Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

ALEM+RITU Regimen

Alemtuzumab-Rituximab

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 relapsed or refractory chronic lymphocytic leukemia (CLL)

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B - Drug Regimen

Week 1:

alemtuzumab[a, b, c]	3 mg	IV / Subcut	(first dose)
alemtuzumab[a, b, c]	10 mg	IV / Subcut	(second dose)
alemtuzumab[a, b, c]	30 mg	IV / Subcut	(third dose)

(This drug is not publicly funded. Universal compassionate access program is available.)

Weeks 2 to 13:

alemtuzumab[a, b, c]	30 mg	IV / Subcut	3 times per week

(This drug is not publicly funded. Universal compassionate access program is available.)

Can start either concurrently with alemtuzumab (on week one) or after alemtuzumab has already begun:

riTUXimab [d]	375 mg /m²	IV	Once weekly for 4 weeks

(This drug is not currently publicly funded for this regimen and intent)

Note: Different rituximab products are NOT INTERCHANGEABLE.

a. Although not approved by Health Canada, alemtuzumab has been given subcutaneously instead of intravenously; the incidence of infusion reactions may be lower.

b. Gradual dose escalation is required at the initiation of therapy and after treatment interruptions of 7 days or more. In most patients, escalation to 30mg can be accomplished in 3-7 days. Initial doses can be administered in various ways; sequentially (daily on days 1 to 3) and on alternate days (i.e. days 1, 3, and 5). Both schedules were used in clinical trials.

c. Single doses of alemtuzumab greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.

d. The rituximab dose may be split over 2 days for patients with elevated absolute lymphocyte counts.

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C - Cycle Frequency

Alemtuzumab: For a usual total of 13 weeks (1 week dose escalation, 12 weeks maintenance) unless disease progression or unacceptable toxicity occurs.

Rituximab: For a usual total of 4 weeks unless disease progression or unacceptable toxicity occurs.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

Pre-medication (prophylaxis for infusion reactions):

Administer at least 30 minutes prior to treatment:

- H1-receptor antagonist (e.g. diphenhydramine 50 mg IV)
- Acetaminophen 650 mg PO
- Corticosteroid:
  - **Alemtuzumab:** Can consider corticosteroids (methylprednisolone 1g) on the first 3 days
  - **Rituximab**: Corticosteroid (for example, methylprednisolone 80 mg IV) in patients with high bulk disease or pulmonary involvement if no corticosteroids are already being given as part of the chemotherapy regimen.

Other supportive care:

- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- Allopurinol and hydration to reduce the risk of tumour lysis syndrome are recommended.
- Trimethoprim/sulfamethoxazole DS twice daily three times per week and famciclovir (or equivalent) 250mg bid during treatment and for 2 months after or until CD4+ count is ≥ 200 cells/microL.
- Consider prophylaxis with G-CSF for patients at risk of febrile neutropenia.
- Irradiated blood products should be used.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Alemtuzumab:

Toxicity (grade or 10^9)	**1st Occurrence***	**2nd Occurrence***	**3rd Occurrence**
ANC < 0.25 and/or platelet ≤ 25	Hold, restart at same dose when ANC ≥ 0.5 and platelets ≥ 50	Hold, restart at 10mg when ANC ≥ 0.5 and platelets ≥ 50	Discontinue
If baseline ANC ≤ 0.25, and/or platelet ≤ 25 and ↓ 50%	Hold, restart at same dose when ≥ baseline	Hold, restart at 10mg when ≥ baseline	Discontinue
≥ Grade 3 non-hematologic toxicity, including serious infections and CMV viremia	Hold until ≤ grade 2. Consider dose modification		
Autoimmune disorders	Discontinue		
PML, autoimmune anemia or thrombocytopenia	Discontinue		
*If delay between dosing is ≥ 7 days, must re-escalate starting from 3mg Do not modify dose for lymphopenia			

Rituximab:

Toxicity	**Rituximab Dose** / Infusion Rate**
Myelosuppression	No adjustment required.
Other grade 3 toxicity	Delay infusion until ≤ grade 2
• Any pulmonary toxicity • Other grade 4 toxicity	Discontinue

• Severe mucocutaneous toxicity • Serious/life-threatening cardio-pulmonary events • Reactivation of tuberculosis or hepatitis B • Evidence of active hepatitis • PML / PRES/ RPLS	
**Missed or delayed doses may be administered at a later time point, based on physician's discretion.	

Management of administration-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Rituximab IV:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Once symptoms have resolved, restart at 50% of the rate at which the IR occurred.	• Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Alemtuzumab:

Grade	Management	Re-challenge
1-2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate with pre-medications, unless a serious reaction occurred	• No specific recommendations can be made at this time. If reaction was with IV route, switch to SC if possible.
3-4	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate with pre-medications, unless a serious reaction occurred	

Hepatic Impairment

No dosage adjustment required for rituximab. Discontinue if evidence of hepatitis. No information available for alemtuzumab.

Renal Impairment

No dosage adjustment required for rituximab. No information available for alemtuzumab.

Dosage in the Elderly

No dosage adjustment required. Limited experience with alemtuzumab. For rituximab, older patients are more likely to experience serious adverse events (including cardiac, pulmonary, or other grade 3 or 4 toxicity).

