CMF(PO)+TRAS Regimen
Cyclophosphamide (oral)-Methotrexate-Fluorouracil, Trastuzumab

Disease Site
Breast

Intent
Adjuvant
Neoadjuvant
Palliative

Regimen Category
Evidence-Informed:
Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
- Neoadjuvant treatment for locally advanced breast cancer or adjuvant therapy for node-positive and high risk node-negative breast cancer patients, in whom an anthracycline and taxane is contraindicated
- Treatment of advanced breast cancer

Trastuzumab may be used concurrently with or after completion of CMF(PO) if applicable (e.g. HER-2 positive, adequate cardiac function).

Supplementary Public Funding
- **cyclophosphamide**
  ODB - General Benefit (cyclophosphamide - oral tablets) (ODB Formulary)
- **trastuzumab**
  New Drug Funding Program (Trastuzumab (Biosimilar) - Adjuvant Treatment)
for Breast Cancer) (NDFP Website)

**trastuzumab**
Evidence Building Program (Trastuzumab (EBP) - Adjuvant Treatment for Breast Cancer) (EBP Website)

**trastuzumab**
Evidence Building Program (Trastuzumab (EBP) - Adjuvant Treatment for Breast Cancer Supplemental)

**trastuzumab**
New Drug Funding Program (Trastuzumab (Biosimilar) - Second Line - Metastatic Breast Cancer)

**B - Drug Regimen**

**Note:** Different trastuzumab products are NOT INTERCHANGEABLE.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclophosphamide</td>
<td>100 mg /m²</td>
<td>PO</td>
<td>Days 1 to 14</td>
</tr>
<tr>
<td>(Outpatient prescription in multiples of 25mg tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methotrexate</td>
<td>40 mg /m²</td>
<td>IV</td>
<td>Day 1 and 8</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>600 mg /m²</td>
<td>IV</td>
<td>Day 1 and 8</td>
</tr>
</tbody>
</table>

For patients with HER2 positive tumours, Trastuzumab is given for one year starting either concurrently with or after completion of CMF(PO).

**Loading Dose (cycle 1):**

**trastuzumab**
8 mg /kg        IV          Cycle 1, day 1 ONLY

**Maintenance Dose (starting cycle 2):**

**trastuzumab**
6 mg /kg        IV          Day 1
C - Cycle Frequency

CMF(PO):
REPEAT EVERY 28 DAYS
For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

Trastuzumab:
REPEAT EVERY 21 DAYS
Adjuvant: - For a usual treatment duration of one year unless limited by cardiotoxicity risk (may be funded for up to 18 treatments over a maximum period of 14 months)
Palliative - Until disease progression or unacceptable toxicity

D - Premedication and Supportive Measures

Antiemetic Regimen: Low
Consider prophylaxis daily for cyclophosphamide PO

Other Supportive Care:
Also refer to CCO Antiemetic Recommendations.

• Trastuzumab: Nausea and vomiting may be related to infusion-associated reactions. To prevent recurrence of infusion-associated reactions, acetaminophen and diphenhydramine may be given as pre-medication. Refer to Trastuzumab drug monograph for full details.

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Dosage with toxicity

Hematologic Toxicities:
**Worst Toxicity Type / Counts x 10^9/L in Prior Cycle**

<table>
<thead>
<tr>
<th>Worst Toxicity Type / Counts x 10^9/L in Prior Cycle</th>
<th>Cyclophosphamide (% previous dose)</th>
<th>Methotrexate (% previous dose)</th>
<th>Fluorouracil (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia, or Thrombocytopenic bleeding, or Grade 4 ANC ≥ 7 d</td>
<td></td>
<td></td>
<td>75% * (or consider GCSF for isolated neutropenia)</td>
</tr>
<tr>
<td>Grade 3 related organ</td>
<td></td>
<td></td>
<td>75% for suspect drug(s)*.</td>
</tr>
<tr>
<td>Grade 4 related organ, Any grade pneumonitis, cardiac or viral reactivation</td>
<td></td>
<td>Discontinue suspect drug(s)</td>
<td></td>
</tr>
</tbody>
</table>

*Do not retreat until toxicity has recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.*

