**NCCP Chemotherapy Regimen**

**Cylophosphamide (IV) Methotrexate and 5-Fluorouracil (CMF) 28 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>00378a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Metastatic breast carcinoma</td>
<td>C50</td>
<td>00378b</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.

Adjuvant treatment: Treatment is administered for 6 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>1,8</td>
<td>5-Fluouracil</td>
<td>600mg/m²</td>
<td>IV bolus</td>
<td>NA</td>
<td>Every 28 days</td>
</tr>
<tr>
<td>2</td>
<td>1,8</td>
<td>Methotrexate</td>
<td>40mg/m²</td>
<td>IV Bolus</td>
<td>NA</td>
<td>Every 28 days</td>
</tr>
<tr>
<td>3</td>
<td>1,8</td>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV*</td>
<td>250 ml 0.9% NaCl over 30 mins</td>
<td>Every 28 days</td>
</tr>
</tbody>
</table>

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

**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

**TESTS:**

**Baseline tests:**

- FBC, renal and liver profile

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NCCP Regimen: CMF (IV) 28 day
Published: 01/12/2016
Review: 26/11/2020
Version number: 2

Tumour Group: Breast
NCCP Regimen Code: 00378
ISMO Contributor: Prof Maccon Keane
Page 1 of 4

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NCCP Chemotherapy Regimen

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>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.5 or &gt;90</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>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 modification of CMF (IV) 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>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>60-80</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>45-60</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>30-45</td>
<td>Clinical Decision</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin (micromole/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</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 counseled 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.
- Sulphamides 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.
- Probenecid 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
- 5-Fluorouracil: L01BC02

**REFERENCES:**

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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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1. ODMS – 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/

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