CHRONIC LYMPHOCYTIC LEUKEMIA

Effective Date: June, 2018
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.

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.

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
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. 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. In determining the optimal treatment for CLL, individual patient characteristics including performance status and disease characteristics must be considered.

GUIDELINE QUESTIONS

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

DEVELOPMENT AND REVISION HISTORY

Portions of this guideline document were adapted, with permission, from recommendations developed by a steering committee consisting of hematologists from across Canada. This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. 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 May, 2010 and subsequently revised in 2013, 2014, 2015, 2017 and 2018.

SEARCH STRATEGY

No formal literature search was conducted for the 2017 update, the update was based on a consensus meeting held in 2016. 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 \(\text{dimCD20/CD19/CD5/CD23/CD43/CD200}^{+}\) positivity and cyclin D1 negativity. Small lymphocytic lymphoma 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 \(\text{does not exceed} 5 \times 10^9/L\). 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 \textit{high-count and low-count} \(\text{CD5}^{+}\) MBL (cut-off \(<0.5 \times 10^9/L\)) with an understanding that only MBL \(>0.5 \times 10^9/L\) is clinically relevant\(^3\).

2. FISH cytogenetic analysis for del(17p) and \(\text{TP53}\) 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).

First-Line Treatment Options:

4. 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).

5. Patient fitness and co-morbidities should be considered to determine whether aggressive treatments can be tolerated. In physically fit CLL patients who are able to tolerate more aggressive treatment, the combination of fludarabine + cyclophosphamide + rituximab (FCR) is recommended. The potential for toxicity of this regimen suggests that patients who have some comorbidities may benefit from less aggressive treatments such as bendamustine + rituximab (BR), fludarabine + rituximab (FR) or chlorambucil + obinutuzumab (CLB-Ob). A subgroup of younger patients with good risk features [mutated IgVH and lack of del(17p) or del(11q)] have a very long PFS following therapy with FCR with a plateau in the PFS curve. These patients should receive FCR whenever possible.

6. In frail patients with significant co-morbidities and competing causes of death, less toxic treatment options are warranted. In such cases, or if a patient declines intravenous treatment, oral chlorambucil is recommended as first choice. Whenever possible, all patients should receive an anti-CD20
monoclonal antibody with first line therapy based on evidence of a PFS and OS advantage when combined with chemotherapy.

7. Patients whose CLL possesses del(17p) usually do not respond to standard chemotherapy options for CLL. In such cases, ibrutinib is the preferred treatment choice.

8. Patients with unmutated IgVH have less durable responses to chemo-immunotherapy than patients with mutated IgVH. Whenever possible, patients with unmutated IgVH should be considered for clinical trials of novel agents.

**Second-Line Treatment Options:**

9. In fit patients, FCR is an effective regimen for rituximab naïve patients. Re-treatment with FCR is also an effective treatment option for patients experiencing a long remission (PFS more than three years) after initial FCR treatment. Because of the concern of second malignancy and/or prolonged cytopenias in patients retreated with fludarabine, BR is a reasonable re-treatment choice for patients who experience a long remission to first line chemo-immunotherapy.

10. High risk patients (those with PFS less than 3 years after chemoimmunotherapy) should be treated with one of the novel agents – ibrutinib or idelalisib + rituximab or considered for a clinical trial.

11. Relapsed patients who are deemed unfit for fludarabine or bendamustine-based therapy should be treated with ibrutinib or idelalisib + rituximab.

12. Venetoclax, a BCL2-inhibitor has efficacy in patients with del(17p) and is the treatment of choice in patients who fail or are intolerant to (or inappropriate for) BCR-inhibitors (ibrutinib or idelalisib + rituximab).

13. Patients who are intolerant to a BCR-inhibitor may respond to the alternate BCR-inhibitor or can be expected to respond to venetoclax.

14. Allogeneic stem cell transplantation (HSCT) should be considered for fit patients who are younger than 65 years of age and, have del(17p) and require treatment, 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 ibrutinib or idelalisib + rituximab; 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 and those with complex karyotypes by conventional cytogenetics.

**Follow-up and Supportive Care:**

15. 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 or FluCam) bendamustine-based therapy and for patients receiving idelalisib therapy. Patients treated with alemtuzumab should also be screened for CMV reactivation with weekly CMV PCR. 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.

13. 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. 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 x 10^9 /L in the peripheral blood, for the duration of at least 3 months. 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.

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. High count MBL progresses to CLL at a rate of one to two percent of patients per year.

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.

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.

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.
Table 1. Rai and Modified Rai Classification System for CLL\(^9,10\)

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

Table 2. Binet Classification System for CLL\(^11\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10(^9)/L and &lt;3 involved nodal areas</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥100 g/L and platelets ≥100 x 10(^9)/L and ≥3 involved nodal areas</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;100 g/L and or platelets &lt;100 x 10(^9)/L and any number of involved nodal areas</td>
<td>2.0-4.0</td>
</tr>
</tbody>
</table>

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 patients\(^7\)

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\(^12\). Patients with trisomy 12 have a treatment advantage over those with del(17p) or del(11q), as they tend to respond better to fludarabine-based therapy. In addition, patients with del(11q) appear to benefit from the addition of cyclophosphamide to fludarabine (FC), and do particularly well with FC plus rituximab (FCR)\(^13\). 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)\(^14\). (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 (ibrutinib and idelalisib + rituximab)\(^15\) or BCL-2 inhibitors \(^7,16\). FISH analysis for del(17p) and TP53 mutations testing is useful in the selection of patients with ultra-high risk disease who might benefit from allogeneic stem cell transplantation. Such patients are at high risk of treatment failure and are likely to become refractory to treatment or to relapse early after fludarabine-based therapy\(^17\). 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.

