Regimen: Classical CMF (IV) for Early Breast Cancer

Indication
Adjuvant treatment for early breast cancer in patients who are unsuitable for anthracycline based chemotherapy

Regimen detail

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 8</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV</td>
</tr>
<tr>
<td>1 &amp; 8</td>
<td>Methotrexate</td>
<td>40mg/m²</td>
<td>IV</td>
</tr>
<tr>
<td>1 &amp; 8</td>
<td>Fluorouracil (5-FU)</td>
<td>600mg/m²</td>
<td>IV</td>
</tr>
</tbody>
</table>

Administration
Fluorouracil, methotrexate and cyclophosphamide are given by slow intravenous bolus into the side arm of a fast flowing drip of 0.9% sodium chloride.
Cyclophosphamide may be given in 250-500ml 0.9% sodium chloride over 30 minutes

Frequency
Every 28 days
Maximum 6 cycles

Extravasation
Fluorouracil and methotrexate are inflammants (Group 2)
Cyclophosphamide is a neutral agent (Group 1)

Premedication
Not usually required.

Emetogenicity
This regimen has moderate emetogenic potential – refer to local protocol

Additional recommended supportive medication
Mouthwashes as per local policy
Loperamide 4mg po stat then 2mg prn for diarrhoea
Consider folinic acid (calcium folinate/leucovorin) rescue 15mg po 6 hourly x 6 doses, \textbf{starting 24 hours post methotrexate D1&D8 (only for patients with severe toxicities such as mucositis, sore eyes, diarrhoea, severe renal impairment or “third – space” fluid collection)}

Pre- treatment evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Results Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>Baseline - results valid for 4 weeks</td>
</tr>
<tr>
<td>LFT</td>
<td>Baseline - results valid for 4 weeks</td>
</tr>
<tr>
<td>U&amp;E (inc. SrCr)</td>
<td>Baseline - results valid for 4 weeks</td>
</tr>
</tbody>
</table>

Regular investigation

<table>
<thead>
<tr>
<th>Test</th>
<th>Results Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>Pre D1 – results valid for 72 hours,</td>
</tr>
<tr>
<td>LFT</td>
<td>Pre D1 – results valid for 7 days</td>
</tr>
<tr>
<td>U&amp;E (inc SrCr)</td>
<td>Pre D1 – results valid for 7 days</td>
</tr>
<tr>
<td>Clinical Assessment</td>
<td>Clinically assess patient prior to each cycle, particularly focusing on whether the patient has developed stomatitis or haemorrhagic cystitis</td>
</tr>
</tbody>
</table>
Standard limits for administration to go ahead – if blood results not within range, authorisation to administer must be given by prescriber/consultant

<table>
<thead>
<tr>
<th></th>
<th>Neutrophil count</th>
<th>≥ 1 x 10⁹/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Platelet count</td>
<td>≥100 x 10⁹/l</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>≥ 80ml/min</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;1.5 x ULN</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;2.5 x ULN</td>
<td></td>
</tr>
</tbody>
</table>

### Dose modifications

Reduce the dose of methotrexate if the patient has a pleural effusion or ascites (Is this done empirically or is there a defined dose reduction?)

#### Haematological toxicity

Delay 1 week if neutrophils <1.0 x 10⁹/l and/or platelets <100 x 10⁹/l. Dose reduction should be considered if myelosuppression results in delay of subsequent courses.

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. Contact relevant consultant.

#### Renal impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cyclophosphamide dose</th>
<th>Methotrexate dose</th>
<th>Fluorouracil (5FU) 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>50-59</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>30-50</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>10-30</td>
<td>75%</td>
<td>Contraindicated</td>
<td>100%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
<td>Contraindicated</td>
<td>Consider dose reduction</td>
</tr>
</tbody>
</table>

#### Hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin (x ULN)</th>
<th>ALT (x ULN)</th>
<th>Cyclophosphamide dose</th>
<th>Methotrexate dose</th>
<th>Fluorouracil (5FU) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>&lt;2.5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 – 3</td>
<td>2.5 - 5</td>
<td>100%*</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>&gt; 5</td>
<td>Consider dose reduction / use alternative regimen*</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

* Cyclophosphamide is not recommended in patients if bilirubin > 1.5 x ULN or AST/ALT >2–3xULN, but exposure to active metabolites may not be increased and therefore a dose reduction may not be necessary. Consultant decision

#### NCI Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>ANC &lt;0.5 x 10⁹/l plus fever requiring IV antibiotics +/- hospitalisation</td>
<td>20% reduction of cyclophosphamide only</td>
</tr>
<tr>
<td>Stomatitis &amp; Mucositis</td>
<td>for Grade III painful erythema or ulcers requiring rehydration resolving to Grade I or less painless ulcers of mild soreness</td>
<td>20% dose reduction of methotrexate and fluorouracil. Consider folinic acid rescue (see above)</td>
</tr>
<tr>
<td>Other toxicities</td>
<td>Grade III/IV toxicity (except alopecia)</td>
<td>Continue with 20% dose reduction of suspected causative agent(s)</td>
</tr>
</tbody>
</table>
• Defer treatment for any grade III/IV non-haematological toxicity (excluding alopecia)
• If a delay of more than 3 weeks is required for recovery, or more than 2 dose reductions are necessary, the patient should discontinue treatment

### Adverse effects

<table>
<thead>
<tr>
<th>Rare or Serious Side Effects</th>
<th>Frequently occurring Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 febrile neutropenia</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Risk of second malignancy e.g.</td>
<td>Long term risk of early menopause, reduced fertility</td>
</tr>
<tr>
<td>leukaemia</td>
<td></td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>Stomatitis and mucositis</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Diarrhoea</td>
</tr>
</tbody>
</table>

Other side effects include: alopecia (partial), loss of appetite, taste disturbance, skin sensitivity, gritty eyes, blurred vision, nail changes, bladder irritation (including haemorrhagic cystitis), allergic reactions and altered liver and kidney function.

### Significant drug interactions –

**Co-trimoxazole/trimethoprim** – Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.

**NSAIDs** – Monitor renal function and FBC if used concomitantly as may reduce renal excretion of methotrexate (increased risk in renal impairment).

**Probenecid** – avoid – increases methotrexate toxicity 3-4 fold.

**Antibacterials** – Monitor FBC – penicillins, tetracyclines, sulphamides, doxycycline and ciprofloxacin may reduce methotrexate clearance.

### Comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism – avoid use in patients with known DPD deficiency

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Methotrexate accumulates in 3rd space fluids (pleural effusions, ascites) leading to prolonged elimination time and potentially increased toxicity. Consider folinic acid rescue (as above) starting 24 hours after each dose.

Methotrexate can cause acute or chronic interstitial pneumonitis, which is often associated with blood eosinophilia. Monitor patients for dyspnoea, cough (especially dry, non-productive) and fever. Deaths have been reported.

### Cumulative Doses

None

### References

- Fisher B, Brown AM, Dimitrov NV, Poisson R, Redmond C, Margolese RG, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide,