Canadian evidence-based guideline for the first-line treatment of chronic lymphocytic leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in North America. In Canada, no unified national guideline exists for the front-line treatment of CLL; provincial guidelines vary and are largely based on funding. A group of clinical experts from across Canada developed a national evidence-based treatment guideline to provide health care professionals with clear guidance on the first-line management of CLL. Consensus recommendations based on available evidence are presented for the first-line treatment of CLL.

Key Words Chronic lymphocytic leukemia, CLL, treatment, prognosis, fitness


INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a clinically and biologically heterogeneous disease, and the most common adult leukemia1–4. According to 2016 statistics, the annual incidence of CLL in Canada is about 24005.

Guidelines developed by the International Working Group on CLL provide concise standardized criteria for the diagnosis of CLL that include a clonal B lymphocytosis in the peripheral blood (≥5.0×10^9/L) with a characteristic morphology and immunophenotype6. In most cases, examination of the bone marrow is not required for diagnosis. Heterogeneity in the clinical course of CLL is attributable mainly to variations in the biology of the disease and, particularly, genetic lesions that correlate with response to therapy, the most relevant prognostic factor for overall survival (os)7–9. Two widely accepted clinical staging methods—the Binet and Rai systems—are the simplest and best-validated methods for identifying patients who require treatment and for predicting survival10–12. Clinical staging relies solely on physical examination and standard laboratory tests, and does not require computed tomography imaging. Furthermore, with limited value in predicting patient outcome at diagnosis, computed tomography is not recommended outside of clinical trials13.

Recent advances in treatment since about 2008 have significantly improved outcomes in CLL; however, the disease is still considered incurable except in rare cases of allogeneic hematopoietic stem-cell transplantation (allo-HSCT)4,14. Consequently, the goal of treatment is to achieve effective and durable disease control [measured as progression-free survival (PFS) and OS], with minimal toxicity and acceptable quality of life4–10. With the availability of several new therapeutic options, treatment decisions based on individual and disease characteristics are paramount in achieving the best outcomes for patients.

Several international guidelines for CLL have been published6,14,17–20; however, no unified national CLL guidelines have been developed in Canada. Although individual provinces have created guidelines, those guidelines differ in their recommendations and are based primarily on the availability of therapeutic options in the provincial formulary16,21–23. Accordingly, an evidence-based national treatment guideline that is supported by Canadian hematologists is needed to ensure that all patients with CLL in Canada have access to the best available care. In association with Lymphoma Canada, a group of Canadian CLL experts therefore developed a national evidence-based consensus guideline for the first-line management of patients with CLL.
METHODS

An initial literature search, plus two updates, queried 3 databases (MEDLINE, PubMed, and the Cochrane Database of Systematic Reviews) to identify meta-analyses, randomized controlled trials (RCTs), and single-arm prospective studies published between January 2000 and July 2017 that investigated first-line treatment of CLL. Key search terms for each question were included with the Medical Subject Heading term “leukemia, lymphocytic, chronic, B-cell.” In addition to those searches, abstracts from the proceedings of selected conferences (American Society of Hematology, European Hematology Association, American Society of Clinical Oncology) held between January 2015 and July 2017 were hand-searched. The ClinicalTrials.gov and Cochrane Central Register of Controlled Trials Web sites were also searched for trials in progress. Language of publication was restricted to English. Detailed screening of the full-text versions of all studies was performed to identify the final list of studies. Study selection was limited to those that met these criteria: confirmed diagnosis of CLL; adult study population (≥18 years); prospective design; RCT, comparative, or single-arm trial with 20 or more study participants; evaluation of first-line treatment for CLL; and inclusion of survival outcomes (PFS, OS). When RCR data relating to a particular question were available, only the RCTs were included. When few RCTs relating to a particular question were identified, prospective single-arm studies were considered. National Comprehensive Cancer Network categories of evidence and consensus were used to grade the level of evidence supporting recommendations. Details of those categories are presented in Table 1.

GUIDELINE

Question 1
What prognostic investigations should be performed in patients with previously untreated CLL?

Background
The clinical staging systems described by Rai and Binet more than 40 years ago have proved useful as prognostic tools; however, they are not able to determine an individual patient’s ongoing clinical course, particularly in the early stages. Prognostic biomarkers provide information about a patient’s overall cancer outcome regardless of therapy.

Since about 2004, significant progress has been made in identifying host- and tumor-related prognostic biomarkers, including serum markers, cytogenetic abnormalities, and gene mutations—although relatively few have been prospectively validated within clinical trials. The ability to predict the outcomes of newly diagnosed patients with CLL has remarkably improved, but ideally, the hematology community would like to have predictive biomarkers that can help to determine which therapy will work best for a given patient. To date, however, no predictive biomarkers for CLL have been validated in prospective clinical trials.

