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Chronic Lymphocytic Leukemia

Effective Date: July 2025

Background

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of functionally incompetent monoclonal lymphocytes. CLL is the most common adult leukemia in the Western world, accounting for approximately seven percent of non-Hodgkin lymphomas[1]. In Canada, the median age at diagnosis is approximately 72 years, with ten percent of cases diagnosed in patients younger than 50 years of age. Age-adjusted incidence rates are 7.5 per 100,000 person-years, with males representing approximately 56 percent of the cases. The five-year survival is approximately 80 percent in men and 85 percent in women[2]. In determining the optimal treatment for CLL, individual patient characteristics including performance status and disease characteristics must be considered.

Guideline Questions

1. What are the recommended diagnostic and staging criteria for adult patients in Alberta with CLL?
2. What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL?
3. What are the recommended follow-up and supportive care practices for adult patients in Alberta with CLL?

Search Strategy

No formal literature search was conducted for the 2025 update, the update was based on a consensus meeting held in 2025. An updated review of the literature was conducted by searching journal articles using the Medline (1950 to May, Week 1, 2015), EMBASE (1980 to May, Week 1, 2015), Cochrane Database of Systematic Reviews, and PubMed electronic databases. The MeSH heading “Leukemia, Lymphocytic, Chronic, B-Cell” was combined with the search terms “drug therapy” and “therapy”. The results were limited to adults, practice guidelines, systematic reviews, meta-analyses, multicentre studies, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published before the year 2000. The references and bibliographies of articles identified through these searches were scanned for additional sources. A search for practice guidelines published since January 2000 was conducted by accessing the websites of the following organizations: Cancer Care Ontario, British Columbia Cancer Agency, the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the Italian Society of Hematology/Italian Group for Bone Marrow Transplantation.

Target Population

Adult patients (aged ≥18 years) with suspicion or diagnosis of chronic lymphocytic leukemia.

Recommendations

Diagnosis and Prognosis

1. The initial diagnosis of CLL relies on the detection of a clonal B-lymphocyte count *greater than or equal to* 5 x 10^9 /L in the peripheral blood, for the duration of at least 3 months associated with a

characteristic flow cytometry immunophenotype profile. Small lymphocytic lymphoma (SLL) is diagnosed when a lymph node or other tissue biopsy demonstrates a malignant lymphocytic infiltration with cells showing the same immunophenotype as CLL, but associated with a circulating B-lymphocyte count that *does not exceed* 5 x 10^9/L. CLL and SLL are considered to be biologically the same disease and the management of SLL should follow CLL treatment guidelines (not guidelines for other indolent non-Hodgkin lymphoma sub-types)[3].

2. FISH cytogenetic analysis for del(17p) and *TP53* mutation analysis should be performed at the time when patients require treatment. FISH analysis is not recommended at diagnosis in patients who do not require therapy, outside of clinical trials.
3. IGHV mutation testing should be performed at the time when patients require treatment. This test should not be repeated at later time points (the results will not change over time).
4. Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (anti-HBs), and Hepatitis B Core Antibody (total anti-HBc) must be done prior to initiating therapy. Patients who are HBsAg positive are either acutely or chronically infected and require consultation with Hepatology. Patients who are HBsAg negative/anti-HBc positive (regardless of anti-HBs titre levels) and are going to be treated with B-cell depleting therapy (obinutuzumab or rituximab) should receive prophylactic therapy with entecavir or tenofovir. [4-8]

Triage Guidelines for New CLL Consultation

Referral to a hematologist or oncologist is suggested for new diagnoses of CLL; however, the majority of patients will be diagnosed as early stage CLL (asymptomatic and without cytopenias) and given the indolent nature of CLL, patients can safely wait several months for Hematology/Oncology consultation. It is acknowledged that a cancer diagnosis causes significant anxiety thus, referring physicians are encouraged to inform their patients re: the indolent nature of this diagnosis.

First-Line Treatment Options

1. The majority of patients with early-stage CLL are managed initially with active observation. The decision to initiate treatment should be based upon symptoms, advanced disease (bulky or symptomatic adenopathy/ splenomegaly or cytopenias), or evidence for rapid disease progression (e.g. lymphocyte count doubling within 6 months).
2. Patients whose CLL possesses del(17p) and/or *TP53* mutation have poor responses to standard chemotherapy and as such, targeted therapy with a preference for indefinite Bruton's tyrosine kinase (BTK) inhibitors are the preferred treatment choice for these patients. Venetoclax-obinutuzumab and ibrutinib-venetoclax (IbrVen) may be reasonable alternatives for patients preferring fixed-duration therapy.
3. Fixed duration therapy with VO or IbrVen is favoured over continuous BTKi for most patients due to the resultant meaningful treatment-free interval and to reduced budget impact. VO is preferred over IbrVen due to the rare occurrence of cardiac deaths noted with IbrVen. IbrVen is an option

in younger fit patients with lower predicted cardiac risk and in informed patients who prefer an all-oral combination.

4. Patients with unmutated IGHV have inferior outcomes compared to patients with mutated IGHV when treated with chemo-immunotherapy (CIT), making targeted therapy the preferred first-line treatment for these patients. Relatively shorter remissions are lnoted for unmutated IGHV patients after time-limited targeted therapy; however, duration of time off therapy remains good. Given the lack of head-to-head comparison of indefinite BTKi over fixed duration options, we favour finite therapy in these patients. Patients in whom VO cannot be safely administered (ex. those who reside a long distance from a regional or tertiary cancer centre) may consider IbrVen or continuous BTKi therapy..
5. Patients with mutated IGHV can experience lengthy remissions with many different therapies. In fit (ie. Cumulative Illness Rating Scale (CIRS) <=6) patients with mutated IgHV who are able to tolerate aggressive treatment, the combination of fludarabine + cyclophosphamide + rituximab (FCR) may lead to very durable (possibly indefinite) remissions. However, this therapy is associated with a risk of secondary myeloid malignancies (~6% at 20 years). Fixed duration targeted therapies lead to very long remissions and are the preferred therapy for these patients (VO or IbrVen).

