Novel Therapies for Chronic Lymphocytic Leukemia: A Canadian Perspective

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common adult lymphoproliferative disorder in Western countries. The current standard of care for CLL is chemoimmunotherapy, typically with fludarabine, cyclophosphamide, and rituximab (FCR). However, most patients with CLL are elderly with comorbidities and are unable to tolerate FCR. In order to choose the best treatment for each individual patient, physicians must balance efficacy with toxicity. In addition, most currently available treatments are ineffective in CLL patients with loss of TP53. Two groups of novel therapeutic agents—anti-CD20 monoclonal antibodies and small molecule inhibitors—are attempting to address these issues, and 5 of these agents have progressed to phase 3 trials: obinutuzumab, idelalisib, ibrutinib, venetoclax (ABT-199), and duvelisib (IPI-145). We present the current evidence for these novel agents in the treatment of CLL, along with the perspectives of 4 Canadian oncology experts.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 11, 627-34
Keywords: Chronic lymphocytic leukemia, Duvelisib, Ibrutinib, Idelalisib, Monoclonal antibodies, Obinutuzumab, Small molecule inhibitors, Venetoclax

Introduction

In Western countries, chronic lymphocytic leukemia (CLL) is the most common adult lymphoid malignant disease.[1] Patients with CLL can vary widely with respect to comorbidities, organ function, and age. However, CLL is primarily a disease of the elderly: the median age at which patients are diagnosed is 72 years, and 70% of patients with CLL are at least 65 years of age at diagnosis.[2]

Most patients with CLL (approximately 80%) have a detectable genetic aberration; the most frequent abnormalities include deletions of the long arm of chromosome 13 (del(13q)) or chromosome 11 (del(11q)), and trisomy 12.[3] The mutation that currently informs treatment decisions for CLL is the deletion of the short arm of chromosome 17 (del(17p)) or mutations in the tumor protein 53 (*TP53*) gene in this region. Approximately 7% to 8% of patients with CLL have del(17p) at diagnosis, and a significantly greater proportion acquire it with relapsed CLL.[1,3,4] Patients with the worst median survival times are those with del(17p), followed by patients with del(11q), then patients with trisomy 12 and normal karyotypes; patients with del(13q) have more favorable outcomes with the longest estimated survival times.[3]

The current standard of care for CLL is chemoimmunotherapy with fludarabine and cyclophosphamide (FC) plus rituximab, the first type I anti-CD20 monoclonal antibody (mAb) to be approved by the US Food and Drug Administration (FDA). This standard of care was established on the basis of data from the phase 3 CLL8 study comparing FC with FC plus rituximab (FCR) that showed the addition of rituximab to FC improved response rates, progression-free survival (PFS), and overall survival (OS).[1] However, patients in the CLL8 study experienced significant grade 3/4 toxicities, which is not unusual, given that higher treatment efficacy is typically accompanied by higher rates of toxicity.[5] When FCR was compared with bendamustine plus rituximab (BR) in the CLL10 study, patients treated with FCR had higher complete response (CR) rates and longer PFS than those treated with BR.[6] The patients in each of the CLL8 and CLL10 studies were also considered fit and had a median age of approximately 61 years, which is significantly younger than the median age at which most patients are diagnosed. For elderly (ie, 65 years of age and older), fit patients in the CLL10 study, FCR dose reductions were necessary due to high toxicity and infection rates,

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Submitted: May 19, 2015; Revised: Jul 9, 2015; Accepted: Jul 28, 2015; Epub: Aug 05, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.07.649

which resulted in similar efficacy between the FCR and BR treatment groups.[6] These results suggest that elderly, fit patients could benefit from BR as an alternative treatment because of the lower rates of neutropenia and severe infections reported with BR compared with FCR in this patient population.

Because most patients with CLL are elderly with comorbidities, most are unable to tolerate FCR. Frail patients with CLL are typically treated with chlorambucil, which has less toxicity than more aggressive treatments such as fludarabine and bendamustine. However, chlorambucil is less effective than these therapies in many CLL patients.[7,8] FCR is also unsuitable for patients with del(17p). As shown in the CLL8 study, PFS at 3 years was 65% overall in the FCR group but only 18% in patients with del(17p).[1]

Therefore, 2 major difficulties exist in the current treatment of CLL in Canada. The first is that current treatments require physicians to balance efficacy with toxicity in order to choose the best treatment for each patient. The second is that most current treatments are ineffective in patients with del(17p). New therapeutic agents are attempting to address these issues, and 5 have progressed to phase 3 trials: obinutuzumab, idelalisib, ibrutinib, venetoclax (ABT-199), and duvelisib (IPI-145). The current evidence on these treatments is presented here; key studies are summarized in Table 1, with key study results presented in Supplemental Table 1 in the online version. In addition, the perspectives of 4 Canadian experts from British Columbia, Alberta, Quebec, and Ontario are presented.