Summary of Evidence

Multivariable analyses of known prognostic biomarkers influencing PFS or OS were reported in eight RCTs and two meta-analyses of RCTs evaluating first-line treatment of CLL (Table 1). In the RCTs, del(17p) or TP53 mutation (or both), del(11q), unmutated IGHV (IGHV-u), β2-microglobulin (β2M) concentrations of 3.5 mg/L or greater, and serum thymidine kinase concentrations of 10 U/L or greater were most commonly reported as negative prognostic biomarkers for PFS. Only del(17p) or TP53 mutation (or both), IGHV-u, β2M greater than 3.5 mg/L, and thymidine kinase greater than 10 U/L were independently predictive of reduced OS. Either or both of TP53 mutation and del(17p) were similarly predictive of very poor PFS and OS after chemotherapy or chemoimmunotherapy with purine analogs or alkylating agents. In the CLL8 trial from the German CLL Study Group (gCLLSG), PFS was shorter for patients with del(11q). However, in that subgroup, the 5-year OS with FCR (fludarabine–cyclophosphamide–rituximab) therapy was significantly superior to that with FC (fludarabine–cyclophosphamide), suggesting that, despite the shorter duration of remission conferred by del(11q), these patients respond well to first-line FCR therapy.

The correlation of IGHV mutation status with response to first-line chemoimmunotherapy was evaluated in three RCTs. All studies reported poorer outcomes, in terms of PFS, for patients with IGHV-u. In the gCLLSG CLL8 study, OS values were not reported for the two subgroups, but Kaplan–Meier estimates suggest that OS is significantly shorter in patients with IGHV-u. Longer follow-up in those studies and additional investigation of IGHV mutation status in randomized trials are required to determine how this prognostic biomarker should inform decisions about first-line treatment. The influence of β2M and thymidine kinase on response to treatment has not been prospectively evaluated in randomized studies to date and remains to be defined in the setting of current first-line treatments.

To develop an integrated prognostic index, the gCLLSG analyzed data from three large phase III trials that collectively included 1948 patients; however, of the three trial cohorts analyzed, none included patients treated with chemoimmunotherapy, limiting the adoption of the gCLLSG score in the current era of first-line CLL treatment. More recently, the CLL-IPI (International Prognostic Index) Working Group used pooled data from 3472 patients participating in eight phase III trials (including the CLL8 trial cohort treated with FCR) to develop an integrated prognostic score for patients with CLL, identifying 3 biomarkers independently associated with shorter OS: β2M concentration greater than
<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Analysis</th>
<th>Independent prognostic factors for survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized studies</strong></td>
<td></td>
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<tr>
<td>Byrd et al., 2003, and Woyach et al., 2011&lt;sup&gt;26,27&lt;/sup&gt; (Cancer and Leukemia Group B 9712)</td>
<td>Fludarabine–rituximab (sequential vs. concurrent rituximab)</td>
<td>104</td>
<td>Unmutated IGHV, del(17p) or del(11q)</td>
<td>Unmutated IGHV, del(17p) or del(11q) (combined in multivariable analysis)</td>
</tr>
<tr>
<td>Eichhorst et al., 2009&lt;sup&gt;28&lt;/sup&gt; (German CLL Study Group, CLL5)</td>
<td>Fludarabine vs. chlorambucil</td>
<td>193</td>
<td>Thymidine kinase, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin</td>
<td>β&lt;sub&gt;2&lt;/sub&gt;-Microglobulin≥3.5 mg/L</td>
</tr>
<tr>
<td>Robak et al., 2010&lt;sup&gt;29&lt;/sup&gt; (Polish Adult Leukemia Group, CLL3)</td>
<td>Fludarabine–cyclophosphamide vs. cladribine–cyclophosphamide</td>
<td>423</td>
<td>del(17p), IGHV&lt;sub&gt;mutated&lt;/sub&gt;, TP53 mutation, del(11q), del(13q), unmutated IGHV, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin, thymidine kinase</td>
<td>del(17p), or del(11q) (combined in multivariable analysis)</td>
</tr>
<tr>
<td>Hallek et al., 2010, Stilgenbauer et al., 2014, and Fischer et al., 2016&lt;sup&gt;30–32&lt;/sup&gt; (German CLL Study Group, CLL8)</td>
<td>Fludarabine–cyclophosphamide vs. fludarabine–cyclophosphamide–rituximab</td>
<td>817</td>
<td>del(17p), TP53 mutation, del(11q), del(13q), unmutated IGHV, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin, thymidine kinase</td>
<td>del(17p), del(11q), thymidine kinase≥10 U/L, unmutated IGHV, TP53 mutation</td>
</tr>
<tr>
<td>Oscier et al., 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Fludarabine vs. fludarabine–cyclophosphamide vs. chlorambucil</td>
<td>777</td>
<td>del(17p), del(11q), TP53 del or mutation, del(11q), unmutated IGHV</td>
<td>TP53 del or mutation, unmutated IGHV, β&lt;sub&gt;2&lt;/sub&gt;-Microglobulin≥4 mg/L</td>
</tr>
<tr>
<td>Geisler et al., 2014&lt;sup&gt;34&lt;/sup&gt; (U.K. LRF CLL4)</td>
<td>Fludarabine–cyclophosphamide–alemtuzumab vs. fludarabine–cyclophosphamide</td>
<td>281</td>
<td>del(17p), del(11q), +12, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin</td>
<td>del(17p)</td>
</tr>
<tr>
<td>Eichhorst et al., 2016&lt;sup&gt;35&lt;/sup&gt; (German CLL Study Group, CLL10)</td>
<td>Bendamustine–rituximab vs. fludarabine–cyclophosphamide–rituximab</td>
<td>561</td>
<td>del(11q), del(13q), unmutated IGHV, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin, thymidine kinase</td>
<td>del(11q), thymidine kinase≥10 U/L, unmutated IGHV</td>
</tr>
<tr>
<td>Estenfelder et al., 2016, and Herling et al., 2016&lt;sup&gt;36,37&lt;/sup&gt; (German CLL Study Group, CLL11)</td>
<td>Chlorambucil–obinutuzumab vs. chlorambucil–rituximab vs. chlorambucil</td>
<td>781 (161 included in multivariate analysis)</td>
<td>del(17p), TP53 mutation, del(11q), del(13q), unmutated IGHV, β&lt;sub&gt;2&lt;/sub&gt;-microglobulin, thymidine kinase, ATM mutation</td>
<td>Unmutated IGHV, del(17p) or TP53 mutation (or both), ATM mutation, thymidine kinase≥10 U/L</td>
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<tr>
<td><strong>Meta-analyses</strong></td>
<td></td>
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<tr>
<td>Pflug et al., 2014&lt;sup&gt;38&lt;/sup&gt; (German prognostic score)</td>
<td>3 RCTs from the German CLL Study Group (CLL1, CLL4, CLL5)</td>
<td>1948</td>
<td>Cytogenetics, gene mutations, serum markers, IGHV</td>
<td>Not reported</td>
</tr>
<tr>
<td>International CLL-IPI working group&lt;sup&gt;39&lt;/sup&gt; (international prognostic index)</td>
<td>8 RCTs</td>
<td>3472</td>
<td>Cytogenetics, gene mutations, serum markers, IGHV</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.
3.5 mg/L, IgM, IgA, and P53 gene aberrations [del(17p), TP53 mutation, or both]38. Four risk categories with different OS rates were identified, providing additional prognostic information about OS beyond conventional clinical staging. The CLL-1PI has been validated in unselected patient cohorts and in patients enrolled in the gCLLSG CLLL1 randomized trial that evaluated first-line treatment of older patients with comorbidities48–42. One limitation of that study is that, at the time of the analysis, RCTs of novel targeted therapies did not have sufficiently long follow-up to be included.

