Regimen Monograph

A - Regimen Name

CHLO+OBIN Regimen

Chlorambucil-oBINutuzumab

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
For the treatment of previously untreated (no prior anti-CD20 antibody or any other treatment) chronic lymphocytic leukemia (CLL). Funded by NDFP in patients with adequate renal function and for patients in whom fludarabine use is inappropriate.

Supplementary Public Funding
chlorambucil
ODB - General Benefit (chlorambucil) (ODB Formulary)

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B - Drug Regimen

chlorambucil	0.5 mg /kg	PO	Day 1 and 15 of each cycle

WITH

Cycle 1:

oBINutuzumab	1000* mg	IV	Days 1, 8 and 15

*Cycle 1 first dose may be split over 2 days (100 mg IV day 1 and 900 mg IV day 2). See drug administration section for infusion rate recommendations.

THEN,

Cycles 2 to 6:

oBINutuzumab	1000 mg	IV	Day 1

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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: Minimal

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Obinutuzumab:

Hepatitis B screening should be performed prior to treatment for all patients.

Patients at risk for tumour lysis syndrome should receive adequate hydration and uricostatics or alternative starting 12 to 24 hours prior to infusion.

Consider withholding antihypertensives (if applicable) 12 hours prior to infusion, during infusion and for the first hour after drug administration, and withholding concomitant medications that increase bleeding risk, especially in the first cycle.

Patients with neutropenia should receive antimicrobial prophylaxis; consider use of G-CSF, antiviral and antifungal prophylaxis.

Premedication recommendations:

Treatment cycle, day	Patients	Premedication
Cycle 1, Day 1	All	IV corticosteroid* completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion
Subsequent infusions	Patients with no prior IR during previous infusion	PO analgesic/antipyretic** at least 30 min prior to infusion
	Patients with grade 1 or 2 IR with previous infusion	PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion
	Patients with grade 3 IR with previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment	IV corticosteroid* completed at least 1 hr prior to infusion & PO analgesic/antipyretic** & antihistamine*** at least 30 min prior to infusion

*e.g. 100 mg prednisone or 20 mg dexamethasone. Hydrocortisone should not be used as it has not been effective in reducing IR rates.

**e.g. 1000 mg acetaminophen

***e.g. 50 mg diphenhydramine

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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 and product monographs and may be considered.

Dosage with toxicity

No dose reductions are recommended for obinutuzumab. The infusion may be discontinued, held or its rate reduced as appropriate. Do not re-escalate reduced doses of chlorambucil. Do not treat until ANC and hemoglobin ≤ grade 2 and platelets and non-hematologic toxicity ≤ grade 1.

Toxicity	**Obinutuzumab dose*, ** **	**Chlorambucil dose** (% previous dose)**
Grade 4 hematologic toxicity, febrile neutropenia or thrombocytopenic bleeding	Hold until ≤ grade 2, restart at usual dose. Discontinue if no recovery within 4 weeks.	Hold until ≤ grade 2. Administer G-CSF as required. Day 1: 1st episode: upon recovery restart at 75% 2nd episode: upon recovery restart at 50% 3rd episode: discontinue Day 15: Omit
Grade 2 or 3 related organ/non-hematologic toxicity	Hold until ≤ grade 1 Discontinue if no recovery within 4 weeks.	Hold until ≤ grade 1 Discontinue if no recovery within 4 weeks.
Grade 4 related organ/non-hematologic toxicity	Discontinue	
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue	
Suspected PML	Hold and refer to neurologist for diagnosis and treatment. Discontinue if confirmed.	

Grade 1-2 infusion reaction (IR)	Reduce infusion rate and treat symptoms. Restart once resolved. Escalate*** infusion rate as tolerated at increments appropriate for treatment dose (see drug admin section).	No change
Grade 3 IR	Hold infusion and treat symptoms. Restart once resolved at no more than half the previous rate. Escalate*** infusion rate as tolerated at increments appropriate for treatment dose (see drug admin section).	No change
Grade 4 IR OR 2nd episode of grade 3 IR (during same or subsequent infusion), acute life-threatening respiratory symptoms OR Anaphylaxis/ serum sickness	Discontinue	Discontinue

*Missed doses may be administered later at physician discretion; the q28 day interval should be maintained.
**Hold up to 4 weeks. Before retreatment, major organ toxicities should recover to ≤ grade 1 (or as specified in table above), platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x 10^9/L. If chlorambucil is discontinued due to related toxicity, may continue obinutuzumab based on physician discretion.
***For CLL patients receiving cycle 1, day 1 dose split over 2 days, the infusion rate may be increased back to 25 mg/hr after 1 hr, but not increased further.

Hepatic Impairment

Safety and efficacy of obinutuzumab have not been established in patients with hepatic impairment. For chlorambucil, dose adjustment required with severe hepatic impairment; no details found.

Renal Impairment

For **obinutuzumab**, patients who have a creatinine clearance < 50 mL/min in the pivotal study experienced more serious adverse events, including fatal ones than those with creatinine ≥ 50 mL/min.

CrCl (mL/min)	Obinutuzumab dose	Chlorambucil (% previous dose)
> 30 but < 50 mL/min	No change; use with caution	75%
10 to ≤ 30	No data; omit	75%
<10	No data; omit	50%

Dosage in the Elderly

Obinutuzumab:

No dose adjustment is required. CLL patients ≥ 75 years experienced more serious adverse effects than younger patients. No efficacy differences were observed between older and younger patients.

Chlorambucil:

No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years. Use with caution due to possible decreases in hepatic, renal, or cardiac function.