**IgVH 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 (IgVH) genes. Patients with mutated CLL have improved survival as compared to those with unmutated CLL. Patients with unmutated CLL exhibit faster disease progression, atypical peripheral blood cell morphology, adverse cytogenetic features, and clonal evolution. The VH3.21 gene is also an unfavourable prognostic marker, regardless of IgVH mutational status. Given data from FCR studies showing a plateau in the PFS curve with a large proportion of patients with mutated IgVH showing no progression more than 10 years following FCR, IgVH mutational status should be performed in all patients in whom FCR therapy could be considered (FCR would be favoured over BR in these patients).

**ZAP-70 and CD38 expression.** In the course of identifying surrogate markers for IgVH mutational status, a small number of genes were identified that allow the separation of mutated and unmutated CLL. The most specific of these genes is the one that encodes for a 70-kD zeta-associated protein (ZAP-70). The majority of mutated CLL cases are ZAP-70 negative (defined as ≤20% positive cells), whereas unmutated forms are more often ZAP-70 positive (defined as >20% positive cells). Discordance of ZAP-70 expression and IgVH mutational status is reported in about 25 percent of CLL patients. Positive ZAP-70 predicts more rapid disease progression and poorer survival. At present, ZAP-70 analysis is hampered by variation in technique, leading to inconsistent results across centres and testing is not routinely recommended.

CD38 is an ectoenzyme involved in transmembrane signaling and cell adhesion, and can correlate with unmutated IgVH status, predicting a poor prognosis. Though easy to perform through flow cytometric techniques, CD38 is discordant with IgVH mutational status in a significant proportion of cases and variability in results over time are drawbacks for its use. We do not recommend CD38 or ZAP70 testing.

**Serum markers.** Serum markers such as CD23, thymidine kinase (TK), and β2-microglobulin (β2M) may predict overall or progression-free survival (PFS). 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.

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.

**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. The CIRS assesses co-morbidities in different organ systems by assigning points to various conditions such as heart disease. The physician tabulates the number of points in a variety of body systems, with a low score indicating optimal health. 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.
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 ≤6 and CrCl ≥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 activity⁷. 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/staging⁷,24. Patients in remission should be re-evaluated every three to six months to monitor disease status²⁵,²⁶. 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 therapy⁷. 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 disease⁷.
Table 3. Criteria for Identifying Treatment Response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response (CR)</th>
<th>Partial response (PR)</th>
<th>Progressive disease (PD)</th>
<th>Stable disease (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>None &gt;1.5 cm</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or appearance of any new lesion</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥50%</td>
<td>Increase ≥50% or new enlargement when previously normal</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>&gt;1.5 x 10⁹/L without need for exogenous growth factors</td>
<td>&gt;1.5 x 10⁹/L or &gt;50% improvement over baseline without need for exogenous growth factors</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Circulating clonal B-lymphocytes</td>
<td>None</td>
<td>Decrease ≥50% over baseline</td>
<td>Increase ≥50% over baseline</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt;100 x 10⁹/L without need for exogenous growth factors</td>
<td>&gt;100 x 10⁹/L or increase ≥50% over baseline</td>
<td>Decrease ≥50% from baseline or to &lt;100 x 10⁹/L secondary to CLL</td>
<td>Change of −49% to +49%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;110 g/L (untransfused and without need for exogenous erythropoietin)</td>
<td>&gt;110 g/L or increase ≥50% over baseline</td>
<td>Decrease of &gt;20 g/L from baseline or to &lt;100 g/L secondary to CLL</td>
<td>Increase ≤110 g/L or &lt;50% over baseline, or decrease &lt;20 g/L</td>
</tr>
<tr>
<td>Marrow</td>
<td>Normocellular for age, &lt;30% lymphocytes, no B-lymphoid nodules</td>
<td>No BM requirements to document PR</td>
<td>No BM requirements to document PD</td>
<td>No BM requirements to document SD</td>
</tr>
<tr>
<td></td>
<td>Hypocellular marrow with no clonal infiltrates defines CRi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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 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

Fludarabine has been shown to produce response rates of between 50 and 60 percent in patients refractory to traditional alkylating-agent therapy.31,32 The superior activity of fludarabine has also been confirmed in treatment-naïve patients. In randomized comparisons to alkylating agents, fludarabine has demonstrated a superior clinical response, with response rates of 60 to 80 percent and CR rates of 15 to 20 percent.28,30,33,34 A Cochrane meta-analysis of four randomized trials confirmed the findings of superior PFS with fludarabine (HR=0.70; p <0.00001).35 In addition, in a recent long-term follow-up analysis of a previous study, Rai et al. reported a survival advantage of fludarabine (63 months versus 59 months, p = 0.04).36 Despite improved efficacy, however, rates of neutropenia are higher with fludarabine than with chlorambucil.28,35 Evidence suggests a lack of benefit of fludarabine over chlorambucil in the elderly patient population.37,38 Fludarabine monotherapy is not appropriate for the first line treatment of CLL patients as any patient fit to tolerate fludarabine should be offered chemo-immunotherapy.