**Recommendations**

- Testing for prognostic markers should be performed when therapy is required, but evidence is insufficient to recommend routine prognostic marker testing at diagnosis in asymptomatic patients with early-stage CLL. The decision to initiate therapy should be made independently of prognostic marker results, even in the setting of high-risk disease (level of evidence: category 2A).

- Patients with TP53 abnormalities have a particularly poor prognosis, including significantly reduced OS and OS after standard chemoimmunotherapy, and might benefit from treatment with a novel targeted therapy. The expert panel strongly recommends testing for del(17p) and TP53 mutation before initiation of first-line treatment (level of evidence: category 2A).

- Because the CLL-1PI provides valuable prognostic information, the expert panel recommends testing for IGHV mutation status and β2M concentration (in addition to del(17p) and TP53 mutation) before initiation of first-line therapy (level of evidence: category 2B).

**Question 2**

What criteria should be used to assess fitness in patients with CLL?

**Background**

The advent of newer therapies has led to a greater focus on evaluating the fitness status of patients with CLL. As treatment intensity increases, reliable methods are needed to identify patients who can safely tolerate and benefit from such therapy. Traditionally, fitness was classified based on age alone; it is now well recognized that chronologic age is not a reliable surrogate for physiologic age or fitness43,44. Clinical trials performed in the CLL population are difficult to compare, because the indices used to assess fitness are not standardized, leading to heterogeneity in trial populations. In routine clinical practice, clinical judgment remains the standard of care.

The gCLLSG has used a combination of the Cumulative Illness Rating Scale (CIRS) and creatinine clearance to define fitness status with respect to tolerability of RCR chemoimmunotherapy45. Although the CIRS score establishes a clinically useful division, it has not been externally validated or universally adopted outside of clinical trials.

**Summary of Evidence**

- Few randomized prospective studies of first-line treatment for CLL have evaluated the effect of patient fitness on outcomes. Prospective analyses of defined fitness factors in treatment-naïve patients with CLL receiving current chemoimmunotherapy regimens is limited to subgroup analyses in two randomized studies and four single-arm prospective studies (supplemental Table 1)31,35,46–51. Two meta-analyses investigating the effect of comorbidity or age on response to first-line treatments were also included (supplemental Table 1). Those studies provide insight into some of the fitness parameters that might influence patient response and tolerability to therapy; however, the evidence is currently insufficient to define an optimal method to assess fitness for patients with CLL or to indicate that a fitness score is superior to clinical judgment.

- Patient fitness should be considered when choosing therapy for CLL patients (level of evidence: category 2B).

