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NAVIGATING THE PARADIGM SHIFT IN CHRONIC LYMPHOCYTIC LEUKEMIA TREATMENT FROM CHEMOTHERAPY TO TARGETED THERAPIES

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Introduction

The shift from traditional chemotherapy to more targeted therapies has been a landmark change in chronic lymphocytic leukemia (CLL) treatment. This transformation has implications for treatment efficacy, tolerability, and patient quality of life, along with implications for the Canadian oncology community at large, which must rapidly adapt to these advancements. This rapid development underscores the importance of continued responsiveness in medical practice, including more collaborative work with Canadian institutions and provincial cancer care to deliver these transformative therapies to patients. This review aims to offer practical guidance, from a Canadian perspective, for clinicians in treatment selection in the era of targeted therapies.

Treatment Approaches

When approaching the need for therapy initiation, it is essential to consider the patient's genomic risk through an assessment of molecular (immunoglobulin heavy chain gene [IGHV] mutational status, TP53 gene mutations) and cytogenetic (deletion (17p) status, complex karyotype) analyses.[1] The IGHV mutational status remains unchanged throughout a patient's CLL course and can be completed early at diagnosis. The other assessments are often completed upon treatment initiation considering that new clones harbouring new mutations may arise later. Higher genomic risk disease based on routine laboratory evaluation includes the presence of unmutated IGHV CLL, mutated IGHV Subset #2 CLL, deletion (17p), TP53 mutation and complex karyotypes.[1,2]

Upon treatment initiation, a shared decision-making model ensures that patients are more actively involved in their care and that the treatment plan aligns with their values and lifestyle preferences. Considering that the disease can manifest differently in each individual, a one-size-fits-all strategy would be suboptimal. The choice between time-limited and continuous therapies should take into account the disease characteristics and the patient's life circumstance, including age, frailty, comorbidities, private insurance, and social situations. Since time-limited and continuous treatment options are both viable and effective, an individualized approach based on patient needs and preferences would maximize outcomes by improving patients' adherence to treatment.

Bruton Tyrosine Kinase Inhibitors

Inhibition of Bruton tyrosine kinase (BTK) leads to downstream effects, including reduced cell proliferation and survival.[3] However, these inhibitors do not induce immediate apoptosis in CLL cells. Instead, they inhibit cellular functions and signalling pathways, gradually leading to cell death over weeks to months. The interference with the adhesion and homing of CLL cells to lymph nodes causes these cells to disengage and circulate in the peripheral blood before undergoing cell death, leading to a temporary spike in white blood cell counts.[3] Patient education about this phenomenon will prevent anxiety about this being a failure of the treatment.

The optimal choice of a BTK inhibitor (BTKi) **(Table 1)** should be tailored to each patient's unique clinical profile. Factors such as pre-existing cardiovascular disease, comorbid conditions such as severe headaches, and the potential for drug-drug interactions need to be considered. Based on the ELEVATE-RR (acalabrutinib vs. ibrutinib) and ALPINE (zanubrutinib vs. ibrutinib) trials in relapsed/refractory (R/R) CLL, both the ELEVATE-RR and ALPINE trials have shown that the second generation BTKi has a more favourable side effect profile and demonstrates overall subtle differences in efficacy, with progression-free survival (PFS) non-inferiority for ELEVATE-RR and PFS superiority for ALPINE, although the differing trial inclusion criteria and timeline of study conduct precludes any efficacy comparison between acalabrutinib and zanubrutinib[23,25]. Although these second-generation BTKis have a numerically lower adverse events rate, the side effect profile that includes joint pain, palpitations (associated with atrial fibrillation and cardiac arrhythmias), easy bruising and bleeding, and hypertension belong to a class effect, which underscores the critical role of interdisciplinary care in managing patients.[3] Hypertension and atrial fibrillation may worsen over time in some patients, while other toxicities tend to improve with continued treatment.[4] **(Table 2)** Regular follow-up and monitoring are essential for early detection and appropriate management. In addition, providing patient education on the side effects prior to initiating therapy can make a considerable difference in their experience and potentially improve treatment adherence.

