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Double-Exposed Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Clinical Approach and Management

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Abstract

Managing patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who have been treated with both a covalent Bruton's tyrosine kinase (BTK) and BCL2 inhibitor represents an increasingly common and complex clinical challenge. While some patients may be candidates for retreatment with a covalent BTK and/or BCL2 inhibitor, those who are refractory to both classes have limited therapeutic options beyond phosphoinositide 3-kinase (PI3K) inhibitors or allogeneic hematopoietic stem cell transplantation, which is typically feasible only for highly selected individuals. In this context, enrollment in clinical trials or compassionate access programs provides the best opportunity to access promising novel therapies, including next-generation BTK inhibitors and T-cell–directed immunotherapy approaches. This review provides a practical approach for assessing and managing double-exposed CLL/SLL in the current Canadian context.

Introduction

Although novel targeted therapies, such as the covalent Bruton's tyrosine kinase inhibitors (BTKi) ibrutinib, acalabrutinib, and zanubrutinib or the BCL2 inhibitor (BCL2i) venetoclax, have transformed the treatment landscape of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), these agents are generally not curative and most patients eventually experience disease relapse.[1,2] The management of patients with CLL/SLL who have been exposed to both covalent BTKi and BCL2i has become an increasingly common and challenging scenario, characterized by historically poor outcomes and an unmet need for novel therapies. This article outlines a practical approach to the evaluation and management of double-exposed CLL/SLL, with a focus on real-world considerations in the current Canadian context.

Evaluation of Double-Exposed Disease

When evaluating a patient with relapsed/refractory CLL/SLL, it is essential to review their treatment history, including the depth and duration of response and the timing of disease progression relative to each therapy. This enables a distinction between 'double-exposed' and 'double-refractory' CLL/SLL, which has significant implications for prognosis and subsequent therapy selection.[3-5] Double-exposed CLL/SLL refers to patients who have received both a covalent BTKi and BCL2i and who discontinued one or both treatments for any reason, including disease progression, intolerance, or planned completion of a time-limited regimen. In contrast, double-refractory CLL/SLL describes a high-risk subset of double-exposed patients who experience disease progression while receiving a BTKi, or during treatment with, or by some definitions within 24 months of completing, a BCL2i.[4,5]

A comprehensive clinical assessment is also required to determine whether a double-exposed patient meets International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for new treatment initiation, such as disease-related symptoms, cytopenias, or bulky lymphadenopathy or splenomegaly.[6] Of note, patients with early signs of progression on a BTKi (e.g., asymptomatic lymphocytosis) may not require an immediate change in therapy and can often continue treatment until more definitive progression occurs, thereby maximizing the benefit of this drug class.

Given the enrichment of high-risk genomic features among patients with double-exposed CLL/SLL[5], prognostic testing should include assessment of *IGHV* mutation status (if not previously documented) along with repeat fluorescence in situ hybridization (FISH) for del(17p) and next-generation sequencing for *TP53* mutations (if available). Although not routinely performed in many centres, a complex karyotype may provide additional prognostic information. BTK mutation testing may help identify mechanisms of resistance (e.g., C481S, T474, or L528W mutations) but this testing remains largely inaccessible in Canada and further research is needed before it can be incorporated into routine treatment decision-making.[7]

A subset of patients with double-exposed CLL/SLL may develop a more aggressive clinical presentation, with rapidly enlarging or discordant lymphadenopathy, extranodal involvement, B symptoms, or malignant hypercalcemia. These cases warrant further evaluation with a positron emission tomography/computed tomography (PET/CT) scan and tissue biopsy to exclude the 'accelerated' variant of CLL/SLL or Richter transformation (RT) to diffuse large B-cell lymphoma (DLBCL).[8,9]

Outcomes after Double Exposure

Patients with double-exposed CLL/SLL have historically experienced poor clinical outcomes. However, accurate prognostication remains challenging due to inconsistent definitions and reporting of double-exposed versus double-refractory disease in the literature, as well as heterogeneity in prior treatments (e.g., chemotherapy-era versus targeted therapy-era), the nature of relapse (e.g., CLL versus RT), and the evolving impact of emerging therapies. In heavily pretreated, chemotherapy-exposed patients with resistance to both covalent BTKi and BCL2i, outcomes have been dismal, with a reported median overall survival of only 3.6 months.[10] Similar findings have been observed in Canada, with a recent retrospective study from Alberta reporting a median time to next treatment (TTNT) or death of just 1.2 months following discontinuation of both a covalent BTKi and BCL2i among 70 patients.[11] Encouragingly, outcomes in double-refractory CLL/SLL appear to be improving with the advent of next-generation BTKi and cellular therapies, with a recent study reporting a median overall survival of 26 months in this population.[5] Additionally, patients with double-exposed CLL/SLL who discontinued covalent BTKi or BCL2i for reasons other than disease progression may follow a more indolent clinical course, often allowing for periods of observation and more favourable responses to subsequent therapies.[5]

