

Chronic Lymphocytic Leukemia

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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 lymphomas¹. 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 women². 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 2021 update, the update was based on a consensus meeting held in 2021. 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

The following guidelines apply to adults over 18 years of age. Different principles apply to pediatric patients.

Recommendations

Diagnosis and Prognosis

1. The initial diagnosis of CLL relies on the detection of a circulating B-lymphocyte count *greater than or equal to* $5 \times 10^9 /L$ in the peripheral blood, for the duration of at least 3 months associated with a characteristic flow cytometry immunophenotype profile including dimCD20/CD19/CD5/CD23/CD43/CD200 positivity and cyclin D1 negativity. 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* $5 \times 10^9/L$. As SLL is a rare subtype of CLL/SLL, this entity is only infrequently included in CLL clinical trials. However, 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 subtypes). The diagnostic term “monoclonal B-cell lymphocytosis” (MBL) is used to characterise individuals with a circulating population of clonal B-cells, a total clonal B-cell count of $<5 \times 10^9/L$, and no other features of a B-cell lymphoproliferative disorder. Flow reporting now takes into account high-count and low-count CD5+ MBL (cut-off $<0.5 \times 10^9/L$) with an understanding that only MBL $>0.5 \times 10^9/L$ is clinically relevant³.
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. IgVH mutation testing should be performed at the time when patients require treatment if the result will impact on the treatment selection. 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 chemo/immunotherapy. 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 (e.g. rituximab) should receive prophylactic therapy with entecavir or tenofovir. Those who are HBsAg negative/anti-HBc positive and fall under low or moderate risk as per Table 1 do not require prophylaxis and should undergo serial HBV DNA testing q6-12 months and serial ALT testing q3 months while on immunosuppressive therapy (see Figure 1). Hepatitis B prophylactic therapy should be continued for at least 6 months following the completion of immunosuppressive therapy, except for those treated with anti-CD20 agents who should continue for at least 12-18 months due to the lag in B-cell function recovery. ⁴⁻⁸

Table 1: 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)	<ul style="list-style-type: none"> B-cell depleting agents such as rituximab and obinutuzumab
HBsAg positive	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib
HBsAg positive	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent $> 10-20$ mg/day) Anthracycline derivatives: doxorubicin and epirubicin
Low-risk group (<1%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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.

First-Line Treatment Options

1. The majority of patients with early-stage CLL are managed initially with watchful waiting. 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, indefinite Bruton's tyrosine kinase (BTK) inhibitors are the preferred treatment choice for these patients.
3. Patients with unmutated IgHV have inferior outcomes compared to patients with mutated IgHV when treated with chemo-immunotherapy (CIT), making novel agents the preferred firstline treatment for these patients. Given the lack of head-to-head comparison of indefinite BTKi over venetoclax-obinutuzumab (VO) in this population, we favour finite therapy with VO for reasons of cost. Given the lack of data in young, fit patients with VO and the overall survival (OS) advantage with BTKi compared to CIT, younger (< 70 years), fit patients with unmutated IGVH should receive BTKi monotherapy as firstline treatment. Patients in whom VO therapy cannot be safely administered (ex. those who reside a long distance from a regional or tertiary cancer centre where TLS monitoring can be performed) should receive BTKi inhibitor therapy.
4. 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 and is, thus, recommended. VO is the preferred regimen for patients who are not appropriate for FCR. Other chemo-immunotherapy regimens have demonstrated efficacy in older or less fit patients including bendamustine + rituximab (BR), fludarabine + rituximab (FR) or chlorambucil + obinutuzumab (CLB-Ob) and remain as options for patients with good risk CLL who are not appropriate for VO.