For lower-grade toxicities, attempts can be made for dose reduction. Alternatively, switching to another BTKi could be

Covalent BTK Inhibitor	Initial Dose (mg)	Dose Reduction Levels (mg)	Atrial Fibrillation (%)	Ventricular Tachycardia (%)	Major Bleeding (%)	Hyper-tension (%)	CYP3A4 Interaction	P-gp Interaction	Notes
Acalabrutinib	100 mg PO BID	1st: 100 mg QD; 2nd: Discontinue	3–5	<1	2–4	5–10	Moderate	Yes	Predictable headaches that are transient. May improve with caffeine-containing products
Zanubrutinib	160 mg BID or 320 mg PO QD	1st: 80 mg BID/160 mg QD; 2nd: 80 mg QD	2–4	<1	1–3	6–8	Moderate	No	160 mg PO BID dosing has more reliable BTK occupancy than OD dosing
Ibrutinib	420 mg PO QD	1st: 280 mg QD; 2nd: 140 mg QD	6–9	1–2	4–6	8–15	Moderate	Yes	If causing GI intolerance, consider taking on an empty stomach at night

Table 1. *Profiles, selected side effects, and interactions of BTK inhibitors in CLL; courtesy of Chai Phua, MD and Selay Lam, MD*
Abbreviations: BID, two times a day; BTK, Bruton tyrosine kinase; CYP3A4, cytochrome P450 3A4; GI, gastrointestinal; P-gp, P-glycoprotein; PO, orally; QD, once a day.

considered especially for serious adverse events or to mitigate against prolonged treatment interruptions, to manage side effects without compromising efficacy. Notably, there remains a paucity of data on the impact of dose reduction on overall treatment outcomes.

B-Cell Lymphoma-2 Inhibitor, Venetoclax

B-cell lymphoma-2 (BCL-2) is a protein that plays a central role in regulating apoptosis. By inhibiting BCL-2, venetoclax triggers immediate apoptosis in CLL cells.[5] This rapid induction of cell death is both an advantage and a challenge, because it can lead to tumour lysis syndrome (TLS), a potentially fatal condition in which the rapid breakdown of cells can lead to metabolic imbalances (hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, elevated lactate dehydrogenase) and renal dysfunction.[5]

Owing to the rapid cell lysis, clinicians assess the risk of TLS based on lymph node size and white blood cell count. Generally, depending on the treatment regimen, a lead-in phase with rituximab, obinutuzumab, or BTKi often reduces tumour bulk, reducing the risk of TLS when venetoclax is introduced. For example, a repeat computed tomography scan before venetoclax exposure for the venetoclax-obinutuzumab regimen could help redefine the TLS risk, potentially obviating hospitalization for close monitoring in a subset of patients. In the CLL14 study, 25% of the patients considered high risk for TLS had reduced to approximately 2% after the obinutuzumab lead-in.[6] The dramatic reduction in high TLS risk has substantial implications regarding healthcare resources, especially considering that we can reduce the need for admitting patients to the hospital for TLS monitoring in high-risk patients (any lymph node of $\geq$ 10 cm or absolute lymphocyte count $\geq 25 \times 10^9$/L and lymph node $\geq$ 5 cm) or patients at risk for significant renal injury (i.e. medium TLS risk with creatinine clearance of < 80 mL/min), thus improving patient experience and reducing healthcare costs.

Despite the initial challenges and risks associated with a high treatment burden, the reward is "coming off therapy" in the venetoclax-containing time-limited regimens. Additionally, there is a potential for venetoclax retreatment upon future relapses. Time-limited therapies have added benefits including cost reduction of our global health care costs and avoiding long-term accrual of treatment-related adverse events associated with continuous therapies. Venetoclax therapy is generally well tolerated with common adverse events