- No specific fitness assessment tool has been proved optimal for decision-making about CLL treatment, but the assessment should focus on organ impairment, particularly renal function (level of evidence: category 3).

**Question 3**

How should asymptomatic early-stage CLL be managed?

**Background**

Today, almost 80% of CLL patients are diagnosed at an early clinical stage52. Considerable interest is therefore invested in determining optimal timing of treatment initiation to achieve the best outcomes for this patient cohort. All current international guidelines recommend initiation of treatment in patients with advanced (Binet C, Rai III-IV) or active symptomatic disease; however, they recommend that newly diagnosed patients with asymptomatic early-stage disease (Binet A–B, Rai 0–II) be monitored without therapy unless they have evidence of disease progression4,14,17–20.

**Summary of Evidence**

- No published RCTs evaluating early first-line treatment of Binet A–B or Rai 0–II asymptomatic patients were identified after the year 2000. Studies from the French Cooperative Group on CLL and the Cancer and Leukemia Group B evaluated outcomes of early treatment with chlorambucil in patients with early-stage disease (Table III). Although disease progression and appearance of symptoms could be delayed with early treatment, the use of alkylating agents did not prolong survival. That result was confirmed by a meta-analysis (Table III)55. Furthermore, an increased frequency of fatal epithelial cancers in treated compared with untreated patients was reported54.

- Table III also presents results from one abstract examining early treatment with chemoimmunotherapy56. The randomized German–French cooperative phase III trial analyzed the efficacy of early compared with deferred RCR therapy in treatment-naïve patients with Binet A CLL having a high risk of disease progression. Patients with high-risk CLL were randomized to receive RCR or to be followed in a “watch and wait” strategy. Patients with low-risk CLL were observed only. After a median follow-up of 46 months, event-free survival was significantly improved in patients receiving RCR compared with patients being managed as “watch and wait” (median: not reached vs. 24.5 months; p < 0.0001). However, OS was not significantly different in the
**Recommendation**

For asymptomatic patients with early-stage C.L.L who do not meet the indications for therapy established by the International Working Group on C.L.L guidelines (Table IV), clinical observation only is recommended (level of evidence: category 2A).

**Question 4**

How should advanced symptomatic C.L.L be managed?

**TABLE III** Early therapy compared with observation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pre-chemoimmunotherapy era</th>
<th>Treatment</th>
<th>Pts (n)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shustik et al., 198851</td>
<td>Rai I, II</td>
<td>Observation vs. chlorambucil</td>
<td>48</td>
<td>At 5 years: 75 vs. 75, nonsignificant</td>
</tr>
<tr>
<td>Dighiero et al., 199854</td>
<td>Binet A</td>
<td>Observation vs. chlorambucil</td>
<td>609</td>
<td>At 10 years: 47 vs. 54, nonsignificant</td>
</tr>
<tr>
<td></td>
<td>Binet A</td>
<td>Observation vs. chlorambucil-prednisone</td>
<td>926</td>
<td>At 7 years: 69 vs. 69, nonsignificant</td>
</tr>
<tr>
<td>CLL Trialists' Collaborative Group, 199955</td>
<td>Binet A; Rai I, II</td>
<td>Observation vs. treatment</td>
<td>2001</td>
<td>At 10 years: 44 vs. 47, nonsignificant</td>
</tr>
</tbody>
</table>

**Chemoimmunotherapy era**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Pts (n)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweighofer et al., 201356 (abstract)</td>
<td>Observation vs. fludarabine–cyclophosphamide–rituximab</td>
<td>183</td>
<td>At 3.8 years: not reported, nonsignificant</td>
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</table>

**Summary of Evidence**

**Fit Patients (Without del(17p) or TP53 Mutation):** Purine analogs have replaced Cbl as the backbone of first-line chemotherapy for physically fit patients, based on the results of numerous RCTs (supplemental Table 2). Fludarabine remains the best-studied purine analog and the one most commonly prescribed for C.L.L. Based on improved OS and a 2-year improvement in median PFS, the randomized gcllsg C.L.L8 trial of untreated physically fit patients (CIRS score ≤ 6) is underway to compare the efficacy and safety of ibrutinib with a “watch and wait” approach in Binet A C.L.L with risk of disease progression defined by the comprehensive C.L.L score57. Long-term follow-up of those high-risk patients could provide additional insight about outcomes of early treatment in this patient cohort, but the potential benefit of early intervention with C.L.L drug therapy remains to be proven.

**Background**

Monotherapy with the alkylating agent chlorambucil (Cbl) was the standard-of-care therapy for C.L.L for several decades55. All published international guidelines currently recommend the addition of an anti-CD20 antibody to chemotherapy for the first-line treatment of C.L.L in most patients requiring therapy6,14,17–20. The chemotherapy agents recommended depend on factors such as patient age, functional status, presence of comorbidities, and organ function. For patients with del(17p) or TP53 mutation, recently updated guidelines recommend treatment with the kinase inhibitor ibrutinib14,17–19.
established rituximab–FC (compared with FC chemotherapy alone) as the standard of care. Subgroup analysis of prognostic factors showed that the positive effect of FCR was consistent in most prognostic groups and that the benefit of FCR was most pronounced in patients with mutated IGHV. However, FCR did not improve the survival of patients with del(17p) or TP53 mutation.