Second and Subsequent Line Treatment Options

1. Venetoclax in combination with rituximab 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.
2. BTKi monotherapy leads to lengthy remissions in patients with relapsed/refractory CLL and is another high effective option for secondline therapy.
3. 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 for new start of BTKi. There is no data currently to support switching patients from ibrutinib to second generation BTKi in patients with good disease control and acceptable tolerability.
4. Venetoclax, a BCL2-inhibitor, as indefinite monotherapy, has demonstrated efficacy in patients who fail or are intolerant to BCR-inhibitors (ibrutinib or idelalisib + rituximab). Patients who progress on BTKi have a poor prognosis and should receive indefinite venetoclax therapy and/or

contemplation of clinical trials and/or allo 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 toxicity and is rarely used in Alberta.
6. Chemoimmunotherapy (ex bendamustine and rituximab) may be considered in patients who have failed 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 70 years of age, require treatment and, have progressed on a targeted therapy 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 infiltrates¹. According to the 2008 International Workshop on CLL (IWCLL) guidelines, the diagnosis of CLL requires a circulating B-lymphocyte count *greater than or equal to* 5×10^9 /L in the peripheral blood, for the duration of at least 3 months⁹. 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* $5 \times 10^9/L$.¹

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 $5 \times 10^9/L$) of circulating monoclonal B-cells that are phenotypically identical to CLL cells, but with no evidence of tissue infiltration⁴. High count MBL progresses to CLL at a rate of one to two percent of patients per year^{10, 11}.

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 expression¹.

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 tests¹²⁻¹⁴.

Table 2. Rai and Modified Rai Classification System for CLL^{12, 13}

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 3. Binet Classification System for CLL¹⁴

Stage	Description	Median Survival (years)
A	Hemoglobin \geq 100 g/L and platelets \geq 100 x 10 ⁹ /L and <3 involved nodal areas	> 10
B	Hemoglobin \geq 100 g/L and platelets \geq 100 x 10 ⁹ /L and \geq 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: Interphase fluorescence in situ hybridization (FISH) can be used to identify cytogenetic abnormalities in more than 80 percent of patients. The most common abnormalities include:

- del(13q) in 14 to 40% of patients
- deletions and/or trisomy in chromosome 12 in 11 to 18% of patients
- del(11q) in 10 to 32% of patients
- del(6q) in 2 to 9% of patients
- del(17p) in 3 to 27% of patients⁵

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.¹⁵ Del(17p) leads to loss of the p53 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).¹⁶ (However, such testing is not yet routinely available in Canada). 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)¹⁷ or BCL-2 inhibitors^{10, 18}. 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^{10, 15}. Patients with unmutated CLL exhibit faster disease progression, atypical peripheral blood cell morphology, adverse cytogenetic features, and clonal evolution.¹⁵ The VH3.21 gene is also an unfavourable prognostic marker, regardless of IgHV mutational status.¹⁰ Given data from FCR studies showing a plateau in the PFS curve with a large proportion of patients with mutated IgHV showing no progression more than 10 years following FCR¹⁹, IgVH mutational status should be performed in all patients in whom FCR therapy could be considered. BTK inhibitors appears to be equally efficacious in patients with mutated and unmutated IgHV and have demonstrated an overall survival advantage in younger (<70 years) patients with unmutated IgHV. No survival advantage has been reported in older patients such that the value of routine testing of IgHV in older patients not yet established.

Serum markers: Serum markers such as CD23, thymidine kinase (TK), and β 2-microglobulin (β 2M) may predict overall or progression-free survival (PFS)¹⁰. 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 β 2M are easily available at most Canadian centres and correlate with both clinical stage and overall survival.¹⁵

The value of prognostic markers in elderly patients is questionable with evidence suggesting that most of the reported prognostic factors are not relevant to the elderly CLL population.²⁰

IV. Patient Fitness and Response Assessments

Assessing patient fitness: Patient fitness and co-morbidities should be considered in treatment decisions to determine whether aggressive treatments can be tolerated. Several scales exist for determining patient fitness, two of the most common being the Eastern Cooperative Oncology Group (ECOG) Performance Status and the Cumulative Illness Rating Scale (CIRS), both of which can be found in Appendix A.^{21, 22} The CIRS assesses co-morbidities in different organ systems by assigning points to various conditions. The physician tabulates the number of points in a variety of body systems, with a low score indicating optimal health.²³ The CIRS has been used in combination with creatinine clearance (CrCl) by the German CLL Study Group to assess patient fitness for eligibility in phase III studies.²³