Second and Subsequent Line Treatment Options

1. Venetoclax in combination with rituximab (Ven-R) with a fixed 2-year duration of therapy is a highly effective option for relapse/refractory CLL (after prior CIT) and is the preferred second line therapy for most patients due to its fixed duration of therapy. Retreatment with venetoclax is funded for patients remaining in remission for at least 12 months after a venetoclax-based regimen.
2. BTKi monotherapy leads to lengthy remissions in patients with relapsed/refractory CLL and is another highly effective option for second-line therapy and preferred for patients with *TP53* abnormalities. Second generation BTK inhibitors (acalabrutinib, zanubrutinib) have improved tolerability and lower risk of cardiac and bleeding toxicities compared to 1st generation (ibrutinib) and are thus the preferred choice of BTKi. There is no data currently to support switching patients from ibrutinib to second generation BTKi in individuals with good disease control and acceptable tolerability.
3. Venetoclax, a BCL2-inhibitor, as indefinite monotherapy, has demonstrated efficacy in patients who progress on or are intolerant to BCR-inhibitors (ibrutinib or idelalisib + rituximab). Fixed-duration venetoclax-rituximab is also an effective option for patients progressing on a BCR inhibitor. The BTKi should only be stopped once the full dose of venetoclax is reached to reduce the risk of CLL tumor flare.
4. Patients who progress on BTKi and BCL2i have a poor prognosis and should be considered for clinical trials, a non-covalent BTKi (if accessible), and/or allogeneic HSCT if appropriate. Patients who discontinue BTKi for reasons of intolerance after good disease control should wait to be re-treated at the time of achieving iwCLL treatment criteria and can consider VR or an alternate BTKi.

5. Idelalisib in combination with rituximab can lead to durable responses but has high rates of infectious and immune toxicity and is rarely used in Alberta.
6. Chemoimmunotherapy (ex bendamustine and rituximab) may be considered in patients who have relapsed after all other therapeutic options, particularly in those attempting to progress to curative HSCT, but it is no longer standard of care for relapsed/refractory CLL.
7. Allogeneic stem cell transplantation (HSCT) should be considered for fit patients who are younger than approximately 70 years of age, require treatment and, have progressed on a covalent BTKi (particularly those who have already failed venetoclax) or who have Richter's transformation with remission to the aggressive lymphoma. Allogeneic stem cell transplantation may be delayed in patients achieving responses to novel agents; however HLA typing should be performed to identify a possible transplant donor. High risk features that should prompt earlier consideration of HSCT include patients who have had ≥ 3 prior lines of therapy, those who have confirmed progression on BTKi and those with complex karyotypes by conventional cytogenetics.

Follow-up and Supportive Care

1. Patients with CLL often have compromised immune systems due to either the disease itself and/or the associated treatments. Antibiotic prophylaxis and regular vaccinations are recommended, depending on the type of treatments administered. PCP and anti-viral prophylaxis are strongly recommended for all patients receiving fludarabine-containing regimens (including all patients receiving FCR), bendamustine-based therapy and for patients receiving idelalisib therapy. Primary prophylactic use of G-CSF is not recommended with FCR due to the risk of progressive neutropenia, dose reduction of cytotoxic agents (F +/- C) is preferred.
2. Special attention should be paid to the appearance of autoimmune cytopenias, such as autoimmune hemolytic anemia, immune thrombocytopenia purpura, and pure red-cell aplasia, which occur in up to 11 percent of patients with CLL.

Discussion

I. Diagnosis

CLL is described by the World Health Organization (WHO) as a neoplasm composed of monomorphic small, round-to-slightly irregular B-lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes, admixed with prolymphocytes and paraimmunoblasts forming proliferation centres in tissue infiltrates[1]. According to the 2018 International Workshop on CLL (IWCLL) guidelines, the diagnosis of CLL requires a circulating clonal B-lymphocyte count *greater than or equal to* 5 x 10^9 /L in the peripheral blood, for the duration of at least 3 months[9]. Although CLL and small lymphocytic lymphoma (SLL) are categorized by the WHO as similar entities, the term SLL is used to indicate neoplastic tissue infiltration in lymph nodes, spleen, or other organs associated with a circulating B-lymphocyte count that *does not exceed* 5 x 10^9/L. Of note, the presence of cytopenias due to marrow infiltration is classified as CLL regardless of the peripheral blood lymphocyte count[10].

Monoclonal B-cell lymphocytosis (MBL) is a condition that resembles CLL but does not require treatment. As many as 12 percent of healthy individuals over the age of 40 may have low levels (less than 5 x 10^9/L) of circulating monoclonal B-cells that are phenotypically identical to CLL cells, but with no evidence of tissue infiltration, lymphadenopathy, splenomegaly, cytopenias, or symptoms [4]. High count MBL progresses to CLL at a rate of one to two percent of patients per year[11,12].

Clinical features of CLL vary in their presentation, course, and outcome. Patients are often asymptomatic at diagnosis, but fatigue, autoimmune hemolytic anemia, infections, splenomegaly, hepatomegaly, lymphadenopathy, or extra-nodal infiltrates may be present. Some patients may also exhibit a small serum monoclonal protein, an M-component. Although in rare cases patients may not have lymphocytosis at diagnosis, peripheral blood and bone marrow are usually involved as the disease progresses. Lymph nodes, liver, and spleen are commonly infiltrated, with other extra-nodal sites becoming involved in some patients.[1]

Although some CLL cases may have an atypical immunophenotype, the characteristic profile includes CD19/CD5/CD23/CD43/CD200 positivity with weak CD20 and CD11c positivity and dim surface immunoglobulin expression with restricted light chain expression[1].

II. Staging

Two widely accepted staging methods, the modified Rai and the Binet systems, are used in both patient care and for clinical trials; the modified Rai system is the most commonly used in Canada. These staging systems are relatively simple, relying solely on physical examination and standard laboratory tests[13-15].

Table 1. Rai and Modified Rai Classification System for CLL[13,14]

Stage (Rai)	Description	Risk Status (Modified Rai)	Median Survival (years)
0	Lymphocytosis, with lymphoid cells >30% in the blood and/or bone marrow	Low	11.7
I	Stage 0 with enlarged node(s)	Intermediate	8.3
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	Intermediate	5.8
III	Stage 0–II with hemoglobin <110 g/L	High	2.0-4.0
IV	Stage 0–III with platelets <100 x 10^9/L	High	2.0-4.0

Table 2. Binet Classification System for CLL[15]

Stage	Description	Median Survival (years)
A	Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and <3 involved nodal areas	> 10

B	Hemoglobin ≥100 g/L and platelets ≥100 x 10^9/L and ≥3 involved nodal areas	5
C	Hemoglobin <100 g/L and or platelets <100 x 10^9/L and any number of involved nodal areas	2.0-4.0

III. Prognostic and Predictive Biomarkers

A number of predictive and prognostic markers have been identified that may predict for responsiveness to chemotherapy and survival.