Trial Characteristics					Mutated IGHV CLL		Notes
Trial Name	Phase	(N)	Treatment Characteristics	Median Follow-Up	PFS Response	OS Response	
ECOG 1912[8]	3	529	IBR+R vs. FCR Median age 56 years	69.6 months	5-year PFS 83% IBR+R vs. 68% for FCR (HR: 0.27; P <0.001)	No OS difference	• OS benefit in all patients with a 5-year OS 95% in IBR+R vs. 89% in FCR (HR:0.47; P<0.018)
UK FLAIR[9]	3	771	IBR+R vs. FCR Median age 62 years	52.7 months	NR for IBR+R and FCR (HR: 0.64; P=0.15); 5-year PFS estimate for FCR 81.3%	No OS difference	• No OS benefit in all patients (OS difference seen in ECOG 1912 above may relate to more cardiac-related deaths in UK FLAIR, and differing available salvage therapies between cohorts)
GAIA/CLL 13[10]	3	926	FCR/Ben+R vs. Ven+O vs. Ven+R vs. IBR+Ven+O Median age 61 years	27.9 months	3-year PFS IBR+Ven+O 96%, Ven+O 93.6%, and FCR/Ben+R 89.9%	No OS difference	• The addition of IBR increased toxicity without significant improvement in efficacy for IBR+Ven+O • O reaffirmed as the superior anti-CD20 when compared to R
CAPTIVATE[11]	2	159	IBR for 3 cycles-> IBR+Ven for 12 cycles (Fixed duration cohort), study also included a MRD directed cohort	28.7 months	24-month PFS IBR+Ven 95% in unmutated IGHV vs. 24-month PFS IBR+Ven 97% in mutated IGHV	24-month OS 98%	• Patients who stopped treatment after achieving MRD-negativity experienced MRD-relapses at ~4 years (3 years off therapy) with disease-free survival of approximately 83% • Those who remained on IBR had a disease-free survival of approximately 95% • 36-month PFS for patients with del(17p)/TP53 was 80% vs. 86% in unmutated IGHV

Table 2. *Selected clinical trials in young and fit patients (FCR eligible) with mutated immunoglobulin heavy chain gene and without del(17p) or TP53 mutations; courtesy of Chai Phua, MD and Selay Lam, MD.*
Abbreviations: Ben, Bendamustine; FCR, Fludarabine, Cyclophosphamide, and Rituximab; HR, hazard ratio; NR, not reached; IBR, Ibrutinib; MRD, minimal residual disease; O, Obinutuzumab; OS, overall survival; PFS, progression-free survival; R, Rituximab; Ven, Venetoclax;

including cytopenia and gastrointestinal toxicities, whereas cardiovascular toxicities are deemed rare.

The use of strong and moderate cytochrome P450 3A4 (CYP3A4) inhibitors was shown to decrease venetoclax clearance by 82% and 14%, respectively. Considering this effect of CYP3A4 inhibitors, venetoclax should be taken with a meal without specific fat content and with water at approximately the same time each day to ensure adequate and consistent bioavailability.

Frontline Treatment in FCR eligible patients

Young and fit patients deemed "FCR eligible" (i.e. <65 years with Cumulative Illness Rating Scale [CIRS] <6) with symptomatic mutated IGHV CLL and without deletion (17p) or TP53 mutations could consider time-limited options with fludarabine-cyclophosphamide-rituximab (FCR), or venetoclax-obinutuzumab **(Table 1)** with very durable disease control. Continuous therapy with ibrutinib and rituximab is reasonable; however, treatment until progression may lead to the accrual of long-term side effects and significant healthcare costs.[1] Because there is a lack of benefit with adding rituximab to ibrutinib in the Alliance A041202 phase 3 trial, we would consider ibrutinib as monotherapy until progression. Extrapolation from CLL trials involving older or less fit patients would suggest use of more specific BTK inhibitors, such as zanubrutinib or acalabrutinib, yield similar efficiency with fewer adverse events.[1]

Long-term data from FCR studies have shown potential functional cures in a subset of young and fit patients. However, FCR treatment is associated with a risk for increased toxicity, including the risk of therapy-related myeloid neoplasia (tAML/MDS), which is often associated with a poor prognosis and is rarely curative. Frontline chemoimmunotherapy in patients with CLL demonstrated an approximately 9 fold higher risk for tAML/MDS than that in the general population, and 27 additional tAML/MDS cases per 10,000 person-years treated.[7]

Combining BTK and BCL-2 inhibitors could improve outcomes and deepen responses as single agent BTKi therapy rarely achieves a complete response, though long-term studies are needed to confirm durability of disease control and treatment sequencing. The potential for treatment cessation in patients achieving undetectable minimal residual disease (MRD) is attractive and provides more opportunities for personalization of care. The Health Canada approval for ibrutinib-venetoclax offers another therapeutic consideration for a motivated patient wishing to consider an effective time-limited therapeutic option. The higher propensity for cardiac toxicities in the GLOW study warrants a pause when considering this option in the older patient group with pre-existing cardiac comorbidities. Patients who were MRD undetectable at 3 months after the end of therapy largely maintained an MRD undetectable status at 1-year after treatment. Although follow-up is comparatively short thus far, a significant treatment break would be expected with this regimen. Additional studies combining second-generation BTK and BCL-2 inhibitors are expected to be reported in the coming years.