Addition of Anti-CD20 monoclonal antibodies to Chemotherapy Backbones

As a single agent in CLL, rituximab has only moderate activity, perhaps because of the dim CD20 expression on B-CLL cells. However, with higher doses than are typically used in lymphoma, the activity of single-agent rituximab in CLL is greatly enhanced.39,40 In a study examining the efficacy of rituximab (375 mg/m²) monotherapy in CLL, Byrd et al. reported OR, CR, and PR rates of 45, 3, and 42 percent, respectively.40 Rituximab has been studied in a number of clinical trials evaluating its additional impact in combination therapy. Obinutuzumab is a novel Type II anti-CD20 mAb recently approved for the treatment of CLL in combination with CLB. The addition of rituximab to FC lead to an OS advantage compared to FC alone in the German CLL Study Group (GCLLSG) CLL8 study (in younger fit CLL patients). In the GCLLSG CLL11 study, both obinutuzumab and rituximab lead to an OS advantage in combination with CLB compared to CLB monotherapy (in previously untreated older CLL patients with comorbidities). This data confirms that all CLL patients benefit from an anti-CD20 mAb added to chemotherapy as a part of frontline therapy.

Fludarabine-rituximab (FR). Byrd et al. conducted the randomized CALGB 9712 phase II study to determine the efficacy, safety, and optimal administration schedule for rituximab with fludarabine in previously untreated CLL patients.41 Patients were randomized to receive either six monthly courses of fludarabine concurrently with rituximab, followed two months later by four weekly doses of rituximab as consolidation therapy; or sequential fludarabine monotherapy, followed two months later by rituximab consolidation therapy. An OR rate of 90% and CR rate of 47% was observed in the concurrent group, as compared to an OR rate of 77% and a CR rate of 28% in the sequential group. In a subsequent retrospective analysis published in 2005, patients given FR in the CALGB 9712 trial were compared to
patients given fludarabine monotherapy in the CALGB 9011 trial with a higher PFS and OS in patients treated with FR\textsuperscript{42}. Based on these results, some Canadian centres have adopted the use of FR as the standard first-line treatment in both fit and frail patients. Phase III studies evaluating the FR regimen are required to determine its efficacy and safety compared to regimens with higher quality clinical trial data.

**Fludarabine-cyclophosphamide-rituximab (FCR).**

Three randomized trials comparing fludarabine (F) or fludarabine-cyclophosphamide (FC) for frontline therapy in CLL were published, all showing an improved overall response (OR) rate and PFS for FC compared with F monotherapy but with no statistically significant OS advantage\textsuperscript{26,28}.

Following these studies, the phase III GCLLSG CLL8 trial compared the primary endpoint of PFS after treatment with FCR or FC in younger fit CLL patients\textsuperscript{23}. Study participants included 817 patients selected for minimal co-morbidity (CIRS <6). Patients were randomly assigned to receive six courses of either FC (F: 25 mg/m\textsuperscript{2}, days 1–3 + C: 250 mg/m\textsuperscript{2}, days 1–3) or FC with the addition of rituximab (375 mg/m\textsuperscript{2}, day 0 of the first cycle and 500 mg/m\textsuperscript{2}, day 1 of all subsequent cycles). Median PFS was reported as 32.8 months in the FC arm and 51.8 months in the FCR arm (HR 0.56; \(p <0.0001\)). The PFS observed in the FC arm was similar to that observed in previous studies using FC, which have reported a range of 32 to 48 months\textsuperscript{26}. 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 is the first Phase III study in CLL to demonstrate an OS advantage. Response rates were higher in the FCR group versus the FC group and are the highest reported rates of any chemotherapy regimen used to date. 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; \(p <0.0001\))\textsuperscript{23}. Based on the results from the CLL-8 trial, FCR is currently the best option for the first-line treatment of young, fit patients with CLL\textsuperscript{23}.

The doses of rituximab recommended in clinical practice are: 375 mg/m\textsuperscript{2} for cycle 1, 500 mg/m\textsuperscript{2} for cycles 2 through 6, in combination with 25 mg/m\textsuperscript{2} of fludarabine and 250 mg/m\textsuperscript{2} of cyclophosphamide on days 1–3 of each cycle. A regimen adaptation can be considered to provide the fludarabine and cyclophosphamide as oral agents on Days 2 and 3 with the usual doses of R-F-C on Day 1 and fludarabine 40mg/m2 oral on Days 2-3 and cyclophosphamide 300mg/m2 oral on Days 2-3. There is significant potential toxicity of FCR. Dose reductions and treatment delays are frequently required during FCR therapy. G-CSF prophylaxis should not be used to maintain maximal dosing as this may result in profound and prolonged neutropenia. Late infections are also common with this regimen so prophylactic anti-infectives should be continued for a minimum of 3-6 months post-therapy.