Cytogenetic testing and next generation sequencing: Interphase fluorescence in situ hybridization (FISH) can be used to identify cytogenetic abnormalities in more than 80 percent of patients. In general, patients with a normal karyotype or isolated del(13q) can be categorized as low risk with prolonged time to disease progression and better chances of long-term survival, whereas patients with del(17p), and del(11q) are more likely to have a poor prognosis.[16] Del(17p) leads to loss of the *TP53* tumour suppressor gene, which mediates cell death induced by alkylating agents and purine analogues. Mutations in *TP53* confer the same inferior prognosis as del(17p). Testing for *TP53* mutations is thus recommended in patients who are not already known to harbor del(17p), particularly among those being considered for FCR.[17] Patients with del(17p) and/or *TP53* mutation are typically less responsive to chemo-immunotherapy, but respond well to the novel agents including BCR inhibitors (BTKi and idelalisib + rituximab)[18] or BCL-2 inhibitors[11,19]. FISH studies for del(17p) and *TP53* mutation analysis should thus be performed when therapy is required. Other cytogenetic abnormalities do not impact treatment decision-making and are not routinely required outside of clinical trials.

IgHV mutational status and VH3.21 gene usage: Approximately half of all CLL patients have leukemic cells with somatic hyper-mutations in the immunoglobulin heavy chain variable region (IgHV) genes. Patients with mutated CLL have improved survival as compared to those with unmutated CLL[11,16]. Patients with unmutated CLL exhibit faster disease progression, atypical peripheral blood cell morphology, adverse cytogenetic features, and clonal evolution.[16] The VH3.21 ("subset 2") gene is also an unfavourable prognostic marker, regardless of IgHV mutational status.[11] IgHV mutation status should influence treatment decision. Patients with mutated IgHV have excellent outcomes with fixed duration therapy (FCR, VO, IbrVen). BTK inhibitors appear to be equally efficacious in patients with mutated and unmutated IgHV and thus have most relative benefit in the unmutated IgHV subgroup.

Serum markers: Serum markers such as CD23, thymidine kinase (TK), and ß2-microglobulin (ß2M) may predict overall or progression-free survival (PFS)[11]. Even in cases of early stage disease, serum TK levels correlate with tumour mass and proliferative activity of CLL cells. In addition, high levels of CD23 are associated with diffuse bone marrow infiltration and rapid lymphocyte doubling time. Serum TK and CD23 assays are not routinely available in Canada. Alternatively, serum levels of β2M are easily available at most Canadian centres and correlate with both clinical stage and overall survival.[16]

Initiating treatment: The IWCLL guidelines describe the initiation of treatment based on a combination of clinical staging, the presence of symptoms, and disease activity[5]. These criteria include:

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia
- Massive (at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (at least 10 cm in the longest diameter), or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis, with an increase of more than 50 percent over two months, or lymphocyte doubling time of less than six months (factors contributing to lymphocytosis or lymphadenopathy other than CLL such as infections should be excluded)
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids/standard therapy

In addition, any one of the following symptoms may also be present:

- Unintentional weight loss of ten percent or more within the previous six months
- Significant fatigue
- Inability to work or perform usual activities
- Fever higher than 38.0°C for two weeks or more without other evidence of infection
- Night sweats for more than one month without evidence of infection

Assessing response to treatment: In assessing the response to treatment, a thorough physical examination and blood analysis should be performed. Although useful in clinical trials, imaging studies, including CT scans, are not recommended in general practice for routine screening/staging.[11,20] Patients in remission should be re-evaluated every three to six months to monitor disease status.[21,22] Given data suggesting possibly indefinite responses following FCR and remission of many years following VO, less frequent follow-up and care transitioned back to primary care are appropriate following fixed duration therapy in good risk patients. Additionally, early-stage patients who show limited progression of disease should have their active surveillance transitioned back to their primary care provider.

Table 3. Criteria for Identifying Treatment Response[11]

Parameter	Complete response (CR)	Partial response (PR)	Progressive disease (PD)	Stable disease (SD)
Lymphadenopathy	None >1.5 cm	Decrease ≥50%	Increase ≥50% or appearance of any new lesion	Change of –49% to +49%

Parameter	Complete response (CR)	Partial response (PR)	Progressive disease (PD)	Stable disease (SD)
Liver and/or spleen size	Normal size	Decrease ≥50%	Increase ≥50% or new enlargement when previously normal	Change of –49% to +49%
Constitutional symptoms	None	Any	Any	Any
Polymorphonuclear leukocytes	>1.5 x 10^9/L without need for exogenous growth factors	>1.5 x 10^9/L or >50% improvement over baseline without need for exogenous growth factors	Any	Any
Circulating clonal B-lymphocytes	None	Decrease ≥50% over baseline	Increase ≥50% over baseline	Change of –49% to +49%
Platelet count	>100 x 10^9/L without need for exogenous growth factors	>100 x 10^9/L or increase ≥50% over baseline	Decrease ≥50% from baseline or to <100 x 10^9/L secondary to CLL	Change of –49% to +49%
Hemoglobin	>110 g/L (untransfused and without need for exogenous erythropoietin)	>110 g/L or increase ≥50% over baseline	Decrease of >20 g/L from baseline or to <100 g/L secondary to CLL	Increase ≤110 g/L or <50% over baseline, or decrease <20 g/L
Marrow	Normocellular for age, <30% lymphocytes, no B-lymphoid nodules Hypocellular marrow with no clonal infiltrates defines CRi	No BM requirements to document PR	No BM requirements to document PD	No BM requirements to document SD

V. Treatment

First Line Treatment Options for CLL:

The ultimate treatment goal in CLL is to achieve a long overall survival, while minimizing toxicities and improving quality of life. In the absence of a survival benefit, achieving a long PFS is a reasonable goal of therapy. Consideration of the patient's preference is always important in the determination of any treatment decision.

