About the Authors

Chathuri Abeyakoon, MD

Dr. Chathuri Abeyakoon has recently completed a clinical research fellowship in Lymphoma, Myeloma, and Autologous Stem Cell Transplantation at the Princess Margaret Cancer Centre. Prior to her fellowship in Canada, she completed hematology training in Australia and is a Fellow of both the Royal Australasian College of Physicians and the Royal College of Pathologists Australasia. She has now returned to Melbourne, Australia, to continue her career as a clinician investigator and is a hematologist at Monash Health. Her interest lies in optimizing treatment outcomes with novel and targeted agents in aggressive lymphomas.

Affiliations: Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON
Monash Haematology, Monash Health, Melbourne, VIC, Australia.

Abi Vijenthira, MD

Dr. Abi Vijenthira is a hematologist in the Division of Medical Oncology & Hematology at Princess Margaret Cancer Centre and an assistant professor in the Department of Medicine at the University of Toronto. Her clinical focus is lymphoma, with a special interest in chronic lymphocytic leukemia. Her research focus involves population-based health outcomes research and novel therapy approaches for patients with lymphoma.

Affiliations: Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON.
Department of Medicine, University of Toronto, Toronto, ON

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Front-line Treatment for Chronic Lymphocytic Leukemia in 2025: Finite Duration Versus Continuous Treatment

Chathuri Abeyakoon, MD
Abi Vijenthira, MD

Introduction

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative disorder and is the most common hematologic malignancy in Western populations. In Canada, an estimated 2,000 or more new cases are diagnosed each year.[1] Improvements in diagnostic techniques, enhanced prognostication methods, and the development of targeted treatments have revolutionized the management of CLL over the past decade. Despite an ever-expanding therapeutic landscape (**Figure 1**), the decision to initiate treatment continues to be guided by the International Workshop on CLL criteria.[2]

For patients who require treatment, we now have a choice of two treatment approaches based on current Health Canada approvals: fixed-duration therapy (e.g., chemoimmunotherapy, venetoclax-obinutuzumab [VO], or ibrutinib-venetoclax [IV]) versus continuous treatment until disease progression or toxicity (i.e., Bruton's tyrosine kinase inhibitors [BTKi]). In this review, we will summarize the evidence for these two approaches and provide our views on factors that may influence treatment selection.

Prognostic Factors in the Front-line Setting

The pioneering Rai[3] and Binet[4] staging systems utilize easily accessible clinical and laboratory parameters and have previously predicted overall survival (OS). However, these systems were developed in the chemotherapy era and are no longer used for prognostication. In the modern era, biomarkers such as b2-microglobulin, immunoglobulin heavy chain (*IGHV*) gene mutational status, and the presence of del(17p) and/or *TP53* mutations are well-established prognostic factors.[2,5] These three factors, together with age and clinical stage, have since been combined to form the CLL International Prognostic Index (CLL-IPI), which has been validated in various cohorts with moderate predictive capability in the modern era.[6,7] In the era of targeted therapies such as VO, other cytogenetic prognostic markers, such as del(13q), trisomy 12, del(11q), and even complex karyotype do not appear to have a significant prognostic impact.[8-11]

In the Canadian clinical landscape, next-generation sequencing for recurrently mutated genes in CLL other than *TP53* (e.g., *NOTCH1, SF3B1, ATM*) is not yet widely available. Currently, we lack sufficient data to recommend differing treatment approaches for patients with CLL-related mutations outside of *TP53*.

Deciphering Evidence That May Influence Treatment Choice

When considering treatment choice, it is important to thoughtfully consider the following questions and discuss them with the patient: **1)** is the convenience of an oral BTKi worth the toxicity and costs?; **2)** is the chance of cure for patients with favourable prognostic factors worth the risk of therapy-related myeloid neoplasms (tMN); **3)** is the inconvenience of ramp-up and the risk of B cell depletion during the post-pandemic era worth the treatment-free interval with VO?; **4)** is the convenience of two oral drugs worth the cardiac toxicities, particularly with ibrutinib-venetoclax?; and **5)** what is the best approach for high-risk patients?