Novel Treatments for CLL

The molecular pathways that promote normal B-cell development, expansion, and survival, which includes the B-cell receptor signaling pathway, are proposed to play a key role in CLL pathogenesis.[9,10] Two therapeutic strategies target these pathways: anti-CD20 mAbs and small molecule inhibitors. First, mAbs that target the CD20 antigen on B cells induce tumor killing by a number of mechanisms, including direct induction of apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity.[11] The novel type II mAb obinutuzumab will be described in detail here. Second, small molecule inhibitors have been developed to target the B-cell receptor pathways, including the phosphatidylinositol-3-kinase

Table 1 Summary of Key Studies

Study	Study Design	Key Efficacy Data	Key Safety Data
Obinutuzumab			
CLL11 (Goede et al, *N Engl J Med* 2014; Goede et al, *Leukemia* 2015)	• Clb vs. R-Clb vs. G-Clb • Previously untreated CLL and comorbidities	• PFS: Longer in G-Clb vs. R-Clb: 29.2 vs. 15.4 months (HR, 0.40; $P < .001$) • OS: No statistically significant OS benefit for G-Clb vs. R-Clb (HR, 0.70; $P = .0632$). • OS: G-Clb vs. Clb (HR, 0.47; $P = .0014$) • OS: R-Clb vs. Clb (HR, 0.60; $P = 0.0242$. • MRD negativity: 10-fold higher with G-Clb vs. R-Clb	• Similar toxicity profiles. • Higher rates of IRR and thrombocytopenia with G-Clb vs. R-Clb.
Idelalisib			
Study 116 (Furman et al, *N Engl J Med* 2014)	• Idelalisib + rituximab vs. rituximab • Relapsed CLL with comorbidities	• PFS: Idelalisib + rituximab, not reached vs. rituximab, 5.5 months • OS at 12 months: Idelalisib + rituximab, 92% vs. rituximab, 80% (HR, 0.28, $P = .02$)	• SAEs occurred in 40% of the idelalisib + rituximab group vs. 35% in the rituximab group.
Ibrutinib			
RESONATE (Byrd et al, *N Engl J Med* 2014)	• Ibrutinib vs. ofatumumab • R/R CLL/SLL	• Median PFS: Ibrutinib, not reached vs. Ofatumumab, 8.1 months (HR, 0.22, $P < .001$) • 12-month OS: Ibrutinib, 90% vs. Ofatumumab, 81% (HR, 0.43, $P = .005$)	• Most frequent nonhematologic AEs: diarrhea, fatigue, pyrexia and nausea (Ibrutinib) vs. fatigue, IRRs and cough (Ofatumumab).
Venetoclax (ABT-199)			
Roberts et al, *Blood* 2014; 124:325	• Venetoclax + rituximab • R/R CLL/SLL	• Of the 34 patients evaluable for response: ORR: 88% • CR/CRi: 32%	• The most common grade 3 to 4 AEs were neutropenia (47%), thrombocytopenia (16%) and anemia (14%). Treatment-emergent SAEs occurred in 20 patients (41%); the most common were pyrexia (6%) and febrile neutropenia, IRR, TLS and Richter transformation (4% each). • The recommended phase 2 dose of venetoclax is 400 mg daily.
Duvelisib (IPI-145)			
O'Brien et al, *Blood* 2014; 124:3334	• Duvelisib • R/R CLL	• ORR: Of the 49 evaluable patients, the best ORR was 55%, including 1 CR and 26 PR; ORR was similar regardless of dose or presence of TP53mut/del(17p)	• To date, the most common grade 3 or higher AEs were neutropenia (31%), thrombocytopenia (11%), febrile neutropenia (15%) and pneumonia (11%).

Abbreviations: AE = adverse event; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = CR with incomplete marrow recovery; DLT = dose-limiting toxicity; G-Clb = obinutuzumab, chlorambucil; HR = hazard ratio; IRR = infusion-related reaction; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R-Clb = rituximab, chlorambucil; R/R = relapsed/refractory; SAE = serious adverse event; SLL = small lymphocytic lymphoma; TLS = tumor lysis syndrome.