Once a fitness score has been determined, it is possible to group patients into a *fit* or *frail* group:

- Fit Group
 - ECOG Performance Status 0-2, or
 - CIRS \leq 6 and CrCl \geq 70 mL/min
- Frail Group
 - ECOG Performance Status 3–4, or
 - CIRS $>$ 6 or CrCl $<$ 70 mL/min

Initiating treatment: The IWCLL guidelines describe the initiation of treatment based on a combination of clinical staging, the presence of symptoms, and disease activity⁵. 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.^{10, 24} Patients in remission should be re-evaluated every three to six months to monitor disease status.^{25, 26} Based on the results of the assessment, patients may be categorized as having a complete response (CR), a partial response (PR), progressive disease (PD), or stable disease (SD), as outlined in Table 3. The IWCLL response criteria require an assessment of response no earlier than 2 months after completion of therapy.¹⁰ Patients with a clinically beneficial response include those achieving CR and PR; treatment failure includes those with SD, non-response, PD, or death from any cause. Patients experiencing treatment failure during or within six months of treatment are identified as having refractory disease. Those demonstrating PD more than six months after treatment has ended, who have previously achieved a CR or PR, are identified as having relapsed disease⁵.

Table 4. Criteria for Identifying Treatment Response¹⁰

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%
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. For some frail patients, less aggressive treatments may be required; for others, supportive or palliative treatment may be the best course.²⁷ Consideration of the patient's preference is always important in the determination of any treatment decision.

Chlorambucil

Chlorambucil (CLB) has been used as a frequent treatment for CLL for over 40 years. Many different dosing schedules have been used in CLL, including intermittent dosing from 40 mg/m² every 28 days to 10 mg/m² x 7 days every 28 days, 0.5-0.8 mg/kg q14days or continuous daily dosing of 0.1 mg/kg/day. A convenient oral dosing and well-established side effect profile make CLB a valuable option for frail patients or for those who decline or are unsuitable for more intensive intravenous therapy.²⁸⁻³¹ Given PFS and OS advantages of anti-CD20 monoclonal antibodies (mAbs), even in older frailer patients, and data for an OS advantage of ibrutinib monotherapy over CLB monotherapy, the use of CLB monotherapy should now be restricted to a small minority of very frail patients.

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.

Chlorambucil-obinutuzumab

The GCLLSG CLL11 defined chlorambucil + Obinutuzumab (CLB-O) as the preferred CIT for older and unfit patients.³² The median age of the population was 73, CIRS score was 8 and median GFR was 63 mL/min. CLB-O conferred an overall survival benefit over CLB monotherapy (HR 0.41, $p = 0.002$). Toxicities were similar with the chemoimmunotherapy groups with an increase in infusion-related reactions (IRRs) in the CLB-O-treated patients, with IRRs typically occurring only with Cycle 1. The use of obinutuzumab also improved PFS over rituximab and a larger improvement in OS over CLB monotherapy compared to CLB-R. CLB-O remains an effective therapy for elderly and unfit patients who are being considered for CIT.

Bendamustine-rituximab

The phase III GCLLSG CLL10 trial compared BR to FCR in young, fit CLL patients. With a median follow-up of 37.1 months, there was no OS difference between treatment groups ($p=0.897$). Median PFS was 41.7 months (95%CI: 34.9-45.3) with BR and 55.2 months (95%CI no evaluable) with FCR (HR: 1.643, 90.4%CI: 1.308-2.064). The upper limit of the 90.4% CI was greater than 1.388, therefore, the null hypothesis for the corresponding non-inferiority hypothesis was not rejected. Severe neutropenia and infections were more frequently observed with FCR group compared to the BR group (235(84%) vs. 164(59%), and 109(39%) vs. 69(25%), respectively). These observations were more pronounced in the >65 years population of the study³³ so this remains a therapeutic option for patients >65 years who are considered for chemo-immunotherapy (CIT).