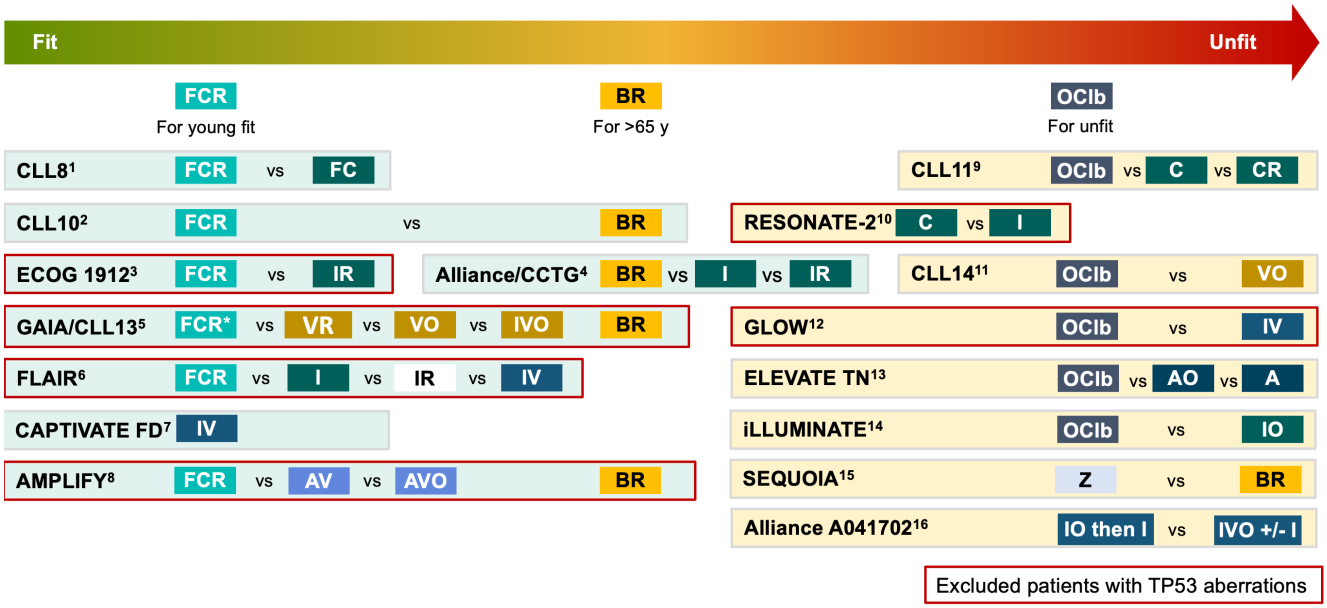

Figure 1. Published front-line treatment approaches for chronic lymphocytic leukemia; *adapted with permission from Dr. Al-Sawaf.*

[1]NCT00281918; [2]NCT00769522; [3]NCT02048813; [4]NCT01886872; [5]NCT02950051; [6]EudraCT number 2013-001944-76; [7]*non-randomized NCT02910583, [8]NCT03836261; [9]NCT01010061; [10]NCT01722487; [11]NCT02242942; [12]NCT03462719; [13]NCT02475681; [14]NCT02264574; [15]NCT03336333, [16]NCT03737981

Abbreviations: A: acalabrutinib; **AO:** acalabrutinib, obinutuzumab; **AV:** acalabrutinib, venetoclax; **AVO:** acalabrutinib, venetoclax, obinutuzumab; **BR:** bendamustine, rituximab; **C:** chlorambucil; **CR :** chlorambucil, rituximab; **FC:** fludarabine, cyclophosphamide; **FCR:** fludarabine, cyclophosphamide, rituximab; **I:** ibrutinib; **IO:** ibrutinib, obinutuzumab; **IR:** ibrutinib, rituximab; **IV:** ibrutinib, venetoclax; **IVO:** ibrutinib, venetoclax, obinutuzumab; **OClb:** obinutuzumab, chlorambucil; **VO:** venetoclax, obinutuzumab; **VR:** venetoclax, rituximab; **Z:** zanubrutinib.