**Bendamustine-rituximab**

A Phase III randomized controlled trial proved that bendamustine was superior to CLB with improved ORR and PFS and time to next treatment (TTNT)\textsuperscript{43}.

Recently, the final analysis from the phase III GCLLSG CLL10 trial was reported. The trial randomized (1:1; \(n=564\)) physically fit CLL patients with low comorbidity burden to FCR or BR. With a median follow-up of 37.1 months, overall response was 95% in the FCR group vs. 96% in the BR group (\(p=1.0\)) and complete response was 40% in the FCR group vs. 31% in the BR group (\(p=0.034\)). 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 study\textsuperscript{44}.

Based on these results, FCR should still be considered the standard of care for those who are young and physically fit as defined by GFR > 70 ml/min and CIRS score ≤ 6. FCR is also favoured in patients with mutated IgVH in the absence of del(17p) or del(11q) because of the chance of prolonged disease control. However, based on the CLL10 study results showing no improvement in OS or PFS in patients aged ≥ 65 years and substantial grade 3 and higher hematologic toxicity and infection in such patients receiving FCR, we favour BR in this patient population.

**Chlorambucil-rituximab and Chlorambucil-obinutuzumab (GA101)**

The optimal frontline therapy for elderly patients with CLL and comorbidities was recently evaluated in a phase 3 randomized clinical trial of chemoimmunotherapy comparing CLB plus obinutuzumab [GA-101] (GClb) with CLB plus rituximab (RClb) versus CLB monotherapy\textsuperscript{45}. The median age of the population was 73, CIRS score was 8 and median GFR was 63 mL/min. Both antibody containing groups (GClb and RClb) proved significantly better than Clb monotherapy in terms of ORR and PFS. GClb was associated with improved PFS compared to RClb (26.7 months versus 15.2 months, p<0.0001). GClb also conferred an overall survival benefit over Clb monotherapy (HR 0.41, p=0.002). Minimal residual disease (MRD) negativity, which in the CLL8 trial was shown to correlate with improved PFS and OS, was observed significantly more frequently with GClb than RClb. Toxicities were similar with the chemoimmunotherapy groups with an increase in infusion-related reactions (IRRs) in the GClb-treated patients, with IRRs typically occurring only with Cycle 1. There was no difference in severe infections or treatment related deaths between the three groups. An update of this trial also reported an improvement in OS in the patients in the RClb group compared to Clb monotherapy.

In patients who are frail or elderly, the addition of an anti-CD20 monoclonal antibody (rituximab or GA101) results in improved PFS and OS over CLB monotherapy. The use of the novel monoclonal anti-CD20 antibody obinutuzumab (GA 101) improves PFS over rituximab and a larger improvement in OS over CLB monotherapy. These results support the use of chemoimmunotherapy in all CLL patients as a part of frontline therapy and justify the replacement of rituximab with obinutuzumab when used in combination with CLB.

The addition of rituximab to other chemotherapy backbones in first-line treatment has been explored in a number of phase II studies. These studies have shown promising results using cyclophosphamide, fludarabine-alemtuzumab-rituximab (CFAR); reduced-dose FCR (FCRLite); pentostatin-cyclophosphamide-rituximab (PCR); rituximab with alemtuzumab; and rituximab with fludarabine-cyclophosphamide-mitoxantrone (R-FCM)\textsuperscript{20,46-50}.

**Ibrutinib**

The open-label, phase III RESONATE-2 trial\textsuperscript{51} randomized (1:1) 269 patients who were at least 65 years of age (range: 85-89; median 73 years) with a diagnosis of CLL or small lymphocytic lymphoma to receive oral ibrutinib (420mg once daily) or up to 12 cycles of chlorambucil monotherapy (dose of 0.5mg/kg on day 1 and 15 of a 28 day cycle, increasing to 0.8mg/kg if no unacceptable levels of toxic effects) (Burger et al. 2015). 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), with a risk of progression or death that was 84% lower with ibrutinib when compared to chlorambucil (HR: 0.16; p<0.001). The 24-month OS was also significantly improved with ibrutinib (98%) vs. chlorambucil (85%), despite a cross-over design of the study, with the relative risk of death being 84% lower with the ibrutinib group (HR: 0.16; p=0.001). Additionally, the overall response rate was higher with ibrutinib when compared to chlorambucil (86% vs. 35%; p<0.001). Adverse events (any grade) occurred in at least 20% of ibrutinib patients, including diarrhea, fatigue, cough, and nausea. Adverse events for chlorambucil also occurred in at least 20% of patients and included nausea, fatigue, neutropenia, anemia, and vomiting. In the ibrutinib group, 4 patients experienced grade 3 hemorrhage and 1 patient experienced grade 4 hemorrhage. 10% of patients experience atrial fibrillation.

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 limits the value of these study results. The comparison of ibrutinib with standard chemo-immunotherapy (ex. FCR, BR, CLB-O) remains to be demonstrated but is of interest. If ibrutinib proves superior in the first line treatment setting to currently approved treatments, this would lead to a change in practice.