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.³⁴ 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. After a median follow-up of 28.1 months, 30 events (disease progression or death) occurred in the venetoclax-obinutuzumab arm compared to 77 in the chlorambucil-obinutuzumab group (HR: 0.35; 95%CI: 0.23-0.53; $p<0.001$). In the venetoclax-obinutuzumab arm, grade 3 or 4 neutropenias occurred in 52.8% (compared to 48.1% in the chlorambucil-obinutuzumab arm), grade 3 or 4 infections occurred in 17.5% (compared to 15.0%) and all-cause mortality occurred in 9.3% (compared to 7.9%); however, none of these differences were significant.

Follow-up data after a median 39.6 months³⁵ 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.

Ibrutinib

The open-label, phase III RESONATE-2 trial³⁶ 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.³⁶ After a median follow-up period of 18.4 months, ibrutinib resulted in significantly longer PFS than chlorambucil (median not reached vs. 18.9 months). 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.

Four 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.³⁷ 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 iLLUMINATE study compared previously untreated CLL patients who were older and/or unfit patients or high risk patients.³⁸ The iLLUMINATE study had several differences compared to the Alliance study in that ibrutinib was combined with obinutuzumab with no ibrutinib monotherapy arm and the chemo-immunotherapy comparator was CLB-O. The study also showed an improvement in PFS of ibrutinib-O compared to CLB-O (79% [95% CI 70-85] versus 31% [23%-40%]) but no difference in OS. The iLLUMINATE trial selected a higher risk population of patients with a large proportion of patients with *TP53* aberrations (20% in the CLB-O arm) which led to a shorter PFS than would normally be expected with CLB-O. Toxicities of ibrutinib in this population of patients with more comorbidities was very high with 9% of deaths in the ibrutinib arm occurring secondary to adverse events (most related to cardiac events). Although one cannot compare outcomes between studies, it is not clear that the obinutuzumab added additional value to the ibrutinib 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.³⁹ 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 difference was demonstrated in PFS in the subgroup of patients with mutated IgHV. 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 patients⁴⁴.

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 trial⁴⁰ randomized (1:1:1) treatment-naive CLL patients to receive acalabrutinib-obinutuzumab, acalabrutinib monotherapy, or obinutuzumab-chlorambucil. Eligible patients (N=675) were >65 years, or 18-65 years with creatinine clearance of 30-69 mL/min or CIRS for Geriatrics score greater than 6. After a median follow-up of 28.3 months, median PFS was longer with acalabrutinib-obinutuzumab and acalabrutinib monotherapy compared with obinutuzumab-chlorambucil (median not reached, median not reached, and 22.6 months, respectively). HR: 0.10; 95%CI: 0.06-0.17; p<0.001 for acalabrutinib-obinutuzumab vs. obinutuzumab-chlorambucil; and HR: 0.20; 95%CI: 0.13-0.30; p<0.001 for acalabrutinib monotherapy vs. obinutuzumab-chlorambucil. Estimated PFS at 24 months was 93% for the acalabrutinib-obinutuzumab arm, 87% for the acalabrutinib monotherapy arm, and 47% for the obinutuzumab-chlorambucil arm. The most common grade 3 or higher adverse event across groups was neutropenia 30% in the acalabrutinib-obinutuzumab group, 9% in the acalabrutinib group, and 41% in the obinutuzumab-chlorambucil group).

Summary of frontline treatment approach in CLL:

These frontline CLL studies demonstrate that BTKi is highly effective therapy and leads to longer PFS compared to CIT in previously untreated CLL patients. Patients with high risk disease (del(17p) and TP53 mutation and/or unmutated IgHV) obtain relatively greater benefit from BTKi over CIT. VO also provides marked benefit over CIT in terms of PFS, but indefinite BTKi therapy has not been compared against finite duration VO. Because of the predicted exponential increase in cost of indefinite BTKi therapy, we favour VO in CLL patients without TP53 aberrations who are not appropriate for FCR. Given the lack of data in young, fit patients with VO and the OS advantage with BTKi, younger (< 70 years), fit patients with unmutated IGHV should receive BTKi monotherapy as firstline treatment.

