# BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma with oBINutuzumab and Chlorambucil

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|---|---|
| ***Protocol Code*** | *LYOBCHLOR* |
| ***Tumour Group*** | *Lymphoma* |
| ***Contact Physician*** | *Dr. Laurie Sehn* |

**ELIGIBILITY**:

Patients must have:

- Patients with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma
- Patients not candidates for fludarabine-based therapy due to co-morbidities or renal insufficiency
- Patients with symptomatic disease requiring systemic treatment

**TESTS**:

- Baseline (required before first treatment): CBC & Diff, creatinine, ALT, total bilirubin, sodium, potassium, uric acid
- Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with Cycle 2: HBsAg, HBsAb, HBcoreAb
- Day 1 of each Cycle: CBC & Diff
- If clinically indicated: phosphate, potassium, calcium, uric acid, HBV viral load, ALT (see protocol SCHBV)

**PREMEDICATIONS**:

- Antiemetic protocol for rare emetogenic chemotherapy - see protocol SCNAUSEA
- Optional prior to Cycle 1 Day 1 oBINutuzumab infusion:
  - dexamethasone 20 mg PO BID the day prior to infusion,
    OR
  - predniSONE 50 mg PO once daily for 3 days prior to infusion (for patients unable to tolerate high-dose dexamethasone)

**Premedication to prevent infusion reactions:**

(Note: patient should bring own supply of oral medications)

Cycle 1: Days 1 and 2:

60 minutes prior to infusion:

- dexamethasone 20 mg IV

30 minutes prior to infusion:

- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

Cycle 1: Days 8 and 15
30 minutes prior to infusion:
- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

If reaction to previous dose was Grade 3 or if lymphocyte count greater than 25 x $10^9$/L before Day 1 of Cycle 1, add dexamethasone 20 mg IV 60 minutes prior to Days 8 and 15 oBINutuzumab infusion

Cycles 2 to 6
30 minutes prior to infusion:
- acetaminophen 650 mg to 975 mg PO
- diphenhydrAMINE 50 mg PO

If previous reaction:
- dexamethasone 20 mg PO BID the day prior to infusion,

OR
- predniSONE 50 mg PO once daily for 3 days prior to infusion (for patients unable to tolerate high-dose dexamethasone),

and
If reaction to previous oBINutuzumab dose was Grade 3 or if lymphocyte count greater than 25 x $10^9$/L before Day 1 of current cycle, add dexamethasone 20 mg IV 60 minutes prior to infusion

Note: Alternative corticosteroids that may be considered on treatment days include methylPREDNISolone 80 mg IV. *Hydrocortisone is ineffective and not recommended as a premedication but may still be used for an infusion-related reaction.*

**SUPPORTIVE MEDICATIONS**:
- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

## TREATMENT:

**oBINutuzumab:**

**Cycle 1**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| oBINutuzumab | 100 mg on Day 1 | IV in 100 mL NS over 4 hours at 25 mg/h |
| | 900 mg on Day 2 | IV in 250 mL NS* |

* Cycle 1 Day 2 infusion: initiate at **50 mg/hour**; after 30 minutes, increase by 50 mg/hour every 30 minutes until rate = 400 mg/hour unless toxicity occurs. Refer to protocol appendix for oBINutuzumab infusion rate titration table.

- For first and second doses (Cycle 1 Days 1 and 2), constant visual observation during dose increases and for 30 minutes after infusion completed.

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| oBINutuzumab | 1000 mg on Days 8 and 15 | IV in 250 mL NS* |

* If no infusion reaction or Grade 1 infusion reaction to previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at **100 mg/hour** for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/h every 30 minutes until rate = 400 mg/hour. Refer to protocol appendix for oBINutuzumab infusion rate titration table.

* If Grade 2 or higher infusion reaction occurred during previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes until rate = 400 mg/hour.

**Cycles 2 to 6**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| oBINutuzumab | 1000 mg on Day 1 | IV in 250 mL NS* |

* If no infusion reaction or Grade 1 reaction with previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at **100 mg/hour** for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/hour every 30 minutes until rate = 400 mg/hour. Refer to protocol appendix for oBINutuzumab infusion rate titration table.

* If Grade 2 or higher infusion reaction occurred during previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes until rate = 400 mg/hour.