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F - Adverse Effects

Refer to alemtuzumab, riTUXimab drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	**Less common (10-24%)**	**Uncommon (< 10%),** **but may be severe or life-threatening**
• Hypersensitivity (may be severe) • Myelosuppression +/- infection (including atypical infections, viral reactivation), bleeding (may be severe) • Grade 1 or 2 local skin reaction (SC alemtuzumab)	• Fatigue • Hypotension • Nausea, vomiting • Headache • Rash (may be severe) • Flu-like symptoms	• Arrhythmia • Cardiotoxicity • Tumor lysis syndrome • Venous thromboembolism • Arterial thromboembolism • GI obstruction, perforation • Disseminated intravascular coagulation (DIC) • Vasculitis • Cholecystitis • Nephrotoxicity • Pancreatitis • Pneumonitis • Secondary malignancy • Autoimmune disorders • Transfusion associated GVHD • Posterior reversible encephalopathy syndrome (PRES) • Leukoencephalopathy (PML)

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G - Interactions

Refer to alemtuzumab, riTUXimab drug monograph(s) for additional details

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration
- Additive effects with medications that can cause hypotension (especially at time of alemtuzumab infusion)
  Additive effects with medications that can increase risk of bleeding when used with alemtuzumab

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H - Drug Administration and Special Precautions

Refer to alemtuzumab, riTUXimab drug monograph(s) for additional details

Note: Different rituximab products are NOT INTERCHANGEABLE.

Rituximab IV and Subcutaneous formulations are not interchangeable. The dosing and concentrations of these products are different.

Administration

Alemtuzumab:

- See the Product Monograph for full details of preparation and administration.
- Full resuscitation facilities and experienced personnel should be available.
- Do not administer as an intravenous push or bolus.
- Mix in 100mL IV bag (5% Dextrose or Normal Saline). Gently invert the bag to mix the solution. Infuse the admixture over 2 hours.
- Other drug substances should not be added or simultaneously infused through the same intravenous line.
- Infusion reactions with subcutaneous alemtuzumab are much milder (off-label route of administration) than IV. Consider subcutaneous administration (except in patients with T-PLL).

Rituximab IV:

- Rituximab 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 1-4 mg/mL in normal saline or D5W.
- To avoid foaming, gently invert the bag to mix the solution.
- Do not admix with other drugs.
- Administer rituximab through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Keep vials refrigerated; do not freeze. Protect from light.

Infusion rates:

- First infusion:
  - Recommended to be administered over a graduated rate: Initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h (about 4.25 hours in total).
- Subsequent infusions:
  - If no severe infusion reaction (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2 (20% of the dose in the first 30 min then the remaining 80% over 60 min).
  - OR initial rate of 100 mg/h, then escalate rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h as tolerated (about 3.25 hours in total).
  - Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.

When bulky disease present or WBC > 25-50 x 10^9/L, consider:

- A slower infusion rate, or
- Split dosing over days 1-2, or
- Delaying rituximab treatment until chemotherapy has reduced the lymphocyte count

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients with known hypersensitivity and anaphylactic reactions to rituximab, proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins or to alemtuzumab or any components of MabCampath
- Patients who have or have had PML, have active and/or severe infections, active hepatitis B, or severely immunocompromised (e.g. AIDS patients with very low CD4 or CD8 counts), or active secondary malignancies
- Avoid the use of live vaccines.

Other warnings/precautions:

- Gradual dose escalation of alemtuzumab to the recommended maintenance dose is required at the initiation of therapy and after interruption of therapy for more than 7 days. Alemtuzumab can result in serious and even fatal infusion reactions.
- Single doses of alemtuzumab greater than 30mg or cumulative doses of more than 90mg per week should not be administered, as they are associated with a higher incidence of pancytopenia.
- Exercise caution in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.
- Anti-viral and anti-Pneumocystis carinii pneumonia prophylaxis are strongly recommended.
- Prior to starting rituximab in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.
- Exercise caution in patients with neutrophil counts < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L due to limited experience in this patient group.
- Use with extreme caution in patients with pre-existing cardiovascular disease or in patients with high tumour burden.
- Consider steroids ± slow infusions or infusions split over 2 days for patients with bulky disease or > 25 x 10^9/L circulating malignant cells.
- Use with caution in patients with pulmonary insufficiency or lung tumour infiltration

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.
- 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).

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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

- CBC; baseline and before each treatment
- Liver and renal function tests; baseline and before each treatment
- CD4+ counts should be assessed after treatment until recovery to ≥ 200 cells/microL
- Clinical assessment of infusion-related reactions / hypersensitivity, tumour lysis syndrome, hypotension, infection, bleeding, GI, pulmonary, skin, CNS, cardiovascular side effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Monitor closely for cardiovascular symptoms for patients who have cardiac conditions
- Consider CMV monitoring

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J - Administrative Information

Approximate Patient Visit	RITU: 3 to 5 hours; ALEM (IV): 2.5 to 3 hours; ALEM (SC): 0.5 to 1 hour
Pharmacy Workload (average time per visit)	11.482 minutes
Nursing Workload (average time per visit)	40.019 minutes

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K - References

Alemtuzumab, rituximab drug monographs, Cancer Care Ontario.

Brown JR, Messmer B, Werner L, et al. A phase I study of escalated dose subcutaneous alemtuzumab given weekly with rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Hematologica. 2013; 98(6): 964-970.

Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. Cancer. 2010 May 15;116(10):2360-5.

Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood. 2003;101:3413-3415.

Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100(3):768-773.

Zent CS, Call TG, Shanafelt TD, et al. Early treatment of high-risk chronic lymphocytic leukemia with alemtuzumab and rituximab. Cancer. 2008 Oct 15;113(8):2110-8.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

November 2023 Modified Pregnancy/breastfeeding 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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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