Current Management Strategies for Double-Exposed CLL/SLL

Retreatment With a Covalent BTKi or BCL2i

Patients previously exposed to both a covalent BTKi and BCL2i who discontinued therapy due to toxicity or completion of a time-limited regimen may be eligible for retreatment with one or both classes. Indeed, patients who stop a covalent BTKi due to toxicity can often be safely observed without therapy for a median of 24 months, particularly if they received

>2 years of prior BTKi treatment.[12] Upon reinitiation, those intolerant to one covalent BTKi may be successfully treated with an alternative second-generation covalent BTKi (e.g., acalabrutinib or zanubrutinib) or a non-covalent BTKi (e.g., pirtobrutinib), with low rates of recurrent adverse events reported in prospective trials.[13-15] However, caution should be exercised regarding BTKi rechallenge if a patient experienced a life-threatening BTKi class toxicity, such as hemorrhage.

Retreatment may also be effective in double-exposed patients who relapse after time-limited therapy. In the 5.5-year follow-up of the CAPTIVATE study, only two subclonal *BCL2* mutations of uncertain significance and no *BTK* or *PLCG2* mutations were detected among 53 evaluable patients who experienced relapse after completing fixed-duration ibrutinib plus venetoclax (I+V) for treatment-naïve CLL/SLL.[16] Among those retreated, the overall response rate (ORR) was 76% with single-agent ibrutinib (n=25) and 82% with I+V (n=11), with corresponding 2-year and 1-year progression-free survival (PFS) rates of 91% and 100%, respectively. The feasibility of venetoclax retreatment has also been observed in more heavily pretreated populations, with an ORR of 56% and median PFS of 15 months among 18 double-exposed patients in a real-world study.[17] The decision to pursue venetoclax retreatment should take into consideration prior response duration, alternative treatment options, and the potential presence of *BCL2* resistance mutations, although routine testing for *BCL2* mutations is not widely available in Canada.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) remains one of the few potentially curative therapies for CLL/SLL, with long-term studies demonstrating durable remissions in approximately one-third of patients owing to a robust graft-versus-leukemia effect.[18] Favourable outcomes have also been reported in small series of patients with double-exposed CLL/SLL.[19,20] However, these benefits are offset by substantial risks of acute and chronic graft-versus-host disease (GVHD), infections, and non-relapse mortality (NRM), although outcomes are improving with the introduction of reduced-intensity conditioning regimens and novel GVHD prophylaxis strategies, including post-transplant cyclophosphamide.[21]