Several phase II studies have been initiated with the intent of improving the FCR regimen (supplemental Table 3); to date, however, few RCTs determining the efficacy of those treatments in comparison with FCR have been reported. Two studies investigated the addition of alemtuzumab to FC, observing greater toxicity related to infections (Table vi)34,58. Preliminary results from a randomized phase II study (Cancer and Leukemia Group B 10404) evaluating FR (fludarabine–rituximab), FR followed by 6 months of lenalidomide consolidation, and FCR in previously untreated patients with CLL have recently been reported (Table vi) and demonstrated shorter PFS with FR than with FCR66.

Bendamustine regimens have also been investigated as first-line therapy in prospective trials (Table v and supplemental Table 3)35,51,59,60. In the international randomized phase III noninferiority study cll10, the glls evaluated the efficacy and tolerability of BR (bendamustine–rituximab) compared with FCR for the first-line treatment of fit patients with CLL without del(17p) (Table vi)35,59,60. Median PFS was significantly longer in the FCR arm. Physically fit subgroups derived the most benefit from FCR therapy, but the difference in PFS between treatment groups was nonsignificant for patients more than 65 years of age and for those with a cirs score of 4–6 or the presence of more than 1 cirs item. After 5 years, no difference in OS was observed between the treatment arms; however, during treatment, infections were more frequent with FCR, especially in patients 65 years of age and older.

Less-Fit Patients (Without del(17p) or TP53 Mutation): The glls CLL11 trial investigated Clb in combination with anti-CD20 antibodies in previously untreated patients with CLL and comorbidities, demonstrating prolonged PFS and OS with the addition of anti-CD20 therapy (Table vi)61,62. Compared with ClbR (Clb–rituximab) treatment, treatment with Clb–obinutuzumab resulted in longer PFS and higher rates of complete response.

The international COMPLEMENT 1 study demonstrated similarly improved PFS with a combination of the anti-CD20 antibody ofatumumab and Clb compared with Clb alone; however, at the time of publication, no difference in OS had been reported64.

The randomized phase III MABLE study evaluated the efficacy and safety of BR compared with ClbR in an older less-fit CLL population (Table vi)65. In previously untreated patients, PFS was longer with BR than with ClbR. The magnitude of the benefit (10 months) was relatively modest; however, the Clb dose was considerably higher than in the CLL11 trial. Grade 3 adverse events were more common with BR than with ClbR, driven by a slightly higher rate of infection.

In the phase III randomized RESONATE-2 trial (pcyc-1115), ibrutinib was compared with Clb monotherapy in previously untreated patients with CLL for whom fludarabine-based therapy was considered inappropriate63. Compared with Clb, ibrutinib was associated with longer PFS (median: not reached vs. 18.9 months), significantly prolonged OS, and an 84% reduction in the risk of disease progression or death. The study has been criticized for its use of Clb monotherapy as a comparator because Clb was not a standard-of-care treatment option at the time of the study.

Patients with del(17p) or TP53 Mutation, or Both: Patients who have del(17p) or TP53 mutation often respond poorly to standard chemotherapy regimens, including FCR. Alemtuzumab, in combination with other agents, has been studied in prospective trials in this high-risk population (Table vi)67,68. The results from those studies suggest that treatment regimens containing alemtuzumab (compared with standard chemoimmunotherapy) might confer a modest improvement in responses for CLL with del(17p) or TP53 mutation; however, confirmatory phase III studies are required to assess the potential benefit of those therapies.

Two prospective phase III trials have reported results for single-agent ibrutinib in previously untreated patients with high-risk CLL (Table vi)69,70. In one study, 51 patients (35 untreated) with del(17p) or TP53 mutation were treated with ibrutinib, achieving impressive PFS and OS results70. Although the experience with ibrutinib as first-line treatment for patients with CLL and a del(17p) or TP53 mutation is still limited, current data suggest that this agent might provide durable disease control in treatment-naïve patients with CLL having del(17p) or TP53 mutation.

Recommendations
- For fit younger patients without del(17p) or TP53 mutation, we recommend RCH as the preferred first-line treatment (level of evidence: category 1).
- For fit elderly patients (more than 65 years of age) without del(17p) or TP53 mutation, BR is a reasonable treatment option and could be used in preference to RCH because of lesser toxicity (level of evidence: category 2A).
- For less-fit patients, for whom fludarabine therapy is considered inappropriate, and who do not have del(17p) or TP53 mutation, treatment with Clb–obinutuzumab or with ibrutinib monotherapy is recommended. In the absence of a prospective RCT comparing ibrutinib therapy with Clb–obinutuzumab (a current standard chemoimmunotherapeutic option in this population in Canada), it is not possible to determine which regimen is optimal in terms of long-term survival and toxicity (level of evidence: category 1).
- Patients with del(17p) or TP53 mutation should be offered ibrutinib as first-line treatment because of demonstrated high response rates and potentially long-lasting remissions in this high-risk population (level of evidence: category 2A).