Fludarabine-cyclophosphamide-rituximab (FCR)

The phase III GCLLSG CLL8 trial compared the primary endpoint of PFS after treatment with FCR or FC in younger fit CLL patients.[23] Study participants included 817 patients selected for minimal co-morbidity (CIRS <6). Median PFS was reported as 32.8 months in the FC arm and 51.8 months in the FCR arm (HR 0.56; *p* <0.0001). Statistically significant differences were observed in OS rates between the two treatment arms (87.2% in the FCR arm versus 82.5% in the FC arm at 37.7 months, *p* = 0.012). This was the first Phase III study in CLL to demonstrate an OS advantage. Grade 3 and 4 hematological toxicity, neutropenia, and leukocytopenia rates were higher in the FCR versus FC arm (55.7% versus 39.6%, 33.7% versus 21%, and 24.0% versus 12.0%, respectively; *p* <0.0001).[23] Based on the results from the CLL-8 trial, FCR became the standard of care chemo-immunotherapy for firstline treatment of young, fit CLL patients. Long term follow-up studies of FCR suggest that the good risk subgroup of patients with mutated IgHV and no *TP53* aberrations may potentially be cured with this approach or at least experience very prolonged PFS.[24]

Venetoclax + Obinutuzumab

Venetoclax-obinutuzumab was compared to chlorambucil-obinutuzumab in a randomized, phase 3, open-label trial of previously untreated CLL patients with coexisting conditions.[25] In total, N=432 patients were randomized (1:1). Median age was 72 years, cumulative Illness Rating Scale score was median 8, and median creatinine clearance was 66.4 mL/min. Follow-up data after a median 39.6 months[26] reported significantly longer PFS in the venetoclax-obinutuzumab arm (not reached) versus the chlorambucil-obinutuzumab arm (35.6 months) (HR: 0.31; 95%CI: 0.22-0.44, p<0.001). Serious adverse events occurred in 53% and 48% respectively. Treatment-related death occurred in n=1 (sepsis) patient in the venetoclax-obinutuzumab arm, and n=2 (n=1 septic shock, n=1 metastatic skin squamous carcinoma) patients in the chlorambucil-obinutuzumab arm. Venetoclax-obinutuzumab was also evaluated in medically fit patients in the CLL13 trial and demonstrated similar PFS as ibrutinib-venetoclax-obinutuzumab and superior PFS compared to Ven-R, FCR, or BR[27].

Chloambucil + Obinutuzumab

The GCLLSG CLL11 defined chlorambucil + Obinutuzumab (CLB-O) as the previous preferred CIT for older and unfit patients. Subsequent trials have showed improved PFS/OS utilizing novel agents. Given a fixed duration of treatment and a 56 month time to next treatment, CLB-O remains an option for very elderly and/or very unfit patients who refuse VO or have contraindications to VO.

BTK inhibitors

Ibrutinib

The open-label, phase III RESONATE-2 trial[28] randomized (1:1) 269 patients who were at least 65 years of age (range: 85-89; median 73 years) with a diagnosis of CLL/SLL to ibrutinib (420mg once daily) or up to 12 cycles of chlorambucil monotherapy.[28] The 24-month OS was also significantly improved with ibrutinib (98%) vs. chlorambucil (85%), despite a cross-over design of the study. Adverse events (any grade) occurred in at least 20% of ibrutinib patients, including diarrhea, fatigue, cough, and nausea. The OS advantage demonstrated by ibrutinib in the firstline treatment of CLL at a short median follow-up is important; however, the comparator arm (chlorambucil monotherapy) was not a standard of care treatment option, which limited the value of this study's results.

Several subsequent Phase 3 studies have compared BTK inhibition with chemo-immunotherapy.

The Alliance A041202 study compared ibrutinib with or without rituximab against bendamustine and rituximab (BR) in previously-untreated, older (≥ 65 years) patients with CLL.[29] PFS was significantly improved with the use of ibrutinib (87%) compared to BR (74%, HR, 0.39; 95% CI, 0.26 to 0.58; p<0.001) while the addition of rituximab (88%) did not improve outcomes over ibrutinib monotherapy (HR, 1.00; 95% CI, 0.62 to 1.62; P = 0.49). Ibrutinib was not without toxicity and non-hematological toxicities were higher than in the BR arm (grade 3-5 non-hematological toxicities 74% for ibrutinib-containing regimens compared to 63% for BR) while hematological toxicities were higher with BR (grade 3-5 hematological adverse events 61% with BR compared to 41% with ibrutinib). Adverse events of interest with ibrutinib including atrial fibrillation and hypertension were common with atrial fibrillation occurring in 17% of patients in the ibrutinib group and 14% in the ibrutinib + rituximab group, compared to 3% with BR. Grade 3 or higher hypertension occurred in approximately 30% of ibrutinib-treated patients. Importantly, several treatment-related deaths occurred with ibrutinib including sudden cardiac deaths and 1 major bleeding event. No overall survival (OS) difference has yet been reported in this study.

The ECOG 1912 study compared ibrutinib + rituximab to chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR) in a young and fit CLL population.[30] The results of the ECOG 1912 study are very important because in contradiction to the other frontline studies of BTKi versus chemo-immunotherapy, this study observed both a PFS and an OS advantage of ibrutinib + R compared to FCR. The hazard ratio for PFS was 0.352 (95% CI 0.223-0.558; p<0.0001) and 0.168 (95% CI 0.053-0.538; p=0.0003, pre-specified boundary for superiority p=0.0005) for OS, both favoured IR. No significant different was demonstrated in PFS in the subgroup of patients with mutated IgHV. The open-label, phase 3, FLAIR trial, randomized previously untreated CLL patients (N=771) to receive ibrutinib and rituximab or FCR (1:1). After a median 53 months of follow-up, median progression free survival was not reached in the ibrutinib +R arm, compared to 67 months in the FCR arm (HR: 0.44; 95%CI: 0.32-0.60; p<0.001). Serious adverse events were reported in 53% of ibrutinib +R patients compared to 54% or the FCR patients.[31] Given data suggesting the possibility of very lengthy remissions and even potential cure with FCR in patients with mutated IGHV, we would

continue to favour FCR in these patients[44]. Ibrutinib toxicities were much less marked in these younger patients with only 1% of patients dying from an unexplained event (likely sudden cardiac death).

Acalabrutinib

The phase 3, multicenter, open-label ELEVATE TN trial[32] randomized (1:1:1) treatment-naive CLL patients to receive acalabrutinib-obinutuzumab, acalabrutinib monotherapy, or obinutuzumab-chlorambucil. Eligible patients (N=535) were ≥65 years, or 18-65 years with creatinine clearance of 30-69 mL/min or CIRS for Geriatrics score >6. After a median follow-up of 46.9 months, median investigator-assessed PFS was not reached (acalabrutinib-containing arms) compared to 27.8 months in the CLB-O arm (both $p<0.001$). Post hoc analysis demonstrated that prolonged PFS was observed in the acalabrutinib+obinutuzumab arm compared to the acalabrutinib arm ($p=0.0296$); however, the study was not powered for this comparison. The estimated 48-month PFS rates were 87% for acalabrutinib-obinutuzumab, 77.9% for acalabrutinib, and 25.1% for CLB-O. Adverse events in the acalabrutinib-obinutuzumab, acalabrutinib and CLB-O arm were 25.1%, 30.7%, and 22.6%, respectively, and this led to treatment discontinuation in 12.8%, 12.3%, and 14.7%, respectively.[33]

Zanubrutinib

The phase 3 SEQUIOA trial randomized 590 patients ≥65 years old or ≥18 years old with comorbidities who had treatment-naïve CLL without del(17p) to continuous zanubrutinib versus BR. Zanubrutinib resulted in superior PFS with no difference in OS. Zanubrutinib was associated with increased risks of hemorrhage/contusion but reduced risks of serious adverse events, rashes, nausea, fever, and neutropenia compared to BR[34].