An MRD-adapted approach is likely ideal, in which treatment duration is personalized based on MRD levels. However, test availability, differing disease kinetics depending on treatment type, and genetic risk make implementation challenging for broader use, especially in the community settings.

Frontline Treatment in FCR ineligible patients

Patients not eligible for FCR treatment without del(17p) or TP53 mutations could consider time-limited options with venetoclax and obinutuzumab, ibrutinib and venetoclax, or continuous BTKi treatments **(Table 3)**. Based on cost-effectiveness analysis, venetoclax and obinutuzumab would be preferable from a publicly funded healthcare system perspective.[12] To date, there is no data to support the survival benefit of continuous therapy over time-limited therapy with targeted agents. We are unlikely to have data until the CLL17 trial (ibrutinib monotherapy versus fixed-duration venetoclax plus obinutuzumab versus fixed-duration ibrutinib plus venetoclax) is completed.

Patients with del(17p) or TP53 mutations confer an adverse prognosis for PFS and OS, particularly with chemoimmunotherapy but also with targeted agents. Continuous BTKi therapy offers the best remission duration data to date. In contrast, time-limited therapy, such as venetoclax and obinutuzumab, compares favourably to chemoimmunotherapy; however, the duration of remission may not be as prolonged as continuous BTKi numerically with cross-trial comparison.

Treatment For Relapsed/Refractory Disease

As outlined in **Table 4**, there are many trials showing efficacy of targeted agents in the relapsed and refractory setting. However, there is a paucity of data to guide the sequencing of targeted agents in different subtypes of patients at this time given the relatively new and variable adoption of time limited treatment.

Given the relatively short follow-up, minimal data exists to inform health care providers of the response to second-line treatment of patients who received venetoclax based regimens (i.e. ven-o) as front-line treatment. Mato AR, et al. reported on treatment selection post-venetoclax and the associated responses and revealed an ORR of 84% with BTKi post-venetoclax if BTKi-naive and a median PFS of 32 months.[28]

However, data is available that can provide insights regarding the mechanism of resistance for BTK inhibitor-treated patients.[29] The most commonly described resistance mechanism in ibrutinib-treated patients is a mutation in BTK itself, which prevents the covalent binding of ibrutinib, or a mutation in *phospholipase C gamma 2* (PLCG2), which acts to bypass the dependency on BTK at the B-cell receptor signalosome.[30, 31] Other genetic mutations include 8p deletion.[32]

The *BTK* Cys481Ser mutation is a specific amino acid substitution involving the cysteine (Cys) change to another amino acid, most commonly serine (Ser) at position 481 in the *BTK* gene, which codes for a crucial enzyme targeted by covalent BTK inhibitors. The *BTK* Cys481Ser mutation diminishes the binding efficacy of the covalent *BTK* inhibitor, transforming it from an irreversible to a reversible interaction. This weakened binding reduces the drug's potency because the drug binds for significantly shorter periods (of approximately 7 minutes), as opposed to irreversible binding. This decreases the drug's efficacy considerably and allows the CLL cells to escape its effects, leading to treatment failure. The *BTK* Cys481 Ser mutation accounts for most relapses in acalabrutinib- and ibrutinib-treated patients. Zanubrutinib-treated patients may develop the *BTK* Leu528Trp mutation in addition to the Cys481Ser *BTK* mutation,[33] which is clinically important as it prevents the binding of pirtobrutinib (see Emerging Therapies, on page 9).[34]

Venetoclax can overcome *BTK* and *PLCG2* mutations. When switching therapy from BTKi to venetoclax, it is crucial to maintain the patient on BTKi therapy during the venetoclax ramp-up phase to avoid rapid disease progression. In some cases, a quick ramp-up strategy of approximately 9 days is safe and effective through close in-hospital monitoring is required (median time to target dose 9 days [range, 5–32 days]).[35] This approach is usually for patients who live far away or those with accelerated CLL

