Regimen Monograph

A - Regimen Name

FCM Regimen

Fludarabine-Cyclophosphamide-mitoXANTRONE

Disease Site	Hematological - Leukemia - Chronic Lymphocytic (CLL)
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	Second-line treatment in patients with CLL.

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B - Drug Regimen

fludarabine	25 mg /m²	IV	Days 1 to 3

cyclophosphamide (Round to nearest 10 mg)	200-250 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 6 cycles in the absence of disease progression or unacceptable toxicity

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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

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 ± bleeding • Infection; including opportunistic (may be severe) • GI (nausea/vomiting, stomatitis, diarrhea, anorexia, constipation) • Fever • Edema • Fatigue • Rash (may be severe), nail changes • Visual changes • Cystitis • Alopecia • ↑ LFTs	• Autoimmune disorders (e.g. hemolytic anemia, TTP) • Encephalopathy, CNS toxicity (e.g. seizures, confusion, agitation) • Pneumonitis • Cardiotoxicity, arrhythmia • SIADH • Arterial thromboembolism • Venous thromboembolism • Secondary malignancies • Tumour lysis syndrome • Renal failure • Pancreatitis • Pneumonitis • Hypersensitivity • Rhabdomyolysis

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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 hepatic 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, fever, infection, hemolysis, GI, skin and pulmonary toxicity); 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

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K - References

Bosch F, Abrisqueta P, Villamor N, et al. Rituximab, Fludarabine, Cyclophosphamide, and Mitoxantrone: A New, Highly Active Chemoimmunotherapy Regimen for Chronic Lymphocytic Leukemia. J Clin Oncol 2009; 27:4578-84.

Bosch F, Ferrer A, Villamor N, et al. Fludarabine, cyclophosphamide, and mitoxantrone as initial therapy of chronic lymphocytic leukemia: high response rate and disease eradication. Clin Cancer Res 2008; 14(1): 155-61.

Bosch F, Ferrer A, Lopez-Guillermo A et al. (2002) Fludarabine, cyclophosphamide and mitoxantrone in the treatment of resistant or relapsed chronic lymphocytic leukaemia. British Journal

of Haematology 2002. 119: 976 –984.

Faderl S, Wierda W, O'Brien, S. Fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline CLL <70 Years. Leukemia Research 2010; 34: 284–8.

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; 45(5): 945-50.

Hillmen P, Pocock C, Cohen D, Cocks K, Sayala H, et al. NCRI CLL201 Trial: A randomized phase II trial of fludarabine, cyclophosphamide, and mitoxantrone (FCM) with or without rituximab in previously treated CLL. (Abstract). Blood. 2007; 110:752.

Schmitt B, Franke A, Burkhard O, et al. ''Fludarabine, Mitoxantrone and Cyclophosphamide combination therapy in relapsed chronic lymphocytic leukemia with or without G-CSF: results of the first interim analysis of a phase III study of the German CLL Group'', Blood. 2002. 100: 364b (abstract 5015).

April 2016 Replaced regimen category with evidence-informed

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M - Disclaimer

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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