Ibrutinib + Venetoclax

Fixed-duration all-oral treatment with 3 cycles of ibrutinib lead-in followed by 12 cycles of I+V was studied in 159 patients ≤70 years old with treatment-naïve CLL in the phase II CAPTIVATE study, achieving a 2-year PFS rate of 95% (PMID: 35196370). The phase III GLOW trial randomized 211 patients ≥65 years old or ≥18 years old with comorbidities who had treatment-naïve CLL to I+V versus chlorambucil-obinutuzumab. I+V resulted in superior PFS and OS, but there appeared to be increased cardiac toxicity and early treatment-related mortality with I+V (PMID: 37944541). As such, I+V is recommended as an effective option for younger fit patients but it is generally not preferred for older patients with comorbidities. Prolonged MRD-driven treatment with I+V was also evaluated in the FLAIR trial and demonstrated superior PFS and OS compared to FCR[35].

Special Consideration

While it is acknowledged that there are no prospective trials for stopping continuous BTKi therapy for those who have achieved a durable remission, consideration could be given to stopping treatment for patients who have a reduced life expectancy due to co-morbidity. Patients who stopped BTKi therapy due to intolerance in a frontline treatment study, were shown to have a lengthy time to recurrence of disease (median 25 months) with an unknown time to next treatment.[37]

Summary of frontline treatment approach in CLL:

Given the improved PFS of targeted therapies over CIT in CLL, the only subgroup of patients who are recommended to consider CIT are the young, favourable risk group who may experience cure or very prolonged remission with FCR. VO is the preferred therapy in patients with favorable risk CLL who are not accepting of the risk of myeloid malignancy associated with FCRIbrVen also represents an effective fixed-duration all-oral targeted therapy alternative to FCR.. Indefinite BTKi therapy has not been compared against finite duration VO or IbrVen. But because of the predicted exponential increase in cost of indefinite BTKi therapy in favourable-risk patients, fixed duration therapy is recommended.

Treatment of Patients with del(17p) and/or TP53 mutation

Patients with *TP*53 aberrations were included in several of the novel therapy vs CIT studies (Alliance, iLLUMINATE, ELEVATE-TN and CLL14). Outcomes in patients with *TP*53 aberrations are inferior to those with intact *TP*53 with all fixed duration regimens examined whereas outcomes were not notably different in *TP53* aberrant vs intact for frontline continuous BTKi studies, making indefinite BTKi the preferred treatment for patients with del(17p) and/or *TP*53 mutation.[38] However, patients preferring a fixed-duration regimen may reasonably be treated with VO (5-year TTNT 48% in CLL14) or IbrVen (54-month PFS 45% in CAPTIVATE)[39].

Second and Subsequent Line Treatment Options for Relapsed and Refractory Patients with CLL:

Recommendations for second-line treatment of CLL should consider individual factors such as comorbidities and choice of prior therapy and its outcome.

BCL2 inhibitor (Venetoclax)

The open-label phase 3 MURANO trial randomized (N=389) relapsed or refractory CLL patients who had received one to three previous treatments (including at least one chemotherapy-containing regimen) to venetoclax- rituximab (VenR) or bendamustine plus rituximab (BR). After 5 years of follow-up, median PFS for VenR vs BR were 53.6 vs 17.0 months, respectively ($p<0.001$). The 5-year OS was 82.1% (95%CI: 76.4-87.8) vs 62.2% (95%CI: 54.8-69.6), respectively ($p<0.001$). VenR was superior to BR regardless of cytogenetic category. Grade 3-4 adverse events occurred in 67% of VenR patients and 53.3% of BR patients.[40,41]

A multicenter, open-labelled, non-randomized, phase 2 trial of adult patients with relapsed or refractory CLL, previously treated with ibrutinib, negative for Richter's transformation, has reported interim outcomes from 91 patients after treatment with indefinite venetoclax monotherapy.[42] After a median follow-up of 12 months, 59 of 91 (65%, 95% CI 53-74) patients had an overall response. Disease progression was responsible for 7 of 17 deaths in the cohort, none of which were treatment-related deaths. A smaller phase 2 study of 36 patients with refractory/relapsed CLL after ibrutinib or idelalisib were treated with venetoclax (20mg daily, followed by ramp-up to 400mg daily).[42] Estimated

12-month progression free survival was 79%, with 2 patients achieving complete remission. Based on these data, indefinite venetoclax monotherapy has been recommended for patients with progression on a BCRi. However, real-world data confirms that fixed-duration Ven-R is also an effective option for patients progressing on a BTKi[43] and may reduce the development of BCL2 mutations which has been observed with continuous venetoclax therapy. Of note, patients switching to venetoclax due to progression on a BTKi should only stop the BTKi once the full dose of venetoclax is reached to reduce the risk of tumor flare provoked by abrupt BTKi discontinuation.

Retreatment with venetoclax is also funded for patients who remain progression-free for ≥12 months after a venetoclax-based regimen, with one real-world study demonstrating ORR 79% and median PFS 25 months after retreatment[44]. The decision to retreat with venetoclax depends on the duration of prior remission, availability of other therapies, tumor burden, and feasibility of TLS monitoring during the dose ramp-up phase.

BTK inhibitors:

Ibrutinib

The multicenter, open-label, phase 3 RESONATE trial randomized 391 patients with relapsed or refractory CLL or small lymphocytic lymphoma to receive daily ibrutinib or ofatumumab. Ibrutinib significantly improved progression free survival and overall survival compared to ofatumumab.[45]

Acalabrutinib

The phase III ASCEND trial[46] randomized (N=398) relapsed/refractory CLL patients to receive acalabrutinib monotherapy, or investigator's choice (idelalisib plus rituximab (IR) (n=119) or bendamustine plus rituximab (BR)(n=36)). After a median follow-up of 16.1 months, median progression-free survival was superior in the acalabrutinib arm (not reached vs. 16.5 months; HR: 0.31; 95%CI: 0.20-0.49; p<0.001; estimated 12-month PFS was 88% vs 68%). Serious adverse events occurred in 29% of patients treated with acalabrutinib, 56% of patients treated with IR, and 26% of patients treated with BR. Deaths occurred in 10%, 11%, and 14%, respectively.