Trial Characteristics				All					Notes
Trial Name	Phase	Treatment Characteristics	Median Follow-Up	PFS Response			OS Response		
				Overall	IGHV unmutated	del(17p)	Overall	IGHV unmutated	
CLL 14[6]	3	Ven+O vs. Clb+O Median age 72 years	65.4 months	5-year 62.6% for Ven+O vs. 27.0% for Clb+O	5-year 55.8% for Ven+O vs. 12.5% for Clb+O	5-year 40.6% for Ven+O vs. 15.6% for Clb+O	5-year OS 81.9% for Ven+O vs. 77% for Clb+O (HR: 0.72; p=0.12)		5-year TTNT rates: 72.1% vs. 42.8%
GLOW[13]	3	1 year IBR+Ven vs. Clb+O; >65 years or 18-64 years with CIRS score >6 Median age 71 years	27.7 months	Median PFS NR in IBR+Ven (HR 0.216; p<0.001)			Median OS NR (HR 1.048)		Variations in disease kinetics, the favourable mutated IGHV CLLs were less likely to achieve MRD negativity compared to high-risk disease
RESONATE 2[14]	3	IBR vs. Clb	88.5 months	Overall	IGHV unmutated		Median OS NR for IBR vs. 89 months for Clb		30-months estimated PFS 57% IBR for patients with del(17p)[15]
				Median PFS NR for IBR vs. 15 months for Clb	7-year PFS 58% for IBR vs. 2% in Clb				
Alliance A041202[16]	3	IBR vs. IBR+R vs. Ben+R Median age 71 years	55 months	48-month PFS estimate 76% for IBR+R vs. 76% for IBR			48-month OS estimate 86% for IBR+R vs. 85% for IBR		12-month PFS 44% for Ben+R vs. 86% for Ben+R+IBR in unmutated IGHV[17]
ELEVATE TN[18]	3	A+O vs. A vs. Clb+O Median age 70 years	58.2 months	Overall	IGHV unmutated	del(17p)	Overall	IGHV unmutated	A-O vs. A had a statistically significant PFS (HR of 0.56) Unmutated IGHV CLL benefited the most with A+O No added benefit in del(17p) or complex karyotype
				60-month PFS 84% for A+O vs. 72% for A vs. 21% for Clb+O	48-month PFS 86% A+O vs. 77% A vs. 4% Clb+O	5-year PFS 71% A+O vs. 71% A vs. 18% Clb+O [19]	48-month OS estimate 93% for A+O vs. 88% for A vs. 88% for Clb-O	5-year OS 90% for A-O vs. 82% for Clb-O (HR 0.55; p=0.0474)	
SEQUOIA[20]	3	Zanu vs. Ben+R Median age 70 years [patients without del(17p)]	26.2 months	Overall	IGHV	del(17p)	24-month OS estimate for non del(17p) randomization 94.3% for Zanu vs. 94.6% for Ben+R (HR 1.07; p=0.87)		Median 43.7 months follow-up update 42-month PFS estimate for Zanu in non-del(17p) 82.4% & del(17p) 79.4%[21]
				24-month PFS 85.5% for Zanu vs. 69.5% for Ben+R	Unmutated IGHV (HR=0.24; p<0.001) no difference in mutated IGHV	24-month PFS 88.9% (non-randomized arm)			

Table 3. *Table 3. Selected clinical trials in Non-FCR eligible patients; courtesy of Chai W. Phua, MD and Selay Lam, MD*
Abbreviations: A, Acalabrutinib; Ben, Bendamustine; CIRS, Cumulative Illness Rating Scale; Clb, Chlorambucil; HR, hazard ratio; IBR, Ibrutinib; IGHV, immunoglobulin heavy chain gene; MRD, minimal residual disease; NR, not reached; O, Obinutuzumab; OS, overall survival; PFS, progression-free survival; R, Rituximab; TTNT, time to next treatment; Ven, Venetoclax; Zanu, Zanubrutinib