**Ibrutinib for Patients with del(17p)**

Recently, results from the phase II RESONATE-17 trial evaluating relapsed/refractory CLL patients with 17p deletion were reported in abstract form. All patients (n=144) had failed at least one therapy, and were enrolled to receive 420 mg oral ibrutinib once daily until progression. The median age was 64 years, 63% of patients Rai Stage III or IV disease, 49% had bulky lymphadenopathy of at least 5 cm, and 10% with lymphadenopathy of at least 10 cm. At median 13-months follow-up, the 12-month PFS was 79.3%. Progressive disease was reported in 20 patients (13.9%). Richter transformation was reported in 11 patients (7.6%), 7 of which occurred within 24 weeks of treatment. Adverse events included diarrhea (36%; grade 3-4 in 2%), fatigue (30%; grade 3-4 in 1%), cough (24%, grade 3-4 in 1%), arthralgia (22%; grade 3-4 in 1%), atrial fibrillation (7.6%; grade 3-4 in 3.5%), and grade 3-4 neutropenia (14%), anemia (8%), pneumonia (8%), and hypertension (8%). Seven patients reported basal or squamous cell skin cancer and 1 patient had plasma cell myeloma. Major hemorrhage was reported in 4.9% of patients all of which were grade 2 or 3. Adverse events were responsible for 16 patients (11.1%) discontinuing treatment, and 8 patients had fatal events (pneumonia, sepsis, myocardial or renal infarction, health deterioration). At the time or data reporting, median treatment durations was 11.1 months, with 101 (70%) patients still on ibrutinib.

While the RESONATE-2 study excluded patients with del(17p), the safety and efficacy of ibrutinib demonstrated in these previously untreated CLL patients suggests that ibrutinib monotherapy would be a safe option for patients with previously untreated CLL with del(17p). As all other therapies (chemo-immunotherapy) have proven ineffective in this patient population, we favour ibrutinib in any patient with deletion 17p irrespective of whether the patient is previously untreated or relapsed/refractory.

**Alemtuzumab for Patients with del(17p)**

With the approval of ibrutinib for patients with CLL and del(17p), alternate treatments will rarely be required. However, alemtuzumab acts via a p53 independent mechanism, and has improved results in patients with del(17p) compared to conventional chemotherapies. Evidence of the role of alemtuzumab in high-risk patients was first shown in the refractory setting in a study by Stilgenbauer et al., who reported a
response rate of 54% in fludarabine-refractory patients with del(17p) or p53 abnormalities\(^54\). In a subsequent trial, Lozanski et al. reported a 31 percent response in patients with this high-risk profile\(^55\). In the first-line setting, results of a randomized controlled trial comparing alemtuzumab to chlorambucil were reported by Hillmen et al. \(^29\). Of the 282 patients who underwent FISH cytogenetic analysis, 20 (7%) patients had del(17p). Patients with del(17p) who were treated with alemtuzumab had a PFS of 10.7 months compared to 2.2 months for patients who received chlorambucil. Although there was a trend of increased PFS in the del(17p) group treated with alemtuzumab, it did not reach statistical significance likely because of small numbers. A single arm, open-label study of patients with CLL with del(17p) also examined alemtuzumab in combination with high dose steroids. The alemtuzumab was provided at 30mg 3x/week for 16 weeks in combination with high dose methylprednisolone 1.0g/m2/day for 5 days on a 28 day cycle for 4 cycles. Eighty-two percent of patients had an objective response with 36% achieving a CR. The median PFS and OS of previously untreated patients were 18.3 months and 38.9 months, respectively, improved compared to all historical controls for this patient population\(^56\).

**Second-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 the length of the disease-free interval. In fit patients, FCR is an effective regimen in patients naïve to rituximab or FC; reuse of FCR or use of BR is also reasonable in patients experiencing a long remission (more than three years) after initial treatment\(^57\). Patients experiencing treatment failure within six months of treatment are identified as having refractory disease and are considered to be ultra high risk, similar to patients with del(17p) or \(TP53\) mutations. These patients, and those who achieve short remissions after FCR (PFS < 3 years), patients with del(17p) and those who are unfit for cytotoxic chemotherapy, should be treated with one of the novel agents - ibrutinib or idelalisib + rituximab \(^30-33\). When initial remission after chemoimmunotherapy with FCR is greater than 3 years, re-treatment with chemoimmunotherapy is appropriate. The median PFS after BR, CLB-R and CLB-O are shorter than after FCR. If patients achieve a PFS of more than 2-3 years with these regimens and remain fit for cytotoxic chemotherapy, they should also be considered for retreatment with chemoimmunotherapy. As the optimal relapsed/refractory regimen has not yet been clearly defined for most CLL patients, all patients should be considered for a clinical trial when available.

**Ibrutinib**

The multicenter, open-label, phase III 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). Median progression free survival was 8.1 months in the ofatumumab group. The hazard ratio for progression or death in the ibrutinib group was 0.22 (\(p<0.001\)). 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; \(p=0.005\)). The overall response rate was significantly higher in the ibrutinib group compared to the ofatumumab group (42.6% compared to 4.1%, respectively; \(p<0.001\)). An additional 20% of patients treated with ibrutinib had a partial response with lymphocytosis. Patients with del(17p) responded similarly to those without \(^58\).