The ELEVATE-R/R was the first Phase 3 study to provide a head-to-head comparison between 2 BTKis (ibrutinib and acalabrutinib in an unblinded comparison).[47] Patients (N=533) with relapsed/refractory CLL with del(17p) and/or del(11q) were randomised 1:1 to ibrutinib or acalabrutinib. The included patients had a median age of 66 years and a median of 2 prior lines of therapy. After a median of 41 months of follow-up, the hazard ratio for PFS was 1.0, (95% CI 0.79–1.27), meeting the primary endpoint of non-inferiority of PFS. The incidence of adverse events atrial fibrillation, hypertension and all grade bleeding were statistically significantly lower in the acalabrutinib treated patients compared to the ibrutinib-treated patients.

Zanubrutinib

The multicenter, randomized phase 3 ALPINE study[48] randomized (1:1) N=652 relapse/refractory CLL patients who had received at least one previous therapy to either zanubrutinib or ibrutinib until

disease progression or unacceptable toxicity. After a median follow-up of 29.6 months, zanubrutinib had superior PFS (HR:0.65; 95%CI: 0.49-0.86; p=0.002). Longer PFS was observed in patients with 17p deletion, *TP53* mutation or both. The safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death.[49]

The ELEVATE-RR and ALPINE studies confirm that second generation BTKi are better tolerated that ibrutinib. The reduced cardiac toxicities are particularly important given that rare cardiac deaths are observed with ibrutinib. These studies were performed in relapsed/refractory patients who were younger than average suggesting that this improved safety effect could be even more notable in the general population of CLL patients who are expected to be older and with more comorbidities than clinical trial selected patients. For this reason, second generation BTKi are favoured for all new BTKi starts (including first-line therapy). Acalabrutinib and zanubrutinib have not been compared head-to-head in a randomized trial so both represent good treatment options with their respective pros and cons (see table). At this time, there is no compelling data to favor one over the other in terms of efficacy or tolerability.

	Acalabrutinib	Zanubrutinib
Funding	(1) Treatment-naïve CLL/SLL for whom fludarabine-based treatment is inappropriate and who have del(17p), TP53 mutation, and/or unmutated IGHV (2) Relapsed/refractory CLL/SLL after >1 prior therapy	(1) Treatment-naïve CLL for whom fludarabine-based treatment is inappropriate. (2) Relapsed/refractory CLL after >1 prior therapy Patients must not have B-PLL or Richter transformation
Efficacy	Similar PFS as ibrutinib in r/r CLL with del(17p) and/or del(11q)	Superior PFS versus ibrutinib in r/r CLL
Safety	↑ headache and cough versus ibrutinib Similar neutropenia and infection risk as ibrutinib ↓atrial fibrillation, diarrhea, arthralgia, contusion, hypertension, UTI, back pain, muscle spasms, dyspepsia versus ibrutinib	↑neutropenia, URTI, COVID-19 versus ibrutinib Similar infection, hypertension, and hemorrhage risk versus ibrutinib ↓ atrial fibrillation, muscle spasms, diarrhea versus ibrutinib
Schedule	100mg BID	320mg daily or 160mg BID (studied at 160mg BID in clinical trials)
Number of tablets	2 tablets per day	4 tablets per day
Drug interactions	CYP interactions Now PPI compatible	CYP interactions PPI compatible
Cost	Confidential	Confidential

Idelalisib + rituximab

The randomized, multicenter, double-blind, placebo-controlled, phase 3 trial NCT01539512 compared Idelalisib (150 mg twice daily) plus rituximab to placebo plus rituximab in relapsed CLL patients. Patients in the idelalisib + R had improved overall survival at 12-months (92% vs 80%; p=0.02) compared to the placebo arm. Serious, adverse events were reported in 40% of patients in the idelalisib arm, compared to 35% in the placebo arm[50] with the most common serious adverse events being pneumonia (6%), pyrexia (6%), and febrile neutropenia (5%) (rates were similar in the placebo

arm). Grade 3-4 diarrhea on idelalisib has been reported from 16-42%.[45,51,52] This therapy is rarely used in Canada due to high rates of toxicity and treatment discontinuations. It would currently only be recommended as a bridge to allogeneic transplant or clinical trial in motivated patients.

Pirtobrutinib

The non-covalent BTKi pirtobrutinib was studied in a phase II trial of 317 patients with multiply-relapsed CLL and demonstrated an ORR of 82% with median PFS of 20 months among all patients, 17 months among BTKi and BCL2i exposed patients, 17 months among patients with del(17p) or TP53 mutations, and 14 months among patients exposed to CIT, BTKi, BCL2i, and PI3Ki. Pirtobrutinib is not currently funded but may be available through clinical trials or compassionate access programs[53].

Choosing between novel agents ibrutinib, acalabrutinib, venetoclax + rituximab or idelalisib +/- rituximab:

All of the novel agents have demonstrated impressive efficacy in patients with relapsed/refractory CLL. Most of these studies include patients previously treated with CIT so the move to novel therapies frontline should be considered when treating future patients. Several factors can be considered when selecting between agents including expected toxicities and desire for time-limited therapy. No head-to-head studies have compared BTKi to VenR; however, time-limited therapy provides an expected cost savings and improved quality of life due to time of treatment, which favour VenR over BTKi when possible. Patients with del(17p) or *TP53* mutation have better disease control with indefinite BTKi such that BTKi is preferred in those patients. Idelalisib + rituximab has limited role given a lack of efficacy in patients who have failed BTKi, the high rate of toxicities and the availability of multiple BTKi options now.

Allogeneic stem cell transplantation:

Allogeneic stem cell transplantation may be considered for fit patients younger than approximately 70 years who:

- Have refractory CLL
- Have CLL with del(17p) abnormalities (patient should be assessed for HSCT when starting a second novel therapy)
- Have progressed on a targeted therapy (BCR inhibitor, venetoclax, etc)
- Have Richter's transformation after achievement of remission of the aggressive lymphoma

As the novel therapies (BTKi, venetoclax + rituximab and idelalisib + rituximab) have excellent reported response rates in high risk patients, allogeneic HSCT should be individualized in patients receiving novel agents (considering transplant-related factors of donor availability and patient preference). High risk disease features that should prompt earlier consideration of HSCT include 1) poor response or loss of response to novel agent, 2) high risk cytogenetic features including del(17p), *TP53* mutation, del(11q), complex karyotype by conventional cytogenetics 3) ≥ 3 prior lines of therapy.