**Hepatic Impairment**

<table>
<thead>
<tr>
<th>AST/ALT</th>
<th>Bilirubin</th>
<th>Methotrexate (% previous)</th>
<th>Fluorouracil (% previous)</th>
<th>Cyclophosphamide (% previous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 x ULN OR 2-4 x ULN</td>
<td></td>
<td>50% or Discontinue</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>&gt;4 X ULN AND &lt; 4 X ULN</td>
<td></td>
<td>DISCONTINUE</td>
<td>No change</td>
<td>Caution</td>
</tr>
<tr>
<td>&gt; 4 X ULN</td>
<td></td>
<td>DISCONTINUE</td>
<td>Discontinue</td>
<td>Caution</td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Cyclophosphamide (% previous dose)</th>
<th>Methotrexate (% previous dose)</th>
<th>Fluorouracil (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 - 80</td>
<td>100%</td>
<td>50-75%</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 30 - 50</td>
<td>100%</td>
<td>OMIT</td>
<td>100%</td>
</tr>
<tr>
<td>10 - 30</td>
<td>50-75%</td>
<td>OMIT</td>
<td>Consider dose ↓</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50% or OMIT</td>
<td>OMIT</td>
<td>Consider dose ↓</td>
</tr>
</tbody>
</table>

**Dosage in the Elderly**
• No dose modification of cyclophosphamide routinely required, but should be used with caution and monitored closely.
• Methotrexate has not been well studied in the elderly. It should be used with extreme caution because of likely renal and hepatic impairment and reduced folate stores in the elderly.

F - Adverse Effects

Refer to cyclophosphamide, methotrexate, fluorouracil drug monograph(s) for additional details of adverse effects

Refer to trastuzumab drug monograph for adverse effect details (not listed below).

<table>
<thead>
<tr>
<th>Most Common Side Effects</th>
<th>Less Common Side Effects, but may be Severe or Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myelosuppression ± infection / bleeding</td>
<td>• SIADH</td>
</tr>
<tr>
<td>• Cystitis</td>
<td>• Cardiac, AMI, arrhythmia</td>
</tr>
<tr>
<td>• Nausea and vomiting</td>
<td>• Thromboembolism, DIC, HUS, VOD, hemolysis</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Secondary malignancies</td>
</tr>
<tr>
<td>• Stomatitis, anorexia</td>
<td>• Pneumonitis</td>
</tr>
<tr>
<td>• Alopecia</td>
<td>• Leukoencephalopathy (may be delayed)</td>
</tr>
<tr>
<td>• Nephrotoxicity</td>
<td>• Severe rash, photosensitivity</td>
</tr>
<tr>
<td>• ↑ LFTs</td>
<td>• Rhabdomyolysis</td>
</tr>
<tr>
<td>• Reproductive risk</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Conjunctivitis</td>
<td></td>
</tr>
</tbody>
</table>
H - Drug Administration and Special Precautions

Refer to cyclophosphamide, methotrexate, fluorouracil, trastuzumab drug monograph(s) for additional details

**Note:** Different trastuzumab products are **NOT INTERCHANGEABLE.**

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

**Recommended Clinical Monitoring**

- CBC; baseline and before each cycle
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Urinalysis; Baseline and as clinically indicated
- Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan); more frequent with asymptomatic reductions in LVEF; baseline, q3 months during treatment, then q6 months after trastuzumab discontinuation x2 years (and annually up to 5 years after last trastuzumab dose in adjuvant breast cancer patients who received anthracyclines), also as clinically indicated
- Clinical assessment and grading of stomatitis, diarrhea, bleeding, infection, GI, pulmonary, CNS, cystitis, and local site toxicity, skin effects (rash or hand-foot-syndrome), cardiovascular or ophthalmic effects, infusion reactions, thromboembolism; At each visit
- Toxicity ratings of infusion-associated symptoms (especially first infusion); Close monitoring at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

**Suggested Clinical Monitoring**
- Lung function tests if pulmonary toxicity suspected;
- CXR; Baseline
- Hepatitis B and Hepatitis C infection testing; Baseline

J - Administrative Information

Cyclophosphamide: Outpatient prescription for home administration

| Approximate Patient Visit | CMF: 0.5 hour |
| Trastuzumab: 1.5 hours (first dose); 0.5 hour (subsequent doses) |

| Pharmacy Workload (average time per visit) | 24.379 minutes |
| Nursing Workload (average time per visit) | 47.083 minutes |

K - References


Cyclophosphamide, methotrexate, fluorouracil, trastuzumab drug monographs, Cancer Care Ontario.


Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the “Formulary”) is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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