BTKi: Balancing Convenience and Efficacy with Toxicity and Financial Impact

Ibrutinib is a first-generation BTKi, and its efficacy has been demonstrated in both older and younger patients with newly diagnosed CLL. Ten-year extended follow-up of the Phase 3 RESONATE-2 study of older patients (>65 years) confirmed sustained benefit of ibrutinib with a median progression-free survival (PFS) of 8.9 years (95% confidence interval [CI]: 7- not estimable [NE]).[12] Similar excellent efficacy was shown in the E1912 trial in young, fit patients.[13] Remarkably, patients treated with front-line ibrutinib have been shown to have similar OS as age-matched controls.[14]

However, the enthusiasm for BTKi is tempered by its risks. Despite the convenience of an oral treatment option, a significant discontinuation rate of both first- and second-generation BTKi has been noted in clinical trials and real-world evidence, predominantly due to arthralgia, rash, atrial fibrillation (AF), and infection.[15,16] A Canadian population-based cohort study found a high cumulative incidence of serious atrial fibrillation, bleeding, and heart failure in patients on ibrutinib compared to non-ibrutinib-treated CLL controls.[17] Similar risks have been confirmed in other analyses.[18,19] Although there are currently no head-to-head studies comparing first-generation versus second-generation BTKi in the front-line setting, the ELEVATE-RR and ALPINE studies comparing acalabrutinib or zanubrutinib to ibrutinib in the relapsed/refractory setting have demonstrated improved safety of these agents over ibrutinib, hence, second-generation BTKi are preferred over ibrutinib.[20,21] Notably, however, all BTKis are

associated with cardiac risks, including sudden cardiac death, with a black box warning about this risk in 1% of ibrutinib-treated patients.[22] Ventricular arrhythmias and sudden deaths have also been reported with both acalabrutinib and zanubrutinib.[23,24]

From a health economic perspective, continuous BTKi treatment has an associated greater all-cause monthly healthcare cost and CLL-related ongoing costs after the first 12 months of commencing treatment when compared to front-line VO.[25]

FCR: Balancing Potential for a Cure Against the Risk of tMN

Six cycles of FCR (fludarabine, cyclophosphamide, and rituximab) was historically the standard front-line treatment in fit patients based on its superior efficacy demonstrated by the CLL8 and CLL10 trials, in which patients with mutated-IGHV (M-IGHV) were shown to derive the greatest benefit, while the shortest PFS was observed in patients with del(17p) and/or del(11q).[26,27] Durable remission in M-IGHV disease with FCR after a median follow-up of 19 years from a Phase II study raised the possibility of a functional cure with FCR in this subgroup, especially in those achieving measurable residual disease (MRD) negativity at end-of-treatment.[28]

With the enthusiasm of a potential 'functional cure', it is important to consider treatment-related toxicity, in particular tMN, which was observed in a noteworthy 6.3% of patients in the previously mentioned data.[28] It is recognized that pre-existing clonal hematopoiesis of indeterminate potential (CHIP) may be a risk factor for tMN.[29] Therefore, rather than leaving behind a potential cure, perhaps aiming to optimize patient selection by administering FCR only to those with M-IGHV in the absence of *TP53* aberrations and no pre-existing CHIP may be a future research question.

Venetoclax-obinutuzumab

The efficacy of fixed-duration VO was established in the CLL13 and CLL14 trials for fit patients and patients with comorbidities, respectively.[30-33] In the CLL14 study, factors associated with shorter PFS included bulky disease (>5 cm), unmutated-IGHV (U-IGHV), and *TP53* aberrations. However, for the majority of patients, VO is an appealing option with a fixed treatment duration of 48 weeks and an expected significant treatment-free interval. After 6 years of follow-up in CLL14, time to next treatment was approximately 7 years (85 months) in patients with U-IGHV, and not reached in patients with M-IGHV. After 6 years of follow-up in CLL13, 83% of patients with U-IGHV and 96% of patients with M-IGHV have not started any new treatment.

The safety profile of VO appears favourable both in the short- and long-term, with the majority of adverse events (AEs) occurring during treatment (62.7%) and infrequent after treatment (9.9%).[30,32] A major concern with venetoclax is tumour lysis syndrome (TLS), which requires a 5-week dose ramp-up phase with close outpatient monitoring and, in rare cases, inpatient admission, which can be cumbersome. Despite this concern, the incidence of TLS is overall low at 1.4% described on trial and 5.1% in the real-world setting, all of which were solely biochemical.[33,34] Studies that prospectively explore alternative ramp-up schedules that may be more convenient for patients are awaited (e.g., NCT04843904, NCT06428019). While hematological AEs are common, other AEs of interest include infusion-related reactions (grade 3/4: 9%) and infections (grade 3/4: 17.5%).