BTKi for Patients with del(17p) and/or TP53 mutation

Patients with TP53 aberrations were included in several of the novel therapy vs CIT studies (Alliance, iLLUMINATE, ELEVATE-TN and CLL14). Outcomes in patients with TP53 aberrations were inferior to those with intact TP53 in the CLL14 study patients who received VO while outcomes are not notably different in TP53 aberrant vs intact for the BTKi studies making indefinite BTKi the treatment of choice for patients with del(17p) and/or TP53 mutation.⁴¹

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.

The MURANO study was a phase 3 study comparing venetoclax- rituximab (VenR) with BR in relapsed/refractory CLL. After a median follow-up of 3 years, PFS and OS were found to be superior in the VenR group compared to the BR group (HR, 0.16 [95% CI, 0.12 to 0.23]; and HR, 0.50 [95% CI, 0.30 to 0.85], respectively).⁴² VenR patients reached a higher rate of peripheral blood (PB) undetectable minimal residual disease (uMRD) at the end of combination therapy (62% vs 13%), which prognosticated a longer PFS. These results were seen across all subgroups, and validate the previously reported MURANO study findings.⁴³ Follow-up data has demonstrated superior 4-year PFS and OS rates for VenR compared to BR.⁴⁴ The 4-year PFS was 57.3% vs. 4.6% (HR: 0.19; 95%CI: 0.14-0.25) for VenR vs. BR, and 4-year OS was 85.3% vs 66.8% (HR: 0.41; 95%CI: 0.26-0.65), respectively. Further updated 5-year survival data was presented at the ETA 2021 conference, and reported OS of 82.1% in the VenR arm compared to 62.2% in the in the BR arm.⁴⁵

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. At a median follow-up of 9.4 months, ibrutinib significantly improved progression free survival (median duration was not reached in the ibrutinib group; progression-free survival of 88% at 6 months) and overall survival at 12 months was 90% in the ibrutinib group compared to 81% in the ofatumumab group (hazard ratio: 0.43; 95%CI 0.24 to 0.79; $p=0.005$). Patients with del(17p) responded similarly to those without.⁴⁶

Acalabrutinib

The phase III ASCEND trial⁴⁷ 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).⁴⁸ 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 study⁴⁹ randomized (1:1) N=415 relapse/refractory CLL patients to either zanubrutinib or ibrutinib. The primary endpoint of overall response rate was higher with zanubrutinib vs. ibrutinib (78.3% vs. 62.5%, $p < 0.001$). The 12 month PFS (94.9% vs. 84.0%) and OS (97.0% vs. 92.7%) were also superior with zanubrutinib. Rates of adverse events were lower for zanubrutinib vs. ibrutinib: atrial fibrillation (2.5% vs. 10.1%), major bleeding (2.9% vs. 3.9%), adverse events leading to discontinuation (7.8% vs. 13.0%) or death (3.9% vs. 5.8%). Rates of neutropenia were higher with zanubrutinib (24.8% vs. 21.7%).

The ELEVATE-RR and ALPINE studies confirm that second generation BTKi are better tolerated than 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. Small studies have also reported acceptable tolerability with acalabrutinib in patients who have previously discontinued ibrutinib due to toxicity.^{50, 51} However, there is no data to suggest improved outcomes from switching patients who are currently being treated with ibrutinib with good tolerability.

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. Amongst (n=220) patients, median progression-free survival was 5.5 months in the placebo arm and was not reached in the idelalisib + R arm (HR: 0.15; $p < 0.001$). 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 arm⁵² 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%.^{46, 53, 54} This therapy is rarely used in Canada due to high rates of toxicity and treatment discontinuations.

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, 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. Although there is less data for BTKi treatment following VenR failure, small series have reported reasonable response rates⁵⁵ in this setting and there is no biological rationale that BTKi should not provide benefit after venetoclax failure. Idelalisib + rituximab has limited role given a lack of efficacy in patients who have failed BTKi and the availability of multiple BTKi options now.