Question 5
In which patients should additional treatment be considered after a response to first-line induction therapy?

Background
Although modern treatment options for CLL produce high response rates, almost all patients relapse, likely because...
**TABLE V** Randomized controlled trials of chemoimmunotherapy and targeted therapies

<table>
<thead>
<tr>
<th>Reference (study name)</th>
<th>Treatment Characteristics</th>
<th>Patients (n)</th>
<th>Response ORR:</th>
<th>Median follow-up</th>
<th>Survival Medians</th>
<th>Toxicity (grade 3 or 4)</th>
</tr>
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<tbody>
<tr>
<td>Hallek et al., 2010, Stilgenbauer et al., 2014, and Fischer et al., 2016&lt;sup&gt;10-12&lt;/sup&gt; (GCLLSG CLL8)</td>
<td><strong>Fludarabine-cyclophosphamide-rituximab vs. Fludarabine-cyclophosphamide</strong>&lt;br&gt;Median age: 61 years (range: 30–81 years); Binet C or A/B with active disease; ECOG PS: 0–1; CIRS: ≤6; CrCl ≥70 mL/min</td>
<td>817</td>
<td>90% vs. 80%, p=0.0001 CR: 44% vs. 22%, p=0.0001</td>
<td>5.9 Years</td>
<td>Median: 56.8 vs. 32.9 months; HR: 0.59; 95% CI: 0.50 to 0.69; p=0.001 At 3 years: 65% vs. 45%, p&lt;0.0001</td>
<td>Median: not reached vs. 86.0 months; HR: 0.68; 95% CI: 0.54 to 0.89; p=0.001 At 3 years: 87% vs. 83%, p=0.01</td>
</tr>
<tr>
<td>Lepretre et al., 2012&lt;sup&gt;58&lt;/sup&gt;</td>
<td><strong>Fludarabine-cyclophosphamide-rituximab vs. fludarabine-cyclophosphamide-alemtuzumab</strong>&lt;br&gt;Median age: 57 years (range: 51–64 years); Binet B, C; ECOG PS: &lt;2</td>
<td>165</td>
<td>91% vs. 90%, p=0.79 CR: 33.75% vs. 19.2%, p=0.04</td>
<td>Not reported</td>
<td>At 3 years: 82.6% vs. 72.5%, p=0.021</td>
<td>At 3 years: 90.1% vs. 86.4%, p=0.27</td>
</tr>
<tr>
<td>Eichhorst et al., 2013, Eichhorst et al., 2014, and Eichhorst et al., 2016&lt;sup&gt;55,59,60&lt;/sup&gt; (GCLLSG-CLL10)</td>
<td><strong>Fludarabine-cyclophosphamide-rituximab vs. bendamustine-rituximab</strong>&lt;br&gt;Median age: 61.6 years; Binet C or A/B with active disease; CIRS: ≤6; CrCl ≥70 mL/min</td>
<td>564</td>
<td>97.8% (both arms) CR: 40.7% vs. 31.5%, p=0.026</td>
<td>37.1 Months</td>
<td>Median: all pts—53.7 vs. 43.2 months, p=0.001; ≥65 years, with CIRS 4–6, or with &gt;1 CIRS item—p=NS; mutated IGHV—p=NS; pts with unmutated IGHV—43.9 vs. 34.0, p=0.015</td>
<td>At 3 years: 90.6% vs. 92.2%, p=NS</td>
</tr>
</tbody>
</table>

Recruitment halted because of excess toxicity: 8 patients receiving fludarabine-cyclophosphamide-rituximab died, 3 from lymphoma and 5 from infection.

Neutropenia: grade 3—29.6% vs. 38.7%, p=0.023; grade 4—19.4% vs. 25.26%, p=0.13

Leucocytopenia: grade 3—29.6% vs. 38.7%, p=0.023; grade 4—19.4% vs. 25.26%, p=0.13