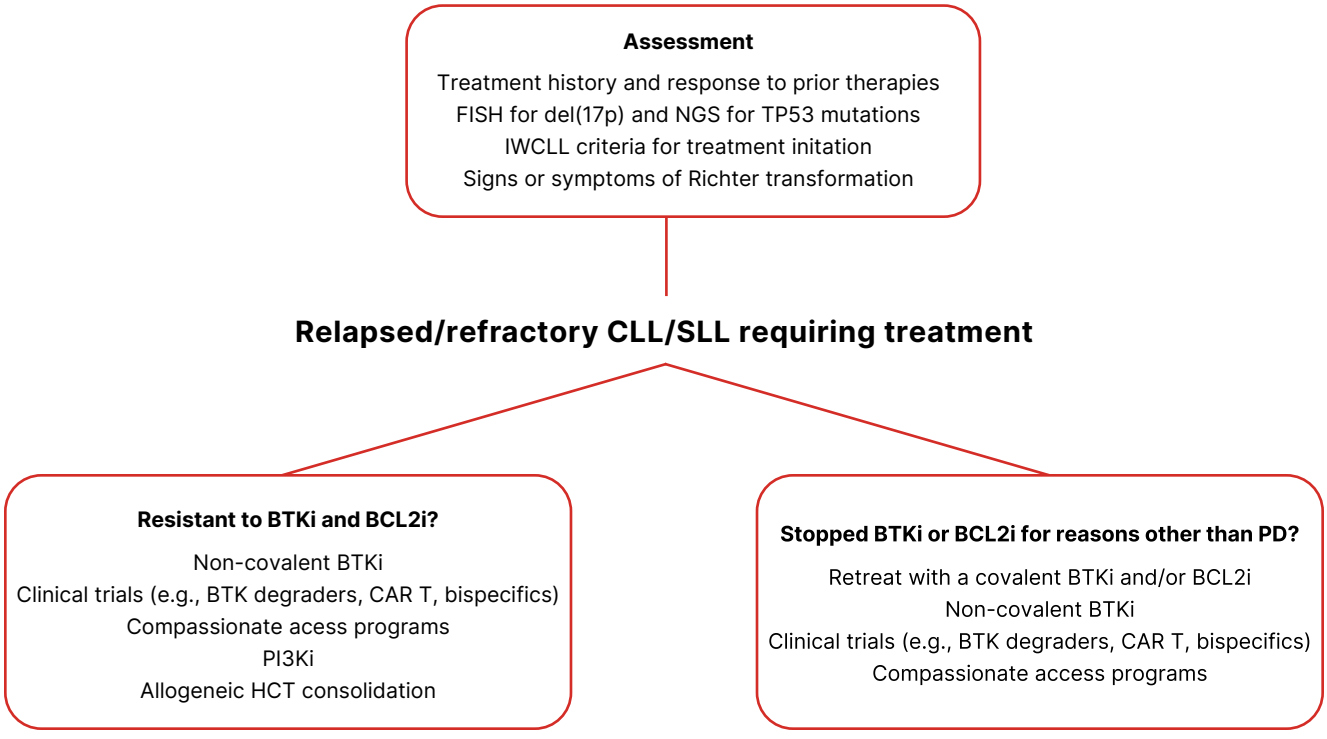

Figure 1. Proposed clinical approach and treatment options for relapsed/refractory double-exposed CLL/SLL; *courtesy of Robert Puckrin, MD, FRCPC*

Allogeneic HSCT is generally reserved for younger, medically fit, and motivated patients with multiply relapsed, genomically high-risk CLL/SLL who have exhausted other treatment options and have an available donor. Timing of allogeneic HSCT should be carefully considered, as outcomes are superior when patients undergo transplantation with well-controlled disease.[21] In the current Canadian setting, allogeneic HSCT can likely be deferred until patients have developed resistance to both a covalent BTKi and BCL2i but remain responsive to their final available line of pre-transplant therapy, such as a non-covalent BTKi.

Phosphoinositide 3-Kinase (PI3K) Inhibitors

Although the PI3K inhibitor (PI3Ki) idelalisib was approved for relapsed/refractory CLL/SLL in Canada in 2015, it was initially evaluated in primarily chemotherapy-exposed populations and has shown limited efficacy in patients previously treated with both a covalent BTKi and BCL2i, with an ORR of 47% and median PFS of only 5 months in one retrospective study of 17 double-exposed patients.[22] In addition, its use has declined due to relatively high rates of infectious and immune-related adverse events. Nevertheless, the BRUIN CLL-321 trial provided the largest prospective dataset of double-exposed patients treated with the control arm therapy of idelalisib-rituximab, reporting a median PFS of approximately 8 months in this subgroup.[23] These findings suggest that idelalisib may still have a role as a disease-holding therapy or bridge to allogeneic HSCT or an upcoming clinical trial when other options are lacking.

Chemoimmunotherapy

Chemoimmunotherapy has a limited role in double-exposed CLL/SLL due to poor efficacy and tolerability in heavily pretreated patients with high-risk genomic features.[24] It is generally considered an option of last resort or a palliative measure for those without access to novel agents.

Clinical Trials and Compassionate Access Programs

In the Canadian treatment landscape, many patients with double-exposed CLL/SLL are ineligible for, or unlikely to derive meaningful benefit from, the limited therapeutic options currently available. For these individuals, enrollment in clinical trials or compassionate access programs should be strongly encouraged, as these pathways offer the potential to receive next-generation therapies with improved efficacy and tolerability, as outlined in the following section.

