A Canadian Perspective on the First-Line Treatment of Chronic Lymphocytic Leukemia

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Abstract

Despite important advances in the treatment of first-line chronic lymphocytic leukemia (CLL) over the past decade, CLL remains an incurable disease with significant unmet needs. The combination of rituximab with fludarabine and cyclophosphamide (FCR) significantly improved overall survival and progression-free survival compared with fludarabine and cyclophosphamide alone in first-line treatment of CLL. However, because of its high toxicity, FCR is only recommended for younger, fit patients who can tolerate the treatment. This excludes a large fraction of CLL patients who are elderly and/or who have comorbidities. Thus, determining the appropriate treatment choices for this group of patients who are unfit for FCR treatment is a significant challenge in CLL. Current treatment choices in Canadian practice include bendamustine with rituximab, fludarabine with rituximab, and chlorambucil with rituximab. Two novel monoclonal antibodies, ofatumumab and obinutuzumab, have also recently received Health Canada approval for the first-line treatment of CLL patients in combination with chlorambucil. In addition, the Bruton tyrosine kinase inhibitor, ibrutinib, has recently been approved by Health Canada for the first-line treatment of CLL patients with deletion 17p. In the coming years, several other novel agents that are being developed are likely to change the CLL treatment landscape dramatically, however, because these novel agents are currently unavailable, the purpose of this review is to recommend the best treatment approaches in Canada using currently available therapies.

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Introduction

Chronic lymphocytic leukemia (CLL) is a hematopoietic neoplasia, characterized by the clonal proliferation and accumulation of small, mature-appearing, immunologically incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen.[1] Of all adult leukemias, CLL is the most common in North America and is a disease of the elderly, with a median age at the time of diagnosis between 67 and 72 years.[1]

According to the most recent cancer statistics in Canada, approximately 2000 patients were diagnosed with CLL in 2010.[2] A recent report suggests that this figure might be substantially greater at 7.99 per 100,000 people per year, based on data collected from 1998 to 2003.[3]

The clinical course of CLL varies widely, with the survival of patients ranging from <1 to 2 years to >15 years.[4] Several prognostic markers have been identified that might explain this clinical heterogeneity. These include negative prognostic factors such as immunoglobulin (Ig) variable heavy chain (IgHV) unmutated status, and high expression levels of CD38 and ZAP-70 (zeta-chain (TCR) associated protein kinase 70kDa).[5,6] A close relationship between cytogenetic abnormalities and prognosis has also been established.[7] With the use of interphase fluorescence in situ hybridization, cytogenetic lesions can be identified in >80% of all patients with CLL.[8] Of the cytogenetic abnormalities identified thus far, patients with del(17p) have demonstrated the worst prognosis, followed by those with del(11q).[7]

Over the past decade, the treatment of CLL has changed significantly, resulting in dramatic improvements in patient outcomes. In the pivotal CLL8 study, the combination of rituximab with fludarabine and cyclophosphamide (FCR) significantly improved overall survival (OS) and progression-free survival (PFS) compared with fludarabine and cyclophosphamide (FC) alone in the first-line treatment of CLL, marking the first ever demonstration

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of an OS advantage in a phase III CLL trial.[9] Based on these encouraging results, FCR was approved by Health Canada in August 2009 for the first-line treatment of patients with CLL,[10] and since then has become the standard of care in many provinces for young and fit patients. Despite the improved efficacy demonstrated by this chemoimmunotherapy regimen, FCR is associated with a high frequency of Grade 3/4 toxicity, and persistent cytopenias lasting up to 9 months after therapy completion.[9,11-13] Consequently, because CLL is a disease of the elderly, with the average patient older than 65 years of age and with at least 3 other health conditions,[14,15] FCR is not suitable as front-line therapy for most patients with CLL. In fact, according to a database analysis by Dr James Johnston, Professor in the Department of Internal Medicine at the University of Manitoba, FCR is only suitable for approximately one-third of all patients with CLL.[16] This highlights the significant need for effective and better tolerated first-line therapy options in patients who are not appropriate candidates for treatment with FCR. In addition, because patients with del(17p) respond poorly to standard chemoimmunotherapy regimens, there is also a significant unmet need for safe and effective first-line therapies for the approximately 5% of CLL patients with 17p deletions.[7,17,18]

To begin to address the need for multiple therapeutic options that can safely and effectively treat CLL patients with diverse patient and disease characteristics, several new treatment options have been developed and are now available in Canada. The purpose of this document is to provide an update on currently approved front-line treatment options for CLL in Canada, and to provide guidance to health care practitioners on how to choose the optimal treatment option.