Venetoclax monotherapy:

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 venetoclax (20mg stepwise dose ramp-up to 400mg over 5 weeks).⁵⁶ After a median follow-up of 12 months, 59 of 91 (65%, 95% CI 53-74) patients had an overall response. The most common treatment-emergent grade 3 or 4 adverse events were neutropenia (51% of patients), thrombocytopenia (29% of patients), anemia (29% of patients), decreased white blood cell count (19% of patients), and decreased lymphocyte count (15% of patients). 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).⁵⁶ Estimated 12-month progression free survival was 79%, with 2 patients achieving complete remission. Based on these data, venetoclax is recommended in patients who fail or are intolerant or inappropriate for BCRi.

Allogeneic stem cell transplantation:

Allogeneic stem cell transplantation may be considered for fit patients younger than 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 pneumococcal polysaccharide (PPV) every five years for patients not yet treated or in remission for more than three months is recommended.^{57, 58} 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 5. 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	Valgancyclovir pre-emptive therapy for increased PCR	n/a	CMV monitoring by PCR every 1–2 weeks
Fludarabine, rituximab, obinutuzumab, BTKi	Hepatitis B	Lamivudine 100 mg/day orally for the entire duration of chemotherapy and 6 months afterwards Or entecavir 0.5mg po daily	n/a	Avoid in patients with known prior hepatitis B
Alemtuzumab	Varicella Zoster	Acyclovir or equivalent	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	
Ibrutinib or idelalisib + rituximab	Community-acquired pneumonia or Pneumocystis jirovecii pneumonia	Septra is required for PJP prophylaxis with idelalisib		CMV monitoring

When infections occur, they should be diagnosed, treated, and reported. The etiology of any infection should be identified as bacterial, viral, or fungal, and the severity should be quantified as:

- Minor: requiring either oral antimicrobial therapy or symptomatic care alone
- Major: requiring hospitalization and systemic antimicrobial therapy
- Fatal: death as a result of the infection

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.⁵⁹

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.⁶⁰ 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).⁶¹

ITP is less common, occurring in two to three percent of CLL patients at diagnosis or during early stage disease.⁶⁰ ITP can be identified where platelet counts are less than or equal to $100 \times 10^9/L$ with no evidence of hypersplenism, no evidence of increased platelet consumption due to other causes, and normal or increased megakaryocytes on bone marrow examination.⁶² PRCA is present in six percent of CLL patients that are tested.⁶⁰ 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.⁶³

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. The incidence of treatment-induced AIHA appears low with combination chemoimmunotherapy with FCR or BR so these regimens remain good options. Alternatively, RCD (rituximab, cyclophosphamide and decadron) appears to have good response rates for control of refractory AIHA and as a CLL-therapy.^{64, 65} Second-line options for AIHA include splenectomy and intravenous immunoglobulins. Good responses have also been obtained using rituximab and BTKi⁵. 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.^{61, 62} Rituximab may be an additional option for the treatment of PRCA, but success rates are lower than those seen for AIHA or ITP.⁶¹

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.⁶⁶⁻⁶⁹ 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.⁶⁹⁻⁷² 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.⁷³ 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.^{73, 74}

Importantly, patients with RT arising from treatment naïve CLL appear to have comparatively better outcomes with R-CHOP and may not require allogeneic HCT.^{68, 69} 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%.⁷³ 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.⁷⁴ 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 allogeneic 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.^{75, 76} As such, there is not an established role for consolidation with HCT in these cases.⁷²

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.⁷⁷

Before the initiation of treatment with anti-CD20 mAb, patients with a white blood cell (WBC) count higher than 50,000/mm³ should be adequately hydrated and monitored frequently. Where overt uremic symptoms are present, dialysis may be necessary in order to prevent acute renal failure. In outpatients, frequent monitoring of serum electrolytes and uric acid is recommended as a preventative measure.⁷⁷ Prophylactic allopurinol (300 mg/day orally) is necessary when a rapid lysis

of large numbers of lymphocytes is anticipated (initial WBC count $>200 \times 10^9/L$). 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. Cardiac activity should be monitored continuously, and frequent monitoring of electrolyte levels is recommended⁷². Rasburicase may also be considered for the treatment of TLS. Close monitoring for tumour lysis syndrome is recommended for patients with lymphocytosis greater than $30 \times 10^9/L$ who are receiving a first cycle of rituximab. Consideration may be given to dividing the dose 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.^{78, 79}

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.

