Regimen Monograph

A - Regimen Name

BEND Regimen

Bendamustine

Disease Site

Hematologic - 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

First-line monotherapy in CLL patients with:

- Binet Stage B or C and
- WHO performance status of ≤ 2 and
- Not medically fit for fludarabine-based regimens but could be treated with other options such as chlorambucil. The phase III trial included patients up to 75 years of age.

Supplementary Public Funding

bendamustine

New Drug Funding Program (Bendamustine - First Line - Chronic Lymphocytic Leukemia) (NDFP Website) (Funded for single agent only)

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B - Drug Regimen

bendamustine	100 mg /m²	IV	Days 1 and 2

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a maximum of 6 cycles in the absence of unacceptable toxicity or disease progression

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

• Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Hypertension should be controlled prior to starting treatment

Pre-medication (only for patients with Grade 1 or 2 reactions with prior infusion):

- Analgesic/antipyretic (e.g. acetaminophen), corticosteroid and an antihistamine (e.g. diphenhydramine) should be considered in subsequent cycles.

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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.

Do not retreat until ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L and non-hematologic toxicity

recovered to ≤ Grade 1.

Dosage with toxicity

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

Dose levels:100 mg/m^2, 50 mg/m^2, 25 mg/m^2

Toxicity	Modification
Grade 4 Hematologic toxicities	Delay until ANC ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L then reduce by 1 dose level
≥ Grade 3 Hypersensitivity reaction	Discontinue
≥ Grade 2 clinically significant Non-hematologic toxicities; ≥ Grade 3 Non-hematologic toxicities	Delay until recovered to ≤ grade 1, then reduce by one dose level

Hepatic Impairment

Bilirubin	AST or ALT or ALP	Bendamustine dose
≤ 1.5 x ULN	≤ 2.5 x ULN	Caution
> 1.5 x ULN	> 2.5 x ULN	Do not use

Renal Impairment

Creatinine Clearance (mL/min)	Bendamustine dose
>80	100%
40 - 80	Caution
< 40	Do not use

Dosage in the Elderly

No dose adjustment required. No clinically significant differences in efficacy and safety were observed in those aged 65 and older and younger patients.

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F - Adverse Effects

Refer to bendamustine drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Nausea, vomiting • Fatigue	• Diarrhea • Fever, chills • Constipation	• Anorexia, weight loss • Mucositis • Headache • Edema • Cough, dyspnea (may be severe) • Musculoskeletal pain • Rash (may be severe) • Abdominal pain • Immunosuppression, atypical infections • Abnormal electrolytes • Dizziness • Dysgeusia • Dyspepsia • Insomnia	• Arrhythmia, Prolonged QT • Arterial thromboembolism • Cardiotoxicity • Hypertension • Hepatotoxicity • Infusion-related reaction • Renal failure • Secondary malignancy • Tumour lysis syndrome • Myelosuppression • ARDS

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G - Interactions

Refer to bendamustine drug monograph(s) for additional details

- CYP1A2 inhibitors my increase bendamustine concentration and toxicity; use with caution

- CYP1A2 inducers (including cigarette smoking) may reduce bendamustine concentration and/or efficacy

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H - Drug Administration and Special Precautions

Refer to bendamustine drug monograph(s) for additional details

Administration:

- CLL - infuse over 30 minutes
- Bendamustine infusions should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.
- DO NOT administer as an IV push or bolus.
- Dilute to a final concentration of 0.2 - 0.6 mg/mL in 500 mL infusion bag of 0.9% sodium chloride or 2.5% dextrose/0.45% sodium chloride.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Do not admix with other drugs.

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components (including mannitol)
- Patients with CrCl < 40 mls/min or moderate/severe hepatic impairment
- Patients with serious infections

Other warnings/precautions:

- Avoid live vaccines, since they may result in serious or fatal infections in patients immunocompromised by bendamustine.
- Avoid in patients with relapsed indolent NHL who did not tolerate prior therapies (including other alkylating agents)
- Use with caution in patients with hypertension and patients with mild renal and hepatic impairment

Pregnancy and lactation:

- Bendamustine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes 2 weeks before, during treatment, and for at least 4 weeks after the last dose.
- Breastfeeding is not recommended

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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

- CBC; Baseline and before each cycle
- Blood pressure; Baseline and before each dose
- Electrolytes, including sodium, potassium, magnesium and uric acid; Baseline and before each cycle
- Hepatitis B surface antigen; Baseline and as clinically indicated
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Clinical toxicity assessment for infection (including CMV and herpes zoster), renal, cardiac, hepatic and skin toxicity , infusion reactions and secondary malignancies; at each visit

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

Suggested Clinical Monitoring

- Blood glucose; Baseline and periodic
- ECG; As clinically indicated; periodic in the setting of cardiac disorders and electrolyte imbalances
- HIV status; Baseline
- CMV testing in febrile patients

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J - Administrative Information

Approximate Patient Visit	0.5 to 1 hour
Pharmacy Workload (average time per visit)	19.35 minutes
Nursing Workload (average time per visit)	36.667 minutes

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K - References

Bendamustine drug monograph, Cancer Care Ontario.

Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol 2012;159(1):67-77.

Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27(26):4378-84.

April 2017 added dosage in elderly; updated dose mods and adverse effects tables

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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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