**Repeat every 28 days for up to 6 cycles total oBINutuzumab, unless disease progression or unacceptable toxicity.**

**chlorambucil:**

**Cycles 1 to 6**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| chlorambucil | 0.5 mg/kg* on Day 1 and Day 15**<br>**Maximum dose: 0.8 mg/kg every 2 weeks**.<br>Subsequently, if ANC greater than 3.5 x $10^9$/L, increase dose by 0.1 mg/kg, adjusting dose to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x $10^9$/L.<br>**Maximum dose: 0.8 mg/kg every 2 weeks**. | PO |

* Round to nearest 2 mg (2 mg tablet film-coated tablets)

** Additional chlorambucil dosing options available, see BC Cancer Protocol LYCHLOR

**Repeat every 28 days for up to 6 cycles, unless disease progression or unacceptable toxicity.**

**DOSE MODIFICATIONS**

- No dose reductions are recommended for oBINutuzumab. The infusion may be discontinued, held or its rate reduced as appropriate.
- If chlorambucil is discontinued due to related toxicity, may continue oBINutuzumab based on physician discretion

**1. Infusion reactions to oBINutuzumab:**

Refer to SCDRUGRX protocol for management guidelines.

| Infusion reactions | Management |
|---|---|
| Grades 1 or 2 (mild or moderate) | Reduce infusion rate and treat symptoms.<br>Once symptoms resolved, may resume infusion.<br>Titrate infusion rate at increments appropriate to the treatment dose – see BC Cancer Administration Guidelines for oBINutuzumab above |
| Grade 3 (severe) | Hold infusion and treat symptoms.<br>Once symptoms resolved, may resume infusion at no more than half of the rate when reactions occurred (see table below).<br>Titrate infusion rate at increments appropriate to the treatment dose. |
| Grade 4 (life-threatening) | Stop infusion and discontinue oBINutuzumab therapy |

Hydrocortisone may be used but more potent corticosteroids such as methylPREDNISolone may be required for infusion reactions.

**Infusion rate when resuming infusion after Grade 3 symptoms are resolved:**

| Infusion rate when reactions occur (mg/h) | Maximum infusion rate when resuming infusion (mg/h) |
|---|---|
| 25 | 10 |
| 50 | 25 |
| 100 | 50 |
| 150 | 50 |
| 200 | 100 |
| 250 | 100 |
| 300 | 150 |
| 350 | 150 |
| 400 | 200 |

**2. Hematological, for low counts due to treatment, not disease**

| ANC ($x10^9$/L) | Platelets ($x10^9$/L) | Dose (all drugs) |
|---|---|---|
| Greater than or equal to 1.2 | Greater than or equal to 80 | 100% |
| Less than 1.2 | Less than 80 | Delay until recovery |

Missed doses may be administered later at clinician's discretion; the 28 day-interval should be maintained

**PRECAUTIONS**:

1. **Infusion Reactions (IR),** including anaphylaxis, may occur within 24 hours of infusion, usually with the first infusion and decreasing with subsequent infusions. Cycle 1 Day 1 infusion reactions have been most frequently reported at 1 to 2 hours from the start of infusion. Cycle 1 Day 2 infusion reactions were most commonly seen at greater than 5 hours from the start of infusion. Risk factors include a high tumour burden. Symptoms may include nausea, vomiting, chills, hypotension, pyrexia, dyspnea, flushing, hypertension, headache, tachycardia, and diarrhea. Infusion reactions may require rate reduction, interruption of therapy, or treatment discontinuation. For first and second doses, patients are to be under constant visual observation during all dose increases and for 30 minutes after infusion is completed. For all subsequent doses, constant visual observation is not required. Vital signs are not required unless symptomatic. Monitor patients with pre-existing cardiac or pulmonary conditions closely. Consider temporarily withholding antihypertensive therapies for 12 hours prior to, during, and for 1 hour after infusion.
2. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
3. **Progressive Multifocal Leukoencephalopathy (PML)** may occur caused by reactivation of the JC virus. Patients should be evaluated for PML if presenting with new neurologic symptoms such as confusion, vision changes, changes in speech or walking, dizziness or vertigo.