Infections: overall—39.8% vs. 25.4%, p=0.001

≥65 years—48.4% vs. 26.8%, p=0.001
<table>
<thead>
<tr>
<th>Reference (study name)</th>
<th>Treatment</th>
<th>Median follow-up</th>
<th>Patients Characteristics</th>
<th>Response</th>
<th>Survival</th>
<th>Toxicity (grade 3 or 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geisler et al., 201414</td>
<td>Fludarabine-cyclophosphamide-alemtuzumab vs. fludarabine-cyclophosphamide</td>
<td>42.8 Months</td>
<td>Median age: not reported; WHO PS: ≤2; presence of either unmutated IGHV, del(17p), del(11q), or trisomy 12</td>
<td>ORR: 88% vs. 78%, p=0.036 CR: 53% vs. 42%, p=0.071</td>
<td>At 3 years: 53% vs. 37%,Median: 37 vs. 29 months, p&lt;0.01</td>
<td>At 3 years: all pts—NS; pts &lt;65 years—88% vs. 76%, p=0.035 Infections overall: 81 vs. 70, p=NS Opportunistic infections: 28 vs. 11, p=0.002 Organ toxicity: 36 vs. 13, p=0.0005 Flu-like syndrome: 27 vs. 3, p=0.0001</td>
</tr>
<tr>
<td>Goede et al., 2014, and Goede et al., 201563,62 (GCLLSG CLL11)</td>
<td>(A) Chlorambucil-obinutuzumab vs. (B) chlorambucil-rituximab vs. (C) chlorambucil</td>
<td>4 Years</td>
<td>Median age: 73 years; Binet C or symptomatic; CIRS: &gt;6 or CrCl: 30–69 mL/min</td>
<td>ORR: A vs. C—77.3% vs. 31.4%, p&lt;0.001; B vs. C—65.7% vs. 31.4%, p&lt;0.001; A vs. B—78.4% vs. 65.1%, p&lt;0.001 CR: A vs. B—20.7% vs. 7.0%, p&lt;0.001</td>
<td>Median: A vs. C—26.7 vs. 11.1 months, p&lt;0.001; B vs. C—16.3 vs. 11.1 months, p&lt;0.001; A vs. B—29.2 vs. 15.4 months, p&lt;0.001</td>
<td>Median: A vs. C—85% vs. 71%, p=0.0014; B vs. C—81% vs. 71%, p=0.024; A vs. B—87% vs. 81%, p=0.0632 At 4 years: A vs. C—85% vs. 71%, p=0.0014; B vs. C—81% vs. 71%, p=0.024; A vs. B—87% vs. 81%, p=0.0632 Infections: A 11% vs. B 13% vs. C 14% Infusion reactions: A 20% vs. B 4%</td>
</tr>
<tr>
<td>Burger et al., 201563 (RESONATE-2)</td>
<td>Ibrutinib vs. chlorambucil</td>
<td>18.4 Months</td>
<td>Median age: 73 years (range: 65–90 years; 70% ≥70 years); ECOG PS: ≥2</td>
<td>ORR: 86% vs. 35%, p&lt;0.001 CR: not reached vs. 18.9 months</td>
<td>Median: not reached vs. 18.9 months</td>
<td>At 24 months: 98% vs. 85% (estimate); HR: 0.16; 95% CI: 0.05 to 0.56; p=0.001 Low toxicity with both regimens</td>
</tr>
<tr>
<td>Hillmen et al., 201564 (COMPLEMENT 1, OMB110911)</td>
<td>Chlorambucil-ofatumumab vs. chlorambucil</td>
<td>28.9 Months</td>
<td>Median age: 69 years (82% ≥65 years or ≥2 comorbidities, or both)</td>
<td>ORR: 82% vs. 69%, p=0.001 CR: 14% vs. 1%</td>
<td>Median: not reached</td>
<td>Neutropenia: 26% vs. 14% Infections: 12% vs. 9%</td>
</tr>
<tr>
<td>Reference (study name)</td>
<td>Treatment (Characteristics)</td>
<td>Median follow-up (months)</td>
<td>Patients (n)</td>
<td>Response (ORR, CR)</td>
<td>Median (response)</td>
<td>Survival (grade 3 or 4)</td>
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<tr>
<td>Michallet et al., 2015&lt;sup&gt;15&lt;/sup&gt; (MABLE study, abstract)</td>
<td>Bendamustine–rituximab vs. chlorambucil–rituximab</td>
<td>24</td>
<td>Ineligible for fludarabine</td>
<td>65</td>
<td>91% vs. 86%, p=0.304</td>
<td>40 vs. 30 months; HR: 0.523; 95% CI: 0.339 to 0.806; p=0.003</td>
</tr>
<tr>
<td>Ruppert et al., 2017&lt;sup&gt;66&lt;/sup&gt; (Alliance Trial, CALGB 10404)</td>
<td>(A) Fludarabine–cyclophosphamide–rituximab vs. fludarabine–rituximab–lenalidomide vs. fludarabine–rituximab</td>
<td>24</td>
<td>Not reported</td>
<td>342</td>
<td>Not reported</td>
<td>Not reached for any group</td>
</tr>
</tbody>
</table>

GCLLSG = German CLL Study Group; ECOG PS = Eastern Cooperative Oncology Group performance status; CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ORR = overall response rate; CR = complete response rate; HR = hazard ratio; CI = confidence interval; MRD = minimal residual disease; pts = patients; NS = nonsignificant; WHO PS = World Health Organization performance status.

**Summary of Evidence**

**Consolidation or Maintenance Drug Therapy:** Two randomized trials of high-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (HSCT) have been published (Table 5). **Auto-HSCT:** One randomized trial of rituximab-based induction chemotherapy with autologous stem cell transplantation after induction therapy (i.e., clinical trials with autologous HSCT) was identified (supplemental Table 6). The authors reported that patients who received autologous HSCT had significantly longer progression-free survival (PFS) and overall survival (OS) compared to those who did not receive HSCT. **Allo-HSCT:** No prospective studies comparing allo-HSCT with autologous HSCT were identified in the literature. Since about 2008, maintenance treatments are now commonly recommended in other lymphoid malignancies such as follicular lymphoma and mantle-cell lymphoma. Maintenance therapy is a promising concept that can further improve the quality and duration of response in patients with cHL.