Investigational and Emerging Therapies for Double-Exposed CLL/SLL

Next-generation BTKi

The non-covalent BTKi pirtobrutinib binds to a distinct site within the adenosine triphosphate region of BTK and potently inhibits both wildtype and C481S-mutated BTK. In the Phase I/II BRUIN trial, pirtobrutinib was evaluated in 247 patients with relapsed/refractory CLL/SLL post-covalent BTKi, 41% of whom were double-exposed.[25] The ORR was similar between the double-exposed and BCL2i-naïve subgroups at 79% versus 84%, while the median PFS was 16.8 versus 22.1 months, respectively. The subsequent randomized Phase III BRUIN CLL-321 trial confirmed the superiority of pirtobrutinib over idelalisib-rituximab or bendamustine-rituximab in 238 patients with covalent BTKi-exposed relapsed/refractory CLL/SLL.[23] Among the 51% of patients who were double-exposed, pirtobrutinib significantly improved PFS (median 11.4 versus 8.3 months; hazard ratio [HR]: 0.54, 95% confidence interval [CI]: 035-0.83) and TTNT (median 20 versus 9 months, HR: 0.41; 95% CI: 0.26-0.65) compared to control therapies. Due to its high selectivity, pirtobrutinib is generally well tolerated with low rates of BTKi-related cardiovascular toxicity and treatment discontinuation due to adverse events in only 3-5% of patients.[23,25] Pirtobrutinib received accelerated approval for double-exposed relapsed/refractory CLL/SLL by the United States (US) Food and Drug Administration (FDA) in 2023 and is currently under review by Health Canada. Once approved, it will offer a much-needed treatment option for Canadian patients with double-exposed disease, as either a stand-alone therapy or potential bridge to allogeneic HSCT in eligible patients.

Promising early data have also emerged for other next-generation BTKi in development, including the non-covalent BTKi nemtabrutinib[26], the BTK degraders BGB-16673 and NX-5948[27,28], and the dual covalent/non-covalent BTKi LP-168[29], highlighting multiple potential novel strategies to suppress BTK and improve outcomes in relapsed/refractory CLL/SLL.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Some of the earliest reports of successful CD19-directed CAR T-Cell therapy were in patients with relapsed/refractory CLL/SLL, with sustained remissions lasting beyond 10 years and evidence of curative potential in a subset of patients.[30-32] However, the development of CAR T-Cell therapy for CLL/SLL has been limited by suboptimal efficacy, thought to be related to disease-associated T-cell dysfunction. It was not until 2024 that the US FDA granted accelerated approval for the first CAR T-Cell product in CLL/SLL, lisocabtagene maraleucel (liso-cel), based on findings from the Phase I/II TRANSCEND CLL 004 trial.[33] Among 50 patients with predominantly double-refractory disease, liso-cel achieved an ORR of 44%, a complete response (CR) rate of 20%, and an undetectable measurable residual disease (MRD) rate of 64% in blood and 60% in marrow. The median PFS was 11.9 months, with durable responses observed in the subset of patients achieving CR or undetectable MRD.

Patient selection is critical given the intensity of CAR T-Cell therapy, with all-grade/grade ≥3 cytokine release syndrome (CRS) occurring in 85%/8% and neurotoxicity in 45%/19%, respectively. Other notable toxicities include prolonged cytopenias (54%), grade ≥3 infections (18%), and secondary malignancies (9%). Although CAR T-Cell therapy is not yet approved for CLL/SLL in Canada, it may represent a valuable future option for fit, motivated patients as an appealing alternative to allogeneic HSCT. Ongoing research aims to identify individuals most likely to benefit, such as those with lower disease burden[34], and to enhance efficacy and safety, for example through combination approaches that include ibrutinib to improve CAR T-Cell fitness.[35]

Bispecific Antibodies

The Phase I/II EPCORE CLL-1 trial evaluated the CD20xCD3 T-cell-engaging bispecific antibody epcoritamab in 40 patients with relapsed/refractory CLL, all of whom were previously exposed to BTKi and 85% to a BCL2i.[36] Among the double-exposed cohort, the ORR and CR rates were 53% and 37%, respectively, and the median PFS was 12.8 months in the overall study population. High rates of CRS were initially observed, likely due to circulating lymphoma cells in the blood and marrow. However, enhanced CRS prophylaxis and an additional step-up dose introduced during the optimization phase reduced the incidence of grade 2 CRS from 70% to 12% and eliminated grade 3 CRS from 17% to 0%. If validated in larger studies, bispecific antibodies such as epcoritamab may offer a promising, scalable, and potentially more tolerable therapeutic option for patients with double-exposed CLL/SLL, particularly in the Canadian setting, where CAR-T cell therapy may be less accessible.

Conclusion

Double-exposed CLL/SLL represents an increasingly common clinical challenge with limited treatment options. In non-refractory cases, retreatment with a covalent BTKi or BCL2i should be considered, while PI3K inhibitors or allogeneic HSCT retain a potential role for select fit individuals with double-refractory disease. However, enrollment in clinical trials or compassionate access programs represents the most promising pathway to access emerging therapies, including non-covalent BTKi, BTK degraders, and T-cell–directed approaches, which hold potential to improve outcomes for patients with double-exposed CLL/SLL in Canada.

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