In the era of COVID-19, the risk of B-cell depletion with CD20-targeted monoclonal antibodies needs consideration, since the risk of breakthrough infections, hospitalization, and death is noted to be higher in patients with hematologic malignancies compared to matched non-cancer controls, and lowest vaccine seropositivity is noted in patients with CLL and in those who had received an CD20-targeted monoclonal antibody within 12 months.[35-37] Despite the above, a Canadian study showed that in patients who received at least two doses of COVID-19 vaccination, the real-world mortality risk was low at <1%, even in patients who received anti-CD20 antibodies within the last year.[36,37] From that perspective, the most important measures to take are to ensure patients are vaccinated against COVID-19 prior to initiating therapy, keep testing kits at home, and are aware of their eligibility for COVID-19 therapeutics.

Oral Doublets: The Convenience of Two Oral Drugs Against the Risk of Cardiac Toxicity

Three cycles of ibrutinib monotherapy lead-in followed by a combination with venetoclax (IV) for 12 cycles has been investigated in the GLOW (patients >65 years or those with comorbidities) and CAPTIVATE (patients <70 years) trials,[38,39] leading to Health Canada approval for this combination in patients with CLL. The FLAIR trial in young, fit patients found that MRD-guided or maximum treatment duration of 6 years of IV was superior to FCR; however, this approach is unlikely to become standard practice in Canada, given that MRD testing is not widely available.[40] Notably, there are currently no published trials demonstrating the superiority of an MRD-guided approach to a fixed-duration approach.

The predominant safety concern observed in all trials was cardiac toxicity. In the CAPTIVATE trial, one sudden cardiac death (SCD, 1%) was observed in a male patient aged 54 years with a history of hypertension, dyslipidemia, and smoking. In the GLOW trial, four patients (4%) experienced SCD, all of whom had a high Cumulative Illness Rating Scale (CIRS) score and/or Eastern Cooperative Oncology Group (ECOG) performance status of 2, raising caution about the use of this regimen in patients with comorbidities. Rates of hypertension and atrial fibrillation/arrhythmia with IV appear to occur at similar frequencies as observed for ibrutinib monotherapy and remain a concern even with fixed-duration therapy.[38-40]

The recently published AMPLIFY trial studying fixed-duration acalabrutinib-venetoclax +/- obinutuzumab represents an alternative oral doublet with a more appealing safety profile.[41] However, this combination is not yet FDA- or Health Canada-approved.

Approach to High-risk Patients with *TP53* Mutations and/or del(17p)

It is well established that continuous BTKi treatment retains efficacy in patients with *TP53* aberrations. A pooled analysis of four trials of ibrutinib-treated patients, subgroup data from the ELEVATE-TN trial (acalabrutinib), and Arm C from the SEQUOIA trial (zanubrutinib) all demonstrated excellent PFS with the use of these agents, with 4-year PFS ranging from 76–79%.[42-44]

When considering fixed-duration options for this high-risk subgroup, the median PFS was 51.9 months in the CLL14 trial with VO (n=25).[33] Therefore, while BTKis remain the preferred treatment option for patients with high-risk disease, it is not unreasonable to consider fixed-duration VO for patients who highly value a treatment-free interval. Additionally, the CAPTIVATE trial, which included younger patients, demonstrated a 5.5-year PFS of 36% (95% CI: 17–55) with IV in this subgroup (n=27).[45]

Overall, the current favoured treatment option for high-risk patients is BTKi; however, patient preferences are important to consider, as the cumulative efficacy of fixed-duration approaches, including retreatment, has not yet been established. The efficacy of VO retreatment is under study (NCT04895436, NCT04523428). We look forward to the ongoing CLL17 trial, which will provide direct comparative data on fixed-duration IV and VO versus continuous ibrutinib therapy, although it will only include a subgroup of high-risk patients. The CLL16 trial enrolls only high-risk patients and will provide data to determine whether a fixed-duration triplet (acalabrutinib + VO) performs favourably to VO.