**Idelalisib + rituximab**

The randomized, multicenter, double-blind, placebo-controlled, phase III trial NCT01539512 compared idelalisib (150 mg twice daily) plus rituximab to placebo plus rituximab in relapsed CLL patients. Idelalisib is an oral inhibitor of the delta isoform of phosphatidylinositol 3-kinase. Amongst (n=220) patients, median
progression-free survival was 5.5 months in the placebo arm and was not reached in the idelalisib arm (HR: 0.15; p<0.001). Patients in the idelalisib arm had improved overall response (81% vs 13%; p<0.001) and 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 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%.

Fludarabine and alemtuzumab combination therapy (FluCam)

The combination of fludarabine and alemtuzumab (FluCam) was compared in a Phase III study to fludarabine monotherapy in 335 patients with relapsed/refractory CLL after 1 prior line of therapy. Patients in the combination group received fludarabine 30mg/m² per day and alemtuzumab 30mg per day on days 1-3 of a 28 day cycle while patients in the monotherapy arm received fludarabine 25mg/m² on days 1-5. Patients receiving FluCam had a significantly improved PFS (23.7 months compared to 16.5 months [p=0.003]) and had a significantly improved OS (median not reach compared to 52.9 months [p=0.021]). Adverse events were similar in the 2 groups with the exception of cytomegalovirus events (14% in the FluCam group compared to <1% in the fludarabine monotherapy group) and an increase in infusion-related reactions, which were generally mild (Grade 1 or 2). The OS advantage was restricted to patients with Rai stage III or IV disease, suggesting that advanced stage disease is not a contraindication to this treatment. Patients ≥ 65 years also benefited with improved PFS and a trend to improved OS. This regimen will rarely be required in the era of novel agents because of the reduced access to alemtuzumab and the infectious risks and CMV monitoring requirements.

High dose corticosteroids

High dose steroids have been examined as monotherapy or in combination with rituximab in several single centre or Phase II studies. The typical dose of corticosteroid is methylprednisolone 1.0g/m²/day x 5 days every 28 days. While subject numbers are small and many of the reports are retrospective, overall response rates are high, ranging from 62%-94% with responses noted in patients with del(17p) and in patients with fludarabine-refractory disease. High dose steroids +/- rituximab may be considered for patients who have failed novel agents as a bridge to allogeneic HSCT but otherwise should rarely be used in the era of novel agents.

Choosing between novel agents ibrutinib and idelalisib +/- rituximab

Both of the novel agents have demonstrated impressive efficacy in patients with relapsed/refractory CLL. Several factors can be considered when selecting between these agents including expected toxicities and availability/willingness to receive concurrent rituximab. While no head-to-head studies have been performed comparing ibrutinib to idelalisib+ rituximab, recent data suggesting high rates of infections and treatment-related deaths with idelalisib have influenced physicians/patients to favour ibrutinib as the BCR inhibitor of choice.

Ibrutinib:

The most frequent distinct toxicities of ibrutinib (not noted with idelalisib) including bleeding/bruising and atrial fibrillation (AFIB). Major hemorrhage was reported in 4.9% of patients all of which were grade 2 or 3 and patients were not allowed onto the study if they were taking warfarin. Caution is recommended with the use of other anticoagulants and anti-platelet agents. Episodes of AFIB (including Grade 3 events)
have also been reported at a rate of 5.1%\textsuperscript{58} to 5.6%\textsuperscript{68}. Higher rates of AFIB have been reported with longer follow-up with incidence rates of 10-16% reported in studies with follow-ups of more than 24 months on drug\textsuperscript{69}.

*Idelalisib +/-Rituximab:*

The most concerning Grade 3-4 toxicities with idelalisib and rituximab include colitis/diarrhea (any grade: 19%; grade ≥3: 4%), transaminitis (any grade: 35%; grade ≥3: 5%) and pneumonia/pneumonitis (any grade 6%/4%; no grade ≥3)\textsuperscript{59}. Rates of discontinuation of therapy due to adverse events are higher with idelalisib (5.5%)\textsuperscript{59} than with ibrutinib (4%)\textsuperscript{58}. Colitis frequently occurs late (median onset more than 6 months after initiation of therapy) and responds to corticosteroids and drug discontinuation. Drug re-challenge can be successfully performed at a reduced dose of 100mg twice daily though recurrence of colitis may occur and many patients require indefinite co-therapy with budesonide to prevent recurrent colitis. Fatal cases of pneumonitis have been reported and are not predictable based on any factors reported to date. Thus, patients with poor lung function and/or a history of diarrhea are less optimal candidates for idelalisib and rituximab.