VI. Managing Complications and Supportive Care in CLL

Prevention and management of infections:

Patients with CLL often have compromised immune systems due to the disease itself and/or its associated treatments. Infections are therefore common, and prophylaxis is appropriate, depending on the type of treatment given. The use of live vaccines in patients with CLL is not recommended. However, the use of inactivated vaccines such as annual influenza and COVID-19 and pneumococcal vaccination (Canadian guidelines recommend that high risk patients (which includes patients with malignant hematological disorders) receive a Pneumo-C vaccine, followed by a Pneumo-P 8 weeks later. If a patient has received Pneumo-P, they should wait 1 year before receiving Pneumo-C. Pneumo-C (13) is covered by public health for CLL patients in Alberta.) for patients not yet treated or in remission for more than three months is recommended.[54,55] Screening for tuberculosis should be considered in patients from endemic areas. Screening for Hepatitis B is recommended before anti-CD20 monoclonal Ab or BTKi therapy so should be performed in all patients. The new inactivated Varicella Zoster vaccine has not been tested in patients with CLL but should be considered. Vaccinations are not recommended until 6-9 months post-anti-CD20 therapy. Table 6 summarizes antibiotic prophylaxis and recommended vaccinations for patients with CLL.

Table 4. Antibiotic Prophylaxis and Vaccinations in Patients with CLL

Treatment	Possible infection	Antibiotic prophylaxis	Vaccine	Other
Splenectomy	Encapsulated bacteria	Penicillin	Pneumococcal, Hemophilus, and Meningococcal prior to splenectomy	
Alemtuzumab or allogeneic stem cell transplant	CMV VZV	Valgancyclovir pre-emptive therapy for increased PCR Acyclovir or valacyclovir	n/a consider non-live VZV	CMV monitoring by PCR every 1–2 weeks
Fludarabine, rituximab, obinutuzumab, BTKi	Hepatitis B	Or entecavir 0.5mg po dailyor tenofovir	n/a	
Fludarabine- or bendamustine based treatment	Pneumocystis jirovecii pneumonia or Varicella Zoster	Septra or equivalent and acyclovir or equivalent should be used for 12 months	n/a	
BTKi or idelalisib + rituximab	Community-acquired pneumonia or Pneumocystis jirovecii pneumonia	Septra is required for PJP prophylaxis with idelalisib	pneumococcal	CMV monitoring recommended with idelalisib

Where patients experience recurrent infections that require intravenous antibiotics or hospitalization, antimicrobials should be given as needed. In patients with recurrent bacterial infections and where serum IgG is less than 5 g/L, monthly intravenous or subcutaneous immunoglobulins can be given at 0.3–0.5 g/kg; dose and interval should be adjusted to maintain a nadir level of more than 5 to 7 g/L.[56]

Autoimmune cytopenias:

Patients with CLL are at increased risk of developing autoimmune cytopenias, such as autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenia purpura (ITP), and pure red cell aplasia (PRCA). AIHA will develop in approximately 11 percent of advanced-stage CLL patients.[57] AIHA is diagnosed by the presence of at least one marker of hemolysis (increased indirect bilirubin not due to liver disease, increased lactate dehydrogenase without alternative etiology, increased absolute reticulocyte count, increased bone marrow erythropoiesis in the absence of bleeding, or decreased haptoglobin) with direct or indirect evidence of an autoimmune mechanism (positive direct antiglobulin

test (DAT) for either IgG or C3d, cold agglutinins, or at least two markers of hemolysis in the absence of evidence of bleeding or hypersplenism).[58]

ITP is less common, occurring in two to three percent of CLL patients at diagnosis or during early stage disease.[57] ITP can be identified where platelet counts are less than or equal to 100 × 10^9/L with no evidence of hypersplenism, no evidence of increased platelet consumption due to other causes, and normal or increased megakaryocytes on bone marrow examination.[59] PRCA is present in six percent of CLL patients that are tested.[57] PRCA can be diagnosed when hemoglobin concentration is less than or equal to 120 g/L, with reticulocytopenia and isolated absence of erythrocyte precursors in the bone marrow. Parvovirus infection must be ruled out, which can be done by using a blood polymerase chain reaction (PCR) assay.[60]

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. Alternatively, RCD (rituximab, cyclophosphamide and decadron) appears to have good response rates for control of refractory AIHA and as a CLL-therapy.[61,62] Second-line options for AIHA can include splenectomy and intravenous immunoglobulins though these are typically not used currently where effective therapy for CLL is preferred. Good responses have been obtained using rituximab and BTKi[5]. Refractory cases could be considered for immune suppressive therapy with cyclosporine A, azathioprine, or low-dose cyclophosphamide, although these agents are associated with high rates of infection and other complications. Most patients with PRCA will respond to therapy with cyclosporine A or corticosteroids, but prolonged high doses are usually needed; steroid-sparing agents such as cyclophosphamide may therefore be required.[58,59] Rituximab may be an additional option for the treatment of PRCA, but success rates are lower than those seen for AIHA or ITP.[58]

Richter syndrome:

Richter transformation (RT) of CLL into an aggressive DLBCL occurs in 1-5% of patients with CLL. RT is associated with a dismal prognosis with PFS <25% with CHOP-based chemoimmunotherapy and median survival 6-12 months.[63-66] Given these poor outcomes, consolidation with allogeneic HCT should be considered for eligible patients with responding disease who have relapsed RT or other high-risk features, such as previous therapy for CLL, failure to achieve a complete response to R-CHOP, TP53 aberrations, or clonally related RT.[66-69] Although <10% of all patients with RT will ever undergo allogeneic HCT, this may represent a curative therapy for selected cases with 3-year PFS 43%, OS 52%, relapse incidence 30%, and NRM 27% in a CIBMTR study of 118 allogeneic HCT recipients.[70] Outcomes were best for patients in complete response (3-year PFS 66%) or partial response (3-year PFS 43%) at the time of HCT compared to those with resistant disease (3-year PFS 5%). The majority of patients with RT receive reduced intensity conditioning, which has been associated with similar to improved outcomes in this setting compared to myeloablative conditioning.[70,71]