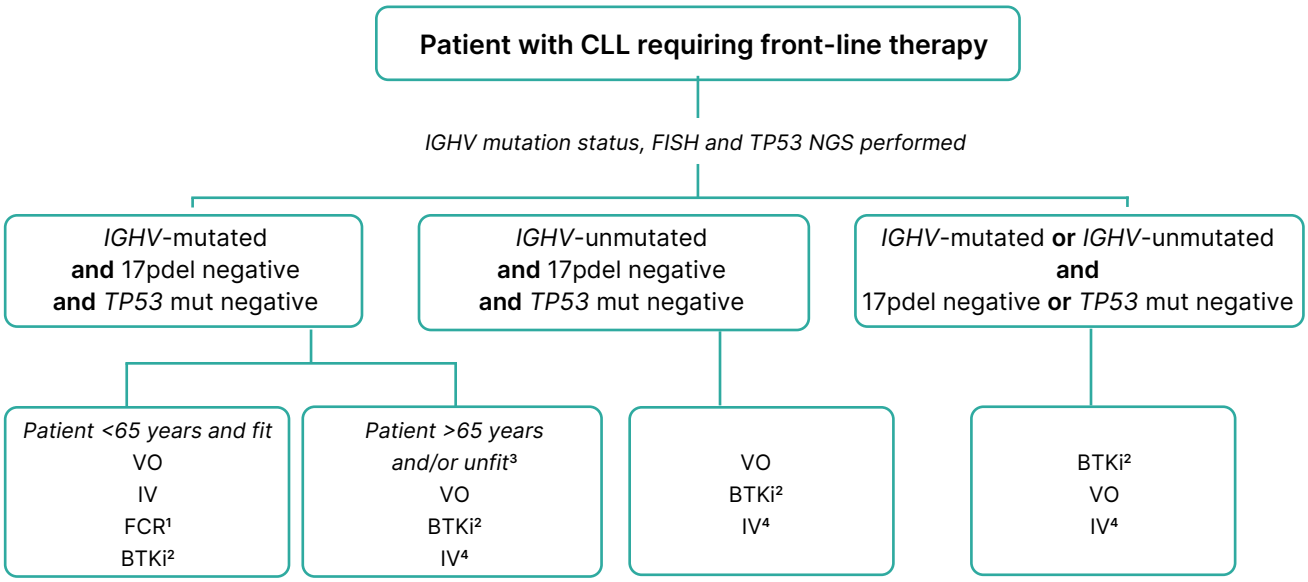

Figure 2. Treatment approach for CLL in the Canadian landscape; *courtesy of Chathuri Abeyakoon, MD and Abi Vijenthira, MD.*

[1]Additional considerations using currently available testing: absence of mutated IGHV subset 2, absence of 11qdel
[2]Second-generation BTKi (acalabrutinib, zanubrutinib) are preferred over ibrutinib
[3]In frail older patients with mutated IGHV in whom simpler time-limited therapy is preferred, chlorambucil-obinutuzumab (5-year PFS: 50%) is reasonable
[4]Caution in less fit patients due to risks of treatment-related mortality based on GLOW trial

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; **CLL:** chronic lymphocytic leukemia; **FISH:** fluorescence *in situ* hybridization; **FCR:** fludarabine, cyclophosphamide, rituximab; **IGHV:** immunoglobulin heavy chain variable region; **IV:** ibrutinib, venetoclax; **mut:** mutation; **NGS:** next-generation sequencing; **PFS:** progression-free survival; **VO:** venetoclax, obinutuzumab; **yrs:** years

Conclusions

The decision between continuous versus fixed-duration treatment in front-line CLL is a personalized choice based on a thorough assessment and discussion with the patient regarding the risks versus benefits of each approach. Treatment choice should be dictated by CLL prognostic factors, comorbidities, and patient preferences. For the majority of patients, a fixed-duration treatment approach is favoured, which can balance efficacy, safety, and costs. Our approach outlined in **Figure 2** ranks treatment choices in order of preference. We also recommend reviewing national guidelines when considering state-of-the-art treatment approaches for patients with CLL in Canada.[46]

Correspondence

Abi Vijenthira, MD
Email: abi.vijenthira@uhn.ca

Financial Disclosures

C.A.: None declared.
A.V.: None declared.

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