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Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Categories⁸⁰

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

Appendix B: Comorbidities

Systems	Scores				
	0	1	2	3	4
Cardiac					
Vascular					
Hematological					
Respiratory					
Ophthalmological and ORL					
Upper Gastrointestinal					
Lower Gastrointestinal					
Hepatic and Pancreatic					
Renal					
Genitourinary					
Musculoskeletal and Tegumental					
Neurological					
Endocrine, Metabolic, Breast					
Psychiatric					
Total Score*					

* Only one score is given to each system; total score is the sum of all the scores.

CIRS Severity Rating

0	no problem affecting that system
1	current mild problem or past significant problem
2	moderate disability or morbidity and/or require first-line therapy
3	severe problem and/or constant and significant disability and/or hard to control chronic problems
4	extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment

Medical Problems by System

Cardiac:

- Any cardiac problem (i.e. angina, myocardial infarction, arrhythmia, valve problems)?
- If affirmative, any medications taken for these problems?
- Any heart surgery in the past?

Vascular:

- Any circulatory problem (i.e. peripheral atherosclerotic disease, aneurysm of the abdominal aorta), hypertension, or cholesterol problem?
- If affirmative, any medications taken for these problems?
- Any vascular surgery in the past (i.e. bypass graft surgery of lower limbs, carotid endarterectomy)?

Hematological:

- Any blood problem (i.e. anemia, leukemia, hypercoagulability or any other problem affecting the blood, blood cells, spleen, or lymphatic system)?
- If affirmative, any medications taken for these problems (i.e. iron)?
- *Note:* patients taking anticoagulants belong to this system if the main problem is of hypercoagulability (i.e. thrombosis or recurrent embolism). If anticoagulants were taken for arrhythmias, rate the problem in “Cardiac”.

Respiratory:

- Any respiratory problem (i.e. asthma, emphysema, bronchitis, pulmonary embolism)?
- If affirmative, any medications taken for these problems? Pressurized aerosols?
- Any lung surgery?
- Cigarette smoking: how many packs per day? For how long?
 - Pack years = number of packs/day x number of years smoked
 - Smoker up to 20 pack-years = rated 1
 - Smoker from 21 to 40 pack-years = rated 2
 - Smoker over 40 pack-years = rated 3

Ophthalmological and Otorhinolaryngology:

- Any problem with eyes (i.e., glaucoma, cataract, vision loss), ears (i.e. important hearing impairment), nose, throat, voice?
- Any medications taken for these problems? Eye drops?
- *Note:* vertigo and dizziness are included in this section, unless they are of neurological origin.

Upper Gastrointestinal:

- Any problems with stomach or digestion (includes esophagus, stomach, and duodenum)?
- If affirmative, any medication taken?
- Surgery for the stomach or esophagus?

Lower Gastrointestinal:

- Any intestinal problems (i.e. intestinal hernias, constipation, anal problems, incontinence)?
- If affirmative, any medications taken?
- Surgery for the abdomen?

Hepatic and Pancreatic:

- Any problem in the liver or the pancreas?
- Any medications taken for these problems?
- Surgery for the liver or the pancreas (i.e. cholecystectomy)?

Renal:

- Any problems in the kidneys (i.e. impairment in function, infection)?
- If affirmative, any medications taken for these problems?
- Surgery for the kidneys?

Genitourinary:

- Any urinary problems (i.e. lithiasis, incontinence)?
- If affirmative, any medications taken for these problems?
- Any surgery for the urinary bladder or for renal lithiasis?