**High-dose therapy (with or without total-body irradiation)** remains a curative treatment option for some patients, but it is not recommended for the frontline treatment of cHL patients in the current era of effective targeted therapies.

**Conclusion of Maintenance Drug Therapy:** Two randomized trials of high-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (HSCT) have been published (Table 5). Although current evidence indicates that the outcomes of HDT with rituximab maintenance are comparable to those of HDT with autologous HSCT, further randomized trials are needed to confirm these findings.
<table>
<thead>
<tr>
<th>Reference (study name)</th>
<th>Treatment</th>
<th>Median follow-up</th>
<th>Patients Characteristics (n)</th>
<th>Response ORR: 85% CR: 65%</th>
<th>Survival Progression-free Median: 18.3 months Overall Median: 38.9 months</th>
<th>Toxicity Neutropenia: 64.1% Thrombocytopenia: 30.8% Anemia: 30.8% Infection (overall): 51.3% Febrile neutropenia: 17.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettitt et al., 2012[^67]</td>
<td>Alemtuzumab–prednisone</td>
<td>Not reported</td>
<td>Median age: 61.5 years; TP53 mutation 17</td>
<td>ORR: 85% CR: 65%</td>
<td>Median: 18.3 months Overall Median: 38.9 months</td>
<td>Neutropenia: 64.1% Thrombocytopenia: 30.8% Anemia: 30.8% Infection (overall): 51.3% Febrile neutropenia: 17.9%</td>
</tr>
<tr>
<td>Mauro et al., 2014[^46]</td>
<td>Fludarabine–alemtuzumab</td>
<td>Not reported</td>
<td>Age: ≤ 60 years; Binet A–C with progressive disease; presence of high-risk genetic features 45</td>
<td>ORR: 95% CR: 30%</td>
<td>At 3 years: 42.5% Overall At 3 years: 79.9%</td>
<td>Neutropenia: 33% Infection: 11%</td>
</tr>
<tr>
<td>Burger et al., 2015, and Jain et al., 2016[^63,^69]</td>
<td>Ibrutinib–rituximab</td>
<td>47 Months</td>
<td>Median age: 65 years; del(p17) or TP53 mutation, or both: untreated and previously treated 40 (previously untreated: 4)</td>
<td>ORR: 95% CR: 23%</td>
<td>Median: 45 months Overall Median: not reached (not specified)</td>
<td>Few grade 3 or 4 adverse events</td>
</tr>
<tr>
<td>Farooqui et al., 2015[^70]</td>
<td>Ibrutinib</td>
<td>24 Months</td>
<td>Median age previously untreated: 62 years (range: 33–82 years); del(p17) or TP53 mutation, or both: untreated and previously treated 51</td>
<td>ORR: 97%, previously untreated PR: 55%, previously untreated At 24 months: all pts—82% (95% CI: 71% to 94%)</td>
<td>At 24 months: previously untreated pts—84% (95% CI: 72% to 100%)</td>
<td>Neutropenia: 24% (no neutropenic fevers) Anemia: 14% Thrombocytopenia: 10%</td>
</tr>
</tbody>
</table>

ORR = overall response rate; CR = complete response; PR = partial response; CI = confidence interval.
search. Although allo-HSCT has curative potential, this treatment option has additional limitations related to age, comorbidity, and donor availability.

**Recommendations**

- No current high-quality evidence supports the use of maintenance therapy in patients with CLL after first-line therapy (level of evidence: category 2A).
- Given the lack of a survival benefit, we do not recommend HDT with auto-HSCT in its current form as a consolidative approach after first-line therapy (level of evidence: category 2A).
- Allo-HSCT is not currently recommended as part of first-line therapy for CLL (level of evidence: category 2B).

**CONFLICT OF INTEREST DISCLOSURES**

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: CO reports personal fees from Roche, Janssen, Gilead, AbbVie, Merck, AstraZeneca, and Lundbeck/Teva outside the submitted work; VB sits on advisory boards for AstraZeneca, AbbVie, Janssen, Lundbeck, Gilead, Roche, and has received grants from Research Manitoba, the Cancer Care Manitoba Foundation, and Lundbeck outside the submitted work; ASG reports personal fees from Janssen, Lundbeck, and AbbVie outside the submitted work; SA reports personal fees from Roche and Pfizer outside the submitted work; CC reports other considerations from Celgene, Janssen, and Gilead outside the submitted work; KSR reports personal fees from Celgene, Janssen, Gilead, Roche, AstraZeneca, and AbbVie outside the submitted work; EL reports grants from Roche, Gilead, and Lundbeck during the conduct of the study; GF reports grants and personal fees from Celgene and AbbVie, and personal fees from Janssen outside the submitted work.

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48. Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): final analysis of an international, randomized study of the German CLL Study Group (gclls). *Blood* 2014;124:19.