Infectious complications including fatal infections have also been reported with idelalisib, particularly when combined with chemo-immunotherapy. All patients receiving idelalisib should be treated with prophylaxis against pneumocystis given reported PJP infections. CMV infection has also been reported such that CMV monitoring should be considered in patients who are CMV serology positive and investigation for CMV infection should be performed in cases of unexplained fevers, cytopenias, etc.\textsuperscript{59}

*Venetoclax*

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).\textsuperscript{70} 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/relapse CLL after ibrutinib or idelalisib were treated with venetoclax (20mg daily, followed by intrapatient ramp-up to 400mg daily).\textsuperscript{71} Estimated 12-month progression free survival was 79%, with 2 patients achieving complete remission. The most common adverse events (AEs; all grades) were neutropenia (56%), diarrhea (42%), upper respiratory tract infection (39%), thrombocytopenia (36%), nausea (31%), fatigue (28%), cough (22%), rash (22%), and anemia (22%). Grade 3 or 4 AEs were primarily hematologic (neutropenia [50%], thrombocytopenia [25%], and anemia [17%]). No patients experienced tumor lysis syndrome.

A single arm, open-label, phase II trial enrolled 107 patients with deletion of chromosome 17p (del[17p]) relapsed or refractory chronic lymphocytic leukemia to receive once daily venetoclax at 400mg after the usual weekly dose ramp-up schedule (20, 50, 100, 200, 400mg) with continuous dosing until disease progression or drug discontinuation for another reason.\textsuperscript{72} With a median follow-up of 12.1 months, the overall response rate was 79.4% (95% CI: 70.5-86.6%).
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 65 years who:
- Have refractory CLL
- Have CLL with del(17p) abnormalities (patient be initiated on a BCR inhibitor and assessed for HSCT)
- 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 (ibrutinib 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.

Timing of HSCT for patients treated with BCR inhibitors should occur before the median expected PFS for the respective risk groups:

| Table 4. Ibrutinib Median Progression-Free Survival |
| --- | --- | --- | --- |
| CLL Characteristics | Median PFS | Median OS | Reference |
| Treatment-naive | PFS at 30 months: 96% | OS at 30 months: 97% | Byrd et al. 2015<sup>68</sup> |
| Previously treated | PFS at 30 months: 69% | OS at 30 months: 79% | Byrd et al. 2015<sup>68</sup> |
| del(17p) | PFS at 30 months: 48% | 28 months | Byrd et al. 2015<sup>68</sup> |
| del(11q) | PFS at 30 month: 74% | 38.7 months | Byrd et al. 2015<sup>68</sup> |
| no del(17p) or del(11q) | PFS at 30 months: 87% | OS at 30 months: 90% | Byrd et al. 2015<sup>68</sup> |

| Table 5. Idelalisib Median Progression-Free Survival |
| --- | --- | --- | --- |
| CLL Characteristics | Median PFS | Median OS | Reference |
| Treatment-naive, age ≥65 | PFS at 36 months: 83% | OS at 36 months: 90% | O'brien et al. 2014<sup>60</sup> |
| Treatment-naive, age ≥65 | PFS at 9 months: 83% | Not Reported | Zelenetz et al. 2014<sup>73</sup> |
| All Patients | 19.4 months | 20.8 months | Sharman et al. 2014<sup>67</sup> |
| Del(17p)/TP53 mutation | 16.6 months | Not Reached | Sharman et al. 2014<sup>67</sup> |
| No Del(17p)/TP53 mutation | 20.3 months | Not Reached | Sharman et al. 2014<sup>67</sup> |
| Del(11q) | 20.3 months | Not Reported | Sharman et al. 2014<sup>67</sup> |
| No Del(11q) | 19.4 months | Not Reported | Sharman et al. 2014<sup>67</sup> |

**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. Screening for tuberculosis should be considered in patients from endemic areas. 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 6. Antibiotic Prophylaxis and Vaccinations in Patients with CLL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Possible infection</th>
<th>Antibiotic prophylaxis</th>
<th>Vaccine</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>Encapsulated bacteria</td>
<td>Penicillin</td>
<td>Pneumococcal, Hemophilus, and Meningococcal prior to splenectomy</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab or allogeneic stem cell transplant</td>
<td>CMV</td>
<td>Valgancyclovir pre-emptive therapy for increased PCR</td>
<td>n/a</td>
<td>CMV monitoring by PCR every 1–2 weeks</td>
</tr>
<tr>
<td>Alemtuzumab, fludarabine, or rituximab</td>
<td>Hepatitis B</td>
<td>Lamivudine 100 mg/day orally for the entire duration of chemotherapy and 6 months afterwards</td>
<td>n/a</td>
<td>Avoid in patients with known prior hepatitis B</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Varicella Zoster</td>
<td>Acyclovir or equivalent</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Fludarabine- or bendamustine based treatment</td>
<td>Pneumocystis jirovecii pneumonia or Varicella Zoster</td>
<td>Septra or equivalent and acyclovir or equivalent should be used for 12 months</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib or idelalisib + rituximab</td>
<td>Community-acquired pneumonia or Pneumocystis jirovecii pneumonia</td>
<td>Septra is required for PJP prophylaxis with idelalisib</td>
<td>CMV monitoring</td>
<td></td>
</tr>
</tbody>
</table>

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, antimiobials 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.

**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\(^76\). 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\(^77\)).