Musculoskeletal and Tegumental:

- Any problem in the skin, joints, bones, or muscles (i.e. arthrosis, osteoporosis, carpal tunnel, any other skin or musculoskeletal problem)?
- *Note:* Fibromyalgia is rated in this section; it may also be rated in “Psychiatric” if necessary.
- Any medication or anti-inflammatory drugs? Infiltrations? Creams prescribed by a doctor?

Neurological:

- Any neurological problem (i.e. cerebrovascular accident, peripheral neuropathy, headaches)?
- If affirmative, any medications taken for these problems?
- Surgery for these problems?

Endocrine, Metabolic, Breast:

- Any problem of the thyroid gland, obesity, diabetes, or any other hormonal problem?
- For obesity body Mass Index (BMI) ≥ 30 = rated 1; BMI ≥ 30 + medication or moderate disability = rated 2; BMI ≥ 45 = rated 3
- Any medication taken for these problems?
- Any surgery for these problems?
- Menopause or andropause in men? Any hormones?
 - Menopause/ andropause without hormone therapy or symptoms = rated 0
 - Menopause/ andropause with hormone therapy or symptoms = rated 1

Psychiatric:

- Any problem of depression, anxiety, alcohol, drug abuse, or other problems?
- If affirmative, any medications taken for these problems?
- *Note:* personality problems are rated in this section, but the patient’s chart should be checked.

Appendix C: Regimens

Relevant Regimens

Chlorambucil:

- 40 mg/m² every 28 days, or
- 10mg/m² days 1-7, every 28 days, or
- 0.1 - 0.2 mg/kg/day for 4-8 weeks, then usually reduce for maintenance.

Fludarabine:

- 25mg/m² IV days 1-5, every 28 days, or
- 40mg/m² PO days 1-5, every 28 days (round down to nearest multiple of 10mg)

Fludarabine + Cyclophosphamide (FC):

- Fludarabine 25 mg/m² IV, days 1–3
- Cyclophosphamide 250 mg/m², days 1–3
- Cycles: every 28 days

Fludarabine + Rituximab (FR):

- Fludarabine 40mg/m² PO days 1-5, every 28 days (round down to nearest multiple of 10mg)
- Rituximab 375 mg/m² day 0 of cycle 1, then 500 mg/m² day 1 for cycles 2-6
- Cycles: every 28 days

Fludarabine + Cyclophosphamide + Rituximab (FCR):

- Fludarabine 25 mg/m² IV days 1-3
- Cyclophosphamide 250 mg/m², days 1-3
- Rituximab 375 mg/m² day 0 of cycle 1, then 500 mg/m² day 1 for cycles 2-6
- Cycles: every 28 days

Fludarabine + Cyclophosphamide + Rituximab (FCR PO alternative):

- Fludarabine 32 mg/m² PO, days 1-5 (round down to nearest multiple of 10mg tablet)
- Cyclophosphamide 600 mg/m² IV, day 1
- Rituximab 375 mg/m² IV day 0 of cycle 1, then 500 mg/m² day 1 for cycles 2-6
- Cycles: every 28 days

Alemtuzumab (for patients with del17p):

- Dose-escalation phase: escalated daily (3, 10, 30 mg) until tolerated at an IV dose of 30 mg over 2 hours
- Subsequently, 30 mg IV three times/ week for no more than 12 weeks, including the dose-escalation phase.

Fludarabine and Alemtuzumab (for relapsed CLL):

- Fludarabine 30mg/m² IV days 1-3
- Alemtuzumab: dose-escalation phase: escalated daily (3, 10, 30 mg) until tolerated at an IV dose of 30 mg over 2 hours. Subsequently, 30mg IV days 1-3

Allogeneic Stem Cell Transplantation:

- May also be considered for patients who are younger than 65 years of age, have not responded to therapy, have progressive disease within one year of fludarabine treatment or

within two years of fludarabine-based combination treatment, or with del(17p) abnormalities requiring treatment.

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 2023. 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 + vincristine + 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.

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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.

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Derek Tilley has nothing to disclose.

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