Regimen Monograph

A - Regimen Name

FCM Regimen

Fludarabine-Cyclophosphamide-mitoXANTRONE

Disease Site	Hematologic - Lymphoma - Non-Hodgkin's Low Grade
Intent	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	Treatment of recurrent follicular or other non-Hodgkin’s indolent B-cell lymphoma

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B - Drug Regimen

fludarabine (Round to nearest 2.5 mg)	25 mg /m²	IV	Days 1 to 3
cyclophosphamide (Round to nearest 10 mg)	200 to 250 mg /m²	IV	Days 1 to 3
mitoXANTRONE (Round to nearest 1 mg)	6 mg /m²	IV	Day 1 ONLY

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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: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

- If high volume disease (e.g. WBC > 25 x 10^9/L), consider prophylaxis for tumour lysis
- Consider prophylactic growth factor support, antiviral and PCP prophylaxis (according to local practice)

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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 have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

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Suggested dose levels for fludarabine are 25, 20 and 15 mg/m^2
Suggested dose levels for cyclophosphamide are 200 and 150 mg/m^2
Suggested dose levels for mitoxantrone are 6, 4.5 and 3 mg/m^2

Toxicity	Fludarabine (% previous dose)	Cyclophosphamide (% previous dose)	Mitoxantrone (% previous dose)
Febrile Neutropenia; Grade 4 myelosuppression ≥ 7 days; Thrombocytopenic bleeding; 1-2 week delay prior cycle	↓ 1 dose level or G-CSF (for isolated neutropenia)*	↓ 1 dose level or G-CSF (for isolated neutropenia)*	↓ 1 dose level or G-CSF (for isolated neutropenia)*
Grade 3 non-hematologic/organ	↓ 1 dose level*	↓ 1 dose level*	↓ 1 dose level*
Grade 4 non-hematologic /organ	Discontinue	Discontinue	Discontinue
Any grade autoimmune, neurotoxicity, pneumonitis, cardiotoxicity, > 2 week delay prior cycle	Discontinue	Discontinue	Discontinue
*Do not retreat until non-hematologic/ organ toxicity recovered to ≤ grade 2, ANC to ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L (or to baseline levels).			

Hepatic Impairment

AST/ALT		Bilirubin	Mitoxantrone (% previous dose)	Fludarabine (% previous dose)	Cyclophosphamide (% previous dose)
3-5 X ULN	And/or	1-2 x ULN	↓ 50%	No data; use with caution	No change
>5 x ULN	And/or	> 2-3 x ULN	Discontinue		Caution

Renal Impairment

Creatinine Clearance (mL/min)	Mitoxantrone (% previous dose)	Fludarabine (% previous dose)	Cyclophosphamide (% previous dose)
> 50 – 70	No change	50%	100%
30 - 50			75%
10 - <30		Discontinue	75%
< 10			Use with extreme caution or Discontinue

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F - Adverse Effects

Refer to fludarabine, cyclophosphamide, mitoXANTRONE 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 (including opportunistic), bleeding (may be severe) • GI (nausea/vomiting, stomatitis, diarrhea, anorexia, constipation) • Fever, flu-like symptoms • Edema • Fatigue • Rash (may be severe) • Visual changes • Cystitis • Alopecia • ↑ LFTs	• Autoimmune disorders (e.g. hemolytic anemia, TTP) • Encephalopathy, CNS toxicity (e.g. seizures, confusion, agitation) • Pneumonitis • Cardiotoxicity, arrhythmia • Arterial thromboembolism • Venous thromboembolism • Secondary malignancies • Tumour lysis syndrome • Pancreatitis • Rhabdomyolysis • Nephrotoxicity

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G - Interactions

Refer to fludarabine, cyclophosphamide, mitoXANTRONE drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to fludarabine, cyclophosphamide, mitoXANTRONE drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and at each visit
- Renal (including urinalysis) and liver function tests; baseline and at each visit
- Baseline and regular cardiac examination for patients with cardiac risk factors (including prior therapy with Epirubicin, Doxorubicin, or other cardiotoxic drug), and cumulative mitoxantrone doses > 140mg/m ^{2}
- Clinical toxicity assessment (including hypersensitivity, CNS toxicity, cardiotoxicity, infection, bleeding, GI, skin and pulmonary toxicity, tumour lysis syndrome, thromboembolism, cystitis); at each visit

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

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J - Administrative Information

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	26.168 minutes
Nursing Workload (average time per visit)	45 minutes

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K - References

Forstpointner R, Dreyling M, Repp R, et al; German Low-Grade Lymphoma Study Group. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2004 Nov 15;104(10):3064-71.

Fludarabine, cyclophosphamide, mitoxantrone drug monographs, Cancer Care Ontario.

Hendry L, Bowen A, Matutes E, et al. Fludarabine, cyclophosphamide and mitoxantrone in relapsed or refractory chronic lymphocytic leukemia and low grade non-Hodgkin's lymphoma. Leuk Lymphoma. 2004 May;45(5):945-50.

Santini G, Nati S, Spriano M, Gallamini A, Pierluigi D, Congiu AM, Truini M, Rubagotti A, Chisesi T,

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Vimercati R, Rossi E, Sertoli MR, Mattei D, Marino G, Gobbi M. Fludarabine in combination with cyclophosphamide or with cyclophosphamide plus mitoxantrone for relapsed or refractory low-grade non-Hodgkin's lymphoma. Haematologica. 2001 Mar;86(3):282-6.

June 2021 removed fludarabine NDFP funding info

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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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