Importantly, patients with RT arising from treatment naïve CLL appear to have comparatively better outcomes with R-CHOP and may not require allogeneic HCT.[65,66] In an Alberta study of 99 patients with RT, those with treatment naïve CLL had higher response rates to first line

chemoimmunotherapy (71% versus 40%) and superior 2-year OS (51% versus 28%) compared to those with previously treated CLL. Nevertheless, 2-year OS remained suboptimal at 53% for the 13 patients ≤70 years old with RT and treatment naïve CLL, which suggests there may be a role to consider consolidation with autologous HCT for these patients, similarly as other high risk aggressive lymphomas. Although data is lacking on the outcomes of autologous HCT as part of first-line therapy for RT, a CIBMTR study of 53 patients undergoing autologous HCT for predominantly relapsed RT reported 3-year PFS 48%, OS 52%, and relapse incidence 37%.[70] In an EBMT study of 34 patients who underwent autologous HCT, only 11 of 17 relapses were related to RT (the remainder were due to CLL), suggesting autologous HCT may eradicate the RT component in many patients even though the underlying CLL may persist.[71] It should be noted that even if allogeneic HCT may not be required as a part of primary therapy for patients with lower-risk RT, a referral for transplant consultation and HLA typing is suggested at diagnosis in all patients who are potentially eligible for allogenic HCT by age and/or comorbidities, given the significant risk of relapse/refractory disease with RT.

Less commonly, patients with CLL may develop a Hodgkin lymphoma variant of RT which is often clonally unrelated to the CLL. Available evidence suggests that Hodgkin-variant RT has similar outcomes with standard chemotherapy as de novo Hodgkin lymphoma in this age group.[72,73] As such, there is not an established role for consolidation with HCT in these cases.[69]

Tumour lysis syndrome:

Tumour lysis syndrome occurs when the release of large amounts of intracellular components of lysed malignant cells leads to a number of metabolic imbalances. Resulting hyperuricemia, hyperkalemia, and hyperphosphatemia may then lead to renal failure and cardiac arrhythmias. Tumour lysis syndrome usually occurs within two or three days after the initiation of therapy, with rare cases occurring after second-line treatment. Major risk factors include high tumour burden, high rate of proliferation, and disease that is highly responsive to therapy.[74]

Before the initiation of treatment with anti-CD20 mAb, patients with a white blood cell (WBC) count higher than 50,000/mm^3 should be adequately hydrated and monitored frequently. In outpatients, frequent monitoring of serum electrolytes and uric acid is recommended as a preventative measure.[74] Prophylactic allopurinol (300 mg/day orally) is necessary when a rapid lysis of large numbers of lymphocytes is anticipated (initial WBC count >200 x 10^9/L). Allopurinol can also be considered for patients with significant renal dysfunction or chronic hyperuricemia. In the advent of TLS, it may be necessary to interrupt treatment until symptoms are resolved. Rasburicase may also be considered for the treatment of TLS. Consideration may be given to dividing the dose of intravenous rituximab over two days for the first infusion.

Specific TLS prophylaxis recommendations exist for venetoclax as the agent has been associated with fatal TLS cases in early phase studies. A slow dose-escalation over 5 weeks is also required for all patients initiating venetoclax therapy to prevent TLS events.[75,76]

Blood product support:

Transfusion-related graft-versus-host disease has been described in patients actively receiving fludarabine, bendamustine or alemtuzumab. Thus, patients treated with fludarabine, bendamustine or alemtuzumab should receive irradiated blood products.

Appendix A

Table A: Risk of HBV reactivation with immunosuppression and chemotherapy in HBsAg-positive and HBsAg-negative/anti-HBc-positive patients.

Risk group and HBV serology	Immunosuppressive or chemotherapy
High-risk group (>10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (high risk regardless of anti-HBs titre levels)	• B-cell depleting agents such as rituximab and obinutuzumab
HBsAg positive	• Anthracycline derivatives such as doxorubicin and epirubicin • Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10-20 mg/day)
Moderate-risk group (1%-10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab • Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib, acalabrutinib, zanubrutinib
HBsAg positive	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day)
HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10-20 mg/day) • Anthracycline derivatives: doxorubicin
Low-risk group (<1%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • Intra-articular corticosteroids • Corticosteroid therapy for ≤ 1 week
HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day)

Adapted from Coffin, Carla S., et al. [4]

Anti-HBc = antibody to HBV core; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; TNF = tumour necrosing factor.

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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2010.

Maintenance

A formal review of the guideline will be conducted in 2026. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

CIRS, Cumulative Illness Rating Scale; CLL, Chronic lymphocytic leukemia; CR, Complete response; CrCl, Creatinine clearance; DAT, Direct antiglobulin test; DLBCL, Diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FC, Fludarabine + cyclophosphamide; FCR, Fludarabine + cyclophosphamide + rituximab; FISH, Fluorescence in situ hybridization; FR Fludarabine + rituximab; HR, Hazard ratio, IgG, Immunoglobulin G; IgVH, Immunoglobulin heavy chain variable regions; ITP, Idiopathic thrombocytopenia purpura; IV, Intravenous; MBL, monoclonal B-cell lymphocytosis; ORR, Overall response rate; OS, Overall survival; PC, Pentostatin + cyclophosphamide; PCR, Pentostatin + cyclophosphamide + rituximab; PD, Progressive disease; PFS, Progression-free survival; PPV, pneumococcal polysaccharide vaccine; PR, partial response; PRCA, pure red cell aplasia; R-CHOP, Rituximab + cyclophosphamide + adriamycin + vinscristine + prednisone; R-FCM, Rituximab + fludarabine + cyclophosphamide + mitoxantrone; SD, Stable disease; SLL, Small lymphocytic lymphoma; TK, Thymidine kinase; WBC, White blood cell.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Dr. Carolyn Owen reports other from Roche, other from AbbVie, other from Astrazeneca, other from Janssen, other from Merck, other from Servier, other from Incyte, other from Beigene.

Dr. Anthea Peters reports other from Gilead, other from Janssen, other from Abbvie, other from Roche, other from Seattle Genetics, other from Astra Zenica, other from Lundbeck, other from Celgene, other from Incyte, during the conduct of the study.

Dr. Robert Puckrin reports honoraria from Beigene and Kite.

Dr. Mona Shafey reports honoraria from Abbvie, Astra-Zeneca, Beigene, and Janssen.

Derek Tilley has nothing to disclose.

Citation

Owen C (lead), Peters A, Puckrin R, Shafey M, Tilley D. Cancer Care Alberta, Alberta Health Services (2022). Clinical Practice Guideline on [CLL, Version 11]. Accessed [Month, Year].