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F - Adverse Effects

Refer to oBINutuzumab, chlorambucil, 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
• Infusion-related reaction (may be severe; immediate or delayed)	• Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Increased LFTs (may be severe) • Increased creatinine (may be severe)	• Cough, dyspnea • Rash (may be severe)	• Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • Tumour lysis syndrome • Secondary malignancy • Hemolysis • Capillary leak syndrome • Pancreatitis • Pneumonitis, ARDS • PML • GI perforation

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G - Interactions

Refer to obinutuzumab, chlorambucil drug monograph(s) for additional details.

- No clinical drug interaction studies have been conducted with obinutuzumab.
- Consider withholding antihypertensives (if applicable) 12 hours prior to obintuzumab infusion, during infusion and for the first hour after drug administration, and withholding concomitant medications that increase bleeding risk, especially in the first cycle.
- Drugs that cause immunosuppression may increase the risk of myelosuppression and infections.
- Phenylbutazone may increase the toxicity of chlorambucil; consider dosage adjustment.
- Co-administration of chlorambucil with succinylcholine may cause prolonged sleep apnea; decrease succinylcholine dose.

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H - Drug Administration and Special Precautions

Refer to obinutuzumab, chlorambucil drug monograph(s) for additional details.

Drug administration

Obinutuzumab:

Treatment cycle	Obinutuzumab dose*	Infusion rate**
Cycle 1, day 1	100 mg	25 mg/hr over 4 hours
Cycle 1, day 2 (or day 1 continued)	900 mg	50 mg/hr if no IR on day 1. May escalate as tolerated by 50 mg/hr q 30 min to max of 400 mg/hr. 25 mg/hr if previous IR. May escalate as tolerated by up to 50 mg/hr q 30 min to max of 400 mg/hr.
Cycle 1, day 8	1000 mg	100 mg/hr if no IR at rates ≥ 100mg/hr on day 2. May escalate as tolerated by 100 mg/hr q 30 min to max of 400 mg/hr. 50 mg/hr if previous IR. May escalate as tolerated by 50 mg/hr q 30 min to max of 400 mg/hr.
Cycle 1, day 15	1000 mg	
Cycles 2 to 6, day 1	1000 mg q 28 days	

*Two infusion bags should be prepared for the first 1000 mg infusion (100 mg for day 1, 900 mg for day 2). If the first bag is completed without needing modifications of infusion rate, the second bag may also be administered on day 1 without a dose delay, if possible.
**For infusion rate modifications in the case of IR, see dosage with toxicity section.

- Obinutuzumab should be administered only as an IV infusion through a dedicated line. Do not administer as an IV push or bolus.
- Withdraw required amount of diluent from vial and dilute in 250 ml PVC or non-PVC polyolefin bags containing 0.9% sodium chloride. See product monograph for details.
- The initial 1000 mg dose should be prepared in two infusion bags of different sizes (i.e. 100 mg in 100 mL and 900 mg in 250 mL NS) to ensure differentiation of the 100 mg dose for day 1 and the 900 mg dose for day 2 (or day 1 continued)
- Gently invert the IV bag to mix. Do not shake.
- If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval should then be maintained between doses.
- Compatible with sodium chloride 0.9%. Do not mix with other IV solutions.

Chlorambucil:

- Administer chlorambucil orally, preferably on an empty stomach at least 1 hour before or 2 hours after a meal.
- Keep refrigerated, but do not freeze.

Contraindications

- Patients who are resistant to chlorambucil or who have developed hypersensitivity to chlorambucil, obinutuzumab or any of its components; there may be cross-sensitivity between chlorambucil and other alkylating agents (especially rash).
- Chlorambucil should not be used within 4 weeks of a full course of radiation therapy or chemotherapy.

Precautions

- Do not give to patients who have an active infection.
- Administer chlorambucil with caution if bone marrow is severely depressed and in patients with seizure disorders.
- Avoid live vaccines during treatment and until B-cell recovery. Following vaccination, do not start treatment until protective antibody titres have been reached.
- Use with extreme caution in patients who are positive for hepatitis.
- Use with caution in patients with recurrent or chronic infections.
- Patients with a history of cardiovascular or respiratory disease should be monitored closely during and after obinutuzumab infusions. Use caution when hydrating patients with history of cardiovascular disease, to prevent fluid overload.
- Patients at acute risk of hypertensive crisis should be assessed for the risk vs benefit of withholding anti-hypertensives.

Pregnancy & lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- In case of exposure to obinutuzumab during pregnancy, newborns should be monitored for B-cell depletion and live vaccines postponed until B cell recovery.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Yes

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- Cardiac tests for all patients with cardiac risk factors; baseline and as clinically indicated.
- CBC; baseline, before each dose and as clinically indicated following treatment completion
- Liver and renal function tests, electrolytes; baseline and before each cycle.
- Infusion-related reactions; during and after the infusion
- Clinical toxicity assessment for infection, bleeding, tumour lysis syndrome, thromboembolism, GI, neurologic, cardiac and respiratory effects; at each visit
- Hepatitis B screening prior to treatment for all patients. Monitor for signs and symptoms of hepatitis B during treatment. Seropositive patients should see hepatologist and be closely monitored for several months after the last infusion.
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration (chlorambucil)

Approximate Patient Visit	4 hours
Pharmacy Workload (average time per visit)	18.249 minutes
Nursing Workload (average time per visit)	74.833 minutes

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K - References

Chlorambucil drug monograph. Ontario Health (Cancer Care Ontario).

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10.

Obinutuzumab drug monograph. Ontario Health (Cancer Care Ontario).

November 2024 Updated Pregnancy/Lactation 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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