations: FBC Baseline & pre D1 & 8
LFTs Baseline & pre D1
U&Es Baseline & pre D1

**DOSE MODIFICATIONS**

**Haematological Toxicity**

In adjuvant treatment, dose reduction and delays can compromise outcome. G-CSF should be considered if more than one delay and / or before dose reduction. If in doubt, contact the relevant Consultant.

Neutrophils ≤ 1.0 x 10⁹/l Delay for 1 week.

or Repeat FBC - If within normal parameters, resume treatment. Dose reduction should be considered if myelosuppression results in delay of subsequent courses.

Platelets < 100 x 10⁹/l

**Renal Impairment**

Epirubicin and Fluorouracil: Consider dose reduction in severe renal impairment (GFR < 10ml/min)

Contact the relevant Consultant for clinical decision

Full Cyclophosphamide dose is not recommended in patients with a plasma creatinine above the upper limit of the normal range at the institution. Dose adjustments for Cyclophosphamide should be made using Cockcroft and Gault, following the guidelines below. EDTA should be requested so that the dose can be adjusted if necessary, according to EDTA result, on all subsequent cycles.
<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cyclophosphamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Give 100%</td>
</tr>
<tr>
<td>10 – 50</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 50%</td>
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</tbody>
</table>

**Methotrexate:** Use with extreme caution in patients with renal impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>Give 100%</td>
</tr>
<tr>
<td>60 – 80</td>
<td>Give 65%</td>
</tr>
<tr>
<td>30 – 59</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

Cyclophosphamide is not recommended in patients with a bilirubin > 17 µmol/L or AST/ALT more than 2 – 3 x upper normal limit, however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Decision should be discussed with the Consultant.

**Epirubicin:** The dose should be adjusted as follows

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Epirubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>51 – 85</td>
<td>Give 25%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Methotrexate is contraindicated in impaired hepatic function. 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.

<table>
<thead>
<tr>
<th>Bilirubin (µmol/l)</th>
<th>AST (µmol/l)</th>
<th>Methotrexate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 52, and</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>53 – 84, or</td>
<td>&gt; 180</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>-</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**5-Fluorouracil** should be used with caution in patients with reduced liver function or jaundice

<table>
<thead>
<tr>
<th>Bilirubin (µmol/l)</th>
<th>AST (µmol/l)</th>
<th>Fluorouracil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85, or</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&gt; 85, or</td>
<td>&gt; 180</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

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 III Painful erythema or ulcers requiring IV rehydration resolving to Grade I or less painless ulcers or mild soreness: give Epirubicin 85% dose and recommend regular mouth care

Toxicities: Myelosuppression: risk of sepsis and thrombocytopenia; cardiotoxicity; fatigue; sore eyes; alopecia; nausea; vomiting; mucositis; stomatitis; diarrhoea; taste disturbance; urine discoloration; potential risk of infertility / early menopause

Drug interactions: Antibiotics: Penicillins, doxycycline, tetracyclines, sulphamides & ciprofloxacin may reduce methotrexate clearance. Monitor FBC
Cimetidine and Ciclosporin: Can increase Epirubicin serum levels
Clozapine: Increased risk of agranulocytosis, avoid concomitant use
Co-trimoxazole/trimethoprim: Increases antifolate effect. Avoid if possible. If must be used, monitor FBC
Digoxin tablets: Reduced absorption (resolved by giving the digoxin in liquid)
Folic acid: Folic 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
Oral hypoglycaemic agents may be potentiated by Cyclophosphamide
Phenytoin: Reduced absorption of the antiepileptic
Probenecid: Increases methotrexate toxicity. Avoid
Retinoids: Increased risk of hepatotoxicity. Avoid
Verapamil: Possibly increases Epirubicin bone marrow depressant effects
Warfarin/coumarin anticoagulants: elevations in INRs have been reported in patients taking warfarin concomitantly. Patients should be switched to low molecular weight heparin for the duration of therapy

Comments: 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.

DPD deficiency- Fluorouracil
Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of fluorouracil

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.

References:
- SPC Cyclophosphamide 50 tablets (Pharmacia) accessed 2nd April 2008 from [www.medicines.org.uk](http://www.medicines.org.uk)
- SPC Methotrexate 25mg/ml injection (Hospira) accessed 2nd April 2008 from [www.medicines.org.uk](http://www.medicines.org.uk)
- SPC Fluorouracil 50mg/ml injection (Hospira) accessed 2nd April 2008 from [www.medicines.org.uk](http://www.medicines.org.uk)
- SPC Epirubicin 2mg/ml injection (Hospira) accessed 20th June 2008 from [www.medicines.org.uk](http://www.medicines.org.uk)
- 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
- ASWCS Chemotherapy Handbook Jan 2005 Update
- CCO Formulary. E-CMF. Revised July 2005
- SWSHCN- Epirubicin-CMF. Approved Network Regimen for Breast Cancer. November’06
- British Oncology Pharmacy Association (BOPA) Guidelines for Dose Adjustment of Cytotoxics in Hepatic and Renal impairment accessed 2 April 2008 from [www.bopawebsite.org](http://www.bopawebsite.org)
- DrugDex Evaluation Methotrexate accessed 2nd April 2008 from [www.micromedex.com](http://www.micromedex.com)
- Stockley’s Drug Interactions accessed 2nd April 2008 from [www.medicinescomplete.com](http://www.medicinescomplete.com)