Regimen Monograph

A - Regimen Name

CMF(PO) Regimen

Cyclophosphamide (oral)-Methotrexate-Fluorouracil

Disease Site	Breast
Intent	Palliative Adjuvant
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	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.
Supplementary Public Funding	**cyclophosphamide** ODB - General Benefit (cyclophosphamide - oral tablets) (ODB Formulary)

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B - Drug Regimen

cyclophosphamide (Outpatient prescription in multiples of 25mg or 50mg tablets)	100 mg /m²	PO	Days 1 to 14
methotrexate	40 mg /m²	IV	Days 1 and 8
fluorouracil	600 mg /m²	IV	Days 1 and 8

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low
Consider prophylaxis daily for cyclophosphamide PO

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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.

Patients should be tested for DPD deficiency before starting treatment with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if grade 2-4 acute toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Hematologic Toxicities:

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

*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

AST/ALT		Bilirubin	Methotrexate (% previous)	Fluorouracil (% previous)	Cyclophosphamide (% previous)
2-4 x ULN	Or	2-4 x ULN	50% or Discontinue	No change	No change
>4 X ULN	AND	< 4 X ULN	Discontinue	No change	Caution
		> 4 X ULN		Discontinue	Caution

Renal Impairment

Creatinine Clearance (mL/min)	Cyclophosphamide (% previous dose)	Methotrexate (% previous dose)	Fluorouracil (% previous dose)
>50 - 80	100%	50-75%	100%
> 30 - 50	100%	OMIT	100%
10 - 30	50-75%	OMIT	Consider dose ↓

<10	50% or OMIT	OMIT	Consider dose ↓

Dosage in the Elderly

- No dose modification of cyclphosphamide routinely required, but should be used with caution.
- 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. Monitor closely. Consider lower doses with intrathecal usage.

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F - Adverse Effects

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

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

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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

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- 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
- Clinical assessment and grading of stomatitis, diarrhea, bleeding, infection, GI, pulmonary, CNS, and local site toxicity, skin effects (rash or hand-foot-syndrome), cardiovascular or ophthalmic effects, cystitis, thromboembolism; 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

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	18.742 minutes

Nursing Workload (average time per visit) 41.667 minutes

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K - References

Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. BMJ doi:10.1136/bmj.38314.622095.8F (published 13 January 2005).

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

Engelsman E, Klijn JCM, et al, “Classical” CMF vs. a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer. Eur J Cancer, 1991; 27: 966-970.

Fisher B, Brown AM, Dimitrov NV, et al. Two months of Doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of Cyclophosphamide, Methotrexate, and 5-Fluorouracil in positive-breast cancer patients with tamoxifen-nonresponsive tumors: results from the NSABP B-15, J. Clin Oncol 1990 Sep:8(9): 1483-1496.

PEBC Advice Documents or Guidelines

- Optimal Systemic Therapy for Early Female Breast Cancer

April 2023 Updated DPD deficiency information in the Dose Modifications section

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M - Disclaimer

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.

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