ITP is less common, occurring in two to three percent of CLL patients at diagnosis or during early stage disease\(^76\). 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\(^78\). PRCA is present in six percent of CLL patients that are tested\(^76\). 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\(^79\).

ITP and AIHA, as a single abnormality caused by CLL, should be treated initially using glucocorticoids. Several case reports and small series have described an increased risk of AIHA following single-agent fludarabine therapy; particularly in patients with a positive DAT. Combination therapy may be preferable in the treatment of patients with CLL with a history of AIHA. 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\(^80,81\). Second-line options for AIHA include splenectomy and intravenous immunoglobulins. Good responses have also been obtained using rituximab or alemtuzumab\(^7\). 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\(^77,78\). Rituximab may be an additional option for the treatment of PRCA, but success rates are lower than those seen for AIHA or ITP\(^77\).

**Richter syndrome.**

The majority of Richter syndrome cases involve the transformation of CLL to diffuse large B-cell lymphoma (DLBCL). The morphology of DLBCL consists of sheets of large neoplastic B-lymphocytes clearly distinguishable from small lymphocytes, with sparse cytoplasm and clumped chromatin typical of CLL. Diagnosis of Richter syndrome requires the pathologic identification of CLL transformation to aggressive lymphoma. Ideally, this should be determined by histology using a biopsy of the index lesion\(^79\). Based on existing data, Richter syndrome may be treated with cytoreductive chemotherapy appropriate for DLBCL (e.g. R-CHOP), with the goal of achieving a response. The role of consolidation therapies previously tested for CLL or DLBCL in patients responding to initial therapy as well as the impact of new first-line therapies, may aid in the development of an ideal treatment approach in these patients\(^79\). Allogeneic stem cell transplantation should also be considered in younger fit patients with Richter syndrome who respond to initial therapy\(^82\).
**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\(^\text{83}\).

Before the initiation of treatment, patients with a white blood cell (WBC) count higher than 50,000/mm\(^3\) should be adequately hydrated and monitored frequently. In patients with previous episodes of tumour lysis syndrome, consultation with a nephrologist should be considered. 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\(^\text{83}\). 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 should also be given to patients with significant renal dysfunction or chronic hyperuricemia. In the advent of tumour lysis syndrome it may be necessary to interrupt treatment until symptoms are resolved. Cardiac activity should be monitored continuously, and frequent monitoring of electrolyte levels is recommended\(^\text{83}\). Rasburicase may also be considered for the prevention and treatment of tumour lysis syndrome in patients with a high WBC count, coexistent renal insufficiency, and an allopurinol intolerance or allergy.

Close monitoring for tumour lysis syndrome is recommended for patients with lymphocytosis greater than 30 x 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\(^\text{84,85}\).

**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.

**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIHA</td>
<td>autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>β2M</td>
<td>beta-2-microglobulin</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CALG-B</td>
<td>Cancer and Leukemia Group B</td>
</tr>
<tr>
<td>CFAR</td>
<td>cyclophosphamide + fludarabine + alemtuzumab + rituximab</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
</tr>
<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>DAT</td>
<td>direct antiglobulin test</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>FC</td>
<td>fludarabine + cyclophosphamide</td>
</tr>
<tr>
<td>FCR</td>
<td>fludarabine + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FR</td>
<td>fludarabine + rituximab</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IgVH</td>
<td>immunoglobulin heavy chain variable regions</td>
</tr>
<tr>
<td>ITP</td>
<td>idiopathic thrombocytopenia purpura</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IWCLL</td>
<td>international workshop on chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>MBL</td>
<td>monoclonal B-cell lymphocytosis</td>
</tr>
<tr>
<td>OR</td>
<td>overall response</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PC</td>
<td>pentostatin + cyclophosphamide</td>
</tr>
<tr>
<td>PCR</td>
<td>pentostatin + cyclophosphamide + rituximab</td>
</tr>
<tr>
<td>PCR assay</td>
<td>polymerase chain reaction assay</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PO</td>
<td>by mouth, orally</td>
</tr>
<tr>
<td>PPV</td>
<td>pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>PRCA</td>
<td>pure red cell aplasia</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>rituximab + cyclophosphamide + Adriamycin + vincristine + prednisone</td>
</tr>
<tr>
<td>R-FCM</td>
<td>rituximab + fludarabine + cyclophosphamide + mitoxantrone</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
</tr>
<tr>
<td>TK</td>
<td>thymidine kinase</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>70 kD zeta associated protein</td>
</tr>
</tbody>
</table>

**DISSEMINATION**

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

**MAINTENANCE**

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2019. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
### Eastern Cooperative Oncology Group (ECOG) Performance Status Categories

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
### APPENDIX B

#### Systems

<table>
<thead>
<tr>
<th>Systems</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Ophthalmological and ORL</td>
<td></td>
</tr>
<tr>
<td>Upper Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Lower Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Hepatic and Pancreatic</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Tegumental</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine, Metabolic, Breast</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Total Score*</td>
<td></td>
</tr>
</tbody>
</table>

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

#### CIRS Severity Rating

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

#### 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?
  o Menopause/ andropause without hormone therapy or symptoms = rated 0
  o 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

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

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

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.
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