Study Name	Patient Type	(N)	Treatment Comparison	Median Follow-Up	PFS Results	OS Results	Notes
RESONATE[22]	≥1 prior therapy; ECOG 0-1; measurable nodal disease	391	IBR vs. Ofatumumab	65.3 months	Median PFS for IBR 44.1 months vs Ofatumumab 8.1 months; HR 0.148 (0.113-0.196)	Median OS for IBR 67.7 months vs. Ofatumumab 65.1 months; HR 0.810 (0.602-1.091)	IBR without or with del(17p) HR: 1.421 (p=0.26)
ELEVATE-RR [23]	≥1 prior therapy; ECOG 0-2. Had the presence of del(17)p and/ or del (11)q	533	A vs. IBR	40.9 months	Median PFS was 38.4 months in both arms	NR	Incidence of all-grade atrial fibrillation/ flutter was 9.4% in A compared to 16% in IBR. Treatment discontinuations due to adverse events was 14.7% with A and 21.3% in IBR.
ASCEND[24]	≥1 prior therapy (non BTK/BCL-2); ECOG 0-1	310	A vs. Idela+R or Ben+R	16.1 months	Median PFS for A NR (estimate 12 months 88%) vs Idela+R/Ben+R 16.5 months (estimate 12 months 68%); (HR 0.31; p<.0001)	Median OS NR. 12-months OS 94% in A vs. 91% Idela+R/ Ben+R (HR, 0.84; 95% CI, 0.42 to 1.66)	With del(17p) and TP53 mutation: A vs. Idela+R/Ben+R HR (95% CI): 0.11 (0.04–0.34) Without del(17p) and TP53 mutation: A vs. Idela+R/Ben+R HR (95% CI): 0.29 (0.19–0.45) Unmutated IGHV A vs. Idela+R/Ben+R HR (95% CI): 0.28 (0.18–0.43) Mutated IGHV A vs.Idela+R/Ben+R HR (95% CI): 0.30 (0.12–0.76)
ALPINE[25]	≥1 prior therapy (non BTKi); ECOG 0-2	652	Zanu vs. IBR	29.6 months	At 24 months, PFS rates: Zanu 78.4% vs. IBR 65.9%	Median OS NR (HR 0.76; 95% CI, 0.51 to 1.11)	For del(17p) or TP53 mutation, or both, those who received Zanu had longer PFS than those who received IBR (HR 0.53; 95% CI, 0.31 to 0.88)
MURANO[26]	1–3 prior treatment lines with ≥1 CIT	389	Ven+R vs. Ben+R	59.2 months	Median PFS for Ven+R 53.6 months (5-year estimate, 37.8%) vs. Ben+R; 17 months (HR 0.19; p<0.0001)	5-year OS for Ven+R 82.1% vs. Ben+R 62.2% (HR 0.40; p<0.0001)	Ven post IBR–12-month PFS estimate 75%[27]

Table 4. *Selected clinical trials in relapsed/refractory CLL; courtesy of Chai W. Phua, MD and Selay Lam, MD.*
Abbreviatons: A, Acalabrutinib; Ben, Bendamustine; BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CI, confidence interval; CIT, chemoimmunotherapy; ECOG, Eastern Cooperative Oncology Group scale; HR, hazard ratio; IBR, Ibrutinib; Idela, Idelalisib; IGHV, immunoglobulin heavy chain gene; OS, overall survival; PFS, progression-free survival; R, Rituximab; Ven, Venetoclax; Zanu, Zanubrutinib

who need therapy urgently. Patient selection is crucial, and those with good cardiac function and able to tolerate fluid hydration and minimal kidney dysfunction are preferred for this approach.

Emerging Therapies

Despite the significant advances in CLL treatment, patients who are refractory to BTKi and venetoclax therapies in the Canadian landscape have an unmet clinical need, because available approved agents are unlikely to be effective in the long-term. Allogeneic stem cell transplantation remains an option for young patients who are "double-refractory" (i.e. refractory to both BTKi and venetoclax). Participation in clinical trials is encouraged to access investigational therapies. Therefore, selecting appropriate therapy after multiple recurrences with varied treatment histories requires careful consideration and knowledge of current clinical trials. Discussing clinical trials as an option early in the treatment planning process could help with the sequencing of therapy.

Pirtobrutinib, a highly selective noncovalent BTKi, inhibiting both wild-type and Cys481Ser mutant *BTK*, has shown clinical efficacy and safety for patients relapsing while taking covalent BTKi as reported in the BRUIN study (median PFS of approximately 18–19 months in R/R CLL; *BTK* Cys481Ser mutations had a median PFS of approximately 16 months). However, Pirtobrutinib is likely ineffective in patients with the *BTK* Leu528Trp mutation.[29] The high selectivity to BTK compared with the second-generation BTKi offers a different toxicity profile, which is estimated to be lower, making pirtobrutinib an attractive option for patients who cannot tolerate other covalent BTK inhibitors. Pirtobrutinib will be a crucial addition to the treatment arsenal for patients with relapsed CLL. While pirtobrutinib appears to be a promising new addition to the BTKi class, a tempered and cautious approach is suggested for frontline use until further data becomes available, as it sets the stage for all subsequent lines of therapy. Concerning adverse mutations that may cause resