Cylophosphamide (IV) Methotrexate and 5-Fluorouracil (CMF) 21 Day Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant treatment for breast carcinoma in patients who are considered unsuitable for anthracycline therapy</td>
<td>C50</td>
<td>00381a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Metastatic breast carcinoma</td>
<td>C50</td>
<td>00381b</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.

TREATMENT:
The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient’s individual clinical circumstances.

Cyclophosphamide, methotrexate and 5-Fluorouracil are administered on day 1 of a 21 day cycle.

Adjuvant treatment: Treatment is administered for 8 cycles
Metastatic: Treatment is administered until disease progression or unacceptable toxicity develops

<table>
<thead>
<tr>
<th>Admin. Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5-fluorouracil</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td>n/a</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Methotrexate</td>
<td>40mg/m²</td>
<td>IV bolus</td>
<td>n/a</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV</td>
<td>250 mL 0.9% NaCl over 30 min</td>
<td>Every 21 days</td>
</tr>
</tbody>
</table>

*Cyclophosphamide may also be administered as an IV bolus over 5-10 mins

ELIGIBILITY:
- Indications as above
- ECOG status 0-2
- Adequate haematological, renal and liver status

EXCLUSIONS:
- Hypersensitivity to cyclophosphamide, methotrexate, fluorouracil or any of the excipients.
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist
NCCP Chemotherapy Regimen

TESTS:

Baseline tests:
FBC, renal and liver profile

Regular tests:
FBC, renal and liver profile prior to each cycle

Disease monitoring:
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant.

Haematological:
Table 1: Dose modification of CMF in haematological toxicity

<table>
<thead>
<tr>
<th>ANC (x10^9 /L)</th>
<th>Platelets (x10^9 /L)</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5 or &gt;90</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>1-1.49 or 70-89</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>&lt;1 or &lt;70</td>
<td></td>
<td>delay</td>
</tr>
</tbody>
</table>

Renal and Hepatic Impairment:
Table 2: Dose modifications in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>Clinical Decision</td>
</tr>
<tr>
<td>Cr Cl (ml/min)</td>
<td>Dose</td>
<td>Bilirubin (micromole/L)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>100%</td>
<td>&lt;50 and &lt;180</td>
</tr>
<tr>
<td>10-20</td>
<td>75%</td>
<td>51-85 or ≥180</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

Methotrexate

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dose</th>
<th>Bilirubin (micromole/L)</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>100%</td>
<td>&lt;50</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>60-80</td>
<td>65%</td>
<td>51-85</td>
<td>or</td>
<td>≥180</td>
</tr>
<tr>
<td>45-60</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>Clinical Decision</td>
<td>&gt;85</td>
<td></td>
<td>Contraindicated</td>
</tr>
<tr>
<td>&lt;30</td>
<td>contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-Fluorouracil

Consider dose reduction in severe renal impairment only

<table>
<thead>
<tr>
<th>Bilirubin (micromole/L)</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;85</td>
<td>Or</td>
<td>&lt;180</td>
</tr>
<tr>
<td>&gt;85</td>
<td>or</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

Clinical decision.
Moderate hepatic impairment; reduce initial dose by 1/3.
Severe hepatic impairment, reduce initial dose by 1/2.
Increase dose if no toxicity
SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (Refer to local policy).

PREMEDICATIONS:
Not usually required

OTHER SUPPORTIVE CARE:
Patients should have an increased fluid intake of 2-3 litres on day 1 and day 8 to prevent haemorrhagic cystitis associated with cyclophosphamide

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pleural effusion or ascites**: Methotrexate should be used with caution in patients with pleural effusion or ascites, as methotrexate may accumulate in third space fluid compartments.
- **DPD deficiency**: This may result in severe and unexpected toxicity to fluorouracil – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.
- **Myocardial ischaemia and angina**: Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.

DRUG INTERACTIONS:

- **CYP3A inhibitors** decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- **CYP3A inducers** may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- **NSAIDs** may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- **Sulphonamides** and **penicillins** may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- **Concomitant administration** of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- **Ciprofloxacin** may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
- **Probencid** may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- **Fluorouracil significantly reduces the metabolism of warfarin**. INR and signs of bleeding should be monitored regularly and dose of warfarin adjusted as required.
- **Concurrent administration** of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
• Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
• Current drug interaction databases should be consulted for more information.

ATC CODE:
Cyclophosphamide    L01AA01
Methotrexate        L01BA01
S-Fluoruracil       L01BC02

REFERENCES:

Version  Date          Amendment                                               Approved By
1         1/12/2016       Updated to new NCCP template. Standardised administration of cyclophosphamide and dosing in renal and hepatic impairment  Prof Maccon Keane
2         26/11/2018

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/