4. **Tumour Lysis Syndrome (TLS)** including acute renal failure, can occur within 12-24 hours after the first infusion. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely. See BC Cancer Agency Cancer Drug Manual oBINutuzumab Drug Monograph for more information.
5. **Cardiovascular events,** such as myocardial infarction and dysrhythmias, including fatal cases can occur. Patients with pre-existing cardiac disease may develop worsening of the cardiovascular disease and should be monitored closely.
6. **Live or attenuated vaccines** are not recommended during treatment and until B-cell recovery has occurred after treatment (i.e., at least 3 months after treatment is discontinued)
7. **Bone Marrow Suppression** can occur when oBINutuzumab and Chlorambucil are used in combination and has resulted in grade 3 and 4 **neutropenia** and **thrombocytopenia**. Monitor for signs/symptoms of infection; antimicrobial prophylaxis is recommended in neutropenic patients. Antiviral and/or antifungal prophylaxis as well as filgrastim (G-CSF) should also be considered. Thrombocytopenia may require dose delays of oBINutuzumab and chlorambucil and/or dose reductions of chlorambucil. Consider withholding platelet inhibitors, anticoagulants, or other medications which may increase bleeding risk (especially during the first cycle). Leukopenia and lymphopenia commonly occur. Monitor blood counts frequently throughout therapy.
8. **Infection,** bacterial, fungal, and new or reactivated viral infections may occur during and/or following therapy; fatal infections have been reported. **Do not administer to patients with an active infection.** Do not administer to patients with an active infection. Patients with a history of recurrent or chronic infections may be at increased risk; monitor closely for signs/symptoms of infection.

**Call Dr. Laurie Sehn or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

**References:**


1. Cartron G, de Guibert S, Dihuydy MS, et al. Obinutuzumab (GA 101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014;124:2196-202.
2. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA 101) in B-cell malignancies. Blood. 2012.
3. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood 2012;119:5118-25.
4. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA 101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS Study. J Clin Oncol 2015;33:3467-74.
5. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-10.
6. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-74.
7. Gerrie AS, Toze CL, Ramadan KM, et al. Fludarabine (F) and rituximab (R) (FR) as initial therapy for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): population-based experience matches clinical trials. Blood 2009;114;abstract 2363.
8. 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;27:4378-84.
9. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences/BC Cancer Agency;2013. 102-4.
10. Bosch F, Illmer T, Turgut M, et al. Preliminary safety results from the phase IIIb GREEN study of obinutuzumab (GA101) alone or in combination with chemotherapy for previously untreated of relapsed/refractory chronic lymphocytic leukemia (CLL). 56th ASH Annual Meeting and Exposition. Abstract 3345.

## Appendix. oBINutuzumab infusion rate titration table

**Cycle 1: Day 1**

| **oBINutuzumab 100 mg IV in 100 mL NS**<br>**Total Volume = 114 mL** | | |
|---|---|---|
| **TITRATION** | **INFUSION RATE** | **VOLUME TO BE INFUSED (VTBI)** |
| 25 mg/h x 240 min | 28 mL/h | 114 mL |

**Cycle 1: Day 2**

| **oBINutuzumab 900 mg IV in 250 mL NS**<br>**Total volume = 311 mL** | | |
|---|---|---|
| **TITRATION** | **INFUSION RATE** | **VOLUME TO BE INFUSED (VTBI)** |
| 50 mg/h x 30 min | 17 mL/h | 9 mL |
| 100 mg/h x 30 min | 34 mL/h | 17 mL |
| 150 mg/h x 30 min | 52 mL/h | 26 mL |
| 200 mg/h x 30 min | 69 mL/h | 35 mL |
| 250 mg/h x 30 min | 86 mL/h | 43 mL |
| 300 mg/h x 30 min | 104 mL/h | 52 mL |
| 350 mg/h x 30 min | 121 mL/h | 61 mL |
| 400 mg/h x 30 min | 138 mL/h | 69 mL |

**Cycle 1: Day 8 and Day 15,**
**and**
**Cycle 2 to Cycle 6: Day 1 only**

| **oBINutuzumab 1000 mg IV in 250 mL NS**<br>**Total volume = 315 mL** | | |
|---|---|---|
| **TITRATION** | **INFUSION RATE** | **VOLUME TO BE INFUSED (VTBI)** |
| 100 mg/h x 30 min | 32 mL/h | 16 mL |
| 200 mg/h x 30 min | 63 mL/h | 32 mL |
| 300 mg/h x 30 min | 94 mL/h | 47 mL |
| 400 mg/h x 105 min | 126 mL/h | 220 mL |