The Treatment of CLL Patients

Decision to Treat

One of the most important treatment decisions in patients with CLL is the decision of when to initiate treatment at all.[8] In 2008, the International Workshop on CLL (iwCLL) published updated guidelines for the management of CLL, which recommends that patients with early-stage CLL (Rai stage 0, Binet stage A) receive regular monitoring without treatment until there is evidence of disease progression. In contrast, treatment can be recommended for patients with advanced-stage CLL (Rai stage II-IV or Binet stage B or C), although some of these patients might be monitored until progressive or symptomatic disease, as defined according to iwCLL criteria (Table 1).[8]

Table 1 National Cancer Institute Minimum Criteria for Initiating Treatment

- Evidence of progressive marrow failure (anemia and/or thrombocytopenia)
- Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Progressive lymphocytosis with an increase of >50% over a 2-month period
- Lymphocyte doubling time of <6 months
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Disease-related symptoms such as unintentional weight loss of 10% or more within the previous 6 months, significant fatigue, fevers of >100.5°F or 38.0° C for ≥2 weeks without other evidence of infection; or night sweats for more than 1 month without evidence of infection

Adapted from Hallek et al.[8]

Goals of Treatment

Although the clinical behavior of untreated CLL varies from a long-term indolent disease to a rapidly progressive one, it remains an incurable condition. Consequently, the goals of treatment and the choice of first-line therapy will depend on the patient characteristics, including age, comorbidities, organ function, performance status, and patient preference.[19,20] Depending on the patient, the goals of CLL treatment might be to induce deep or long-lasting remission, achieve good response that balances efficacy with toxicity, or provide palliative care.[19] Deep remission, which can be quantified by minimal residual disease (MRD) negativity, should be the goal of treatment in younger patients without comorbidities. In patients with a short life expectancy because of other health conditions, palliative treatment is an appropriate goal. The challenge in CLL is that most patients are older or have comorbidities and are thus not able to tolerate aggressive chemoimmunotherapy, instead requiring treatments that balance efficacy with tolerability. In such patients, the goals of treatment are therefore to prolong treatment-free intervals while maintaining quality of life (QoL). An important facet of maintaining QoL is to minimize toxicities associated with therapy. The challenge of balancing the efficacy and toxicity of treatment is compounded by the inadequacy of standard fitness assessment tools in aiding treatment decisions. Although validated fitness assessment tools such as the Cumulative Illness Rating Scale for comorbidities and the Eastern Cooperative Oncology Group score for performance status have become routine in clinical trials, physicians routinely use personal judgement to make treatment decisions.

First-Line Treatment Options

For a summary of key phase III trials for the first-line treatment of CLL, please see Appendix A.[9,22,28,29,31-33,44,45,50,52] A detailed overview of currently available regimens is presented in the following sections.

Single Agents

Chlorambucil. For several decades after its discovery, chlorambucil was considered the "gold standard" for the treatment of CLL.[1] Besides its low cost and convenience of being an oral drug, chlorambucil is associated with a low toxicity profile, which makes it a reasonable option for frail patients. Disadvantages of chlorambucil include the very low complete response (CR) rates (2%-7%), low overall response rate (ORR; 40%-70%), and a PFS of approximately 1 year associated with treatment.[1,21] In addition, its use can be associated with prolonged cytopenia, myelodysplasia, and secondary acute leukemia after prolonged use.[1]

Fludarabine. The purine analogue, fludarabine, was first shown to be effective in patients whose disease was refractory to traditional alkylating agents, with an ORR of approximately 60%.[22,23] Subsequently, fludarabine proved to be effective as a first-line treatment, with studies showing a prolonged PFS (median of approximately 2 years) compared with chlorambucil, and response rates of 60% to 80% and CR rates of 15% to 40%.[22,24-26] In addition, fludarabine monotherapy was more effective than other conventional chemotherapies, including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); CAP (cyclophosphamide, doxorubicin, prednisone); or chlorambucil.[22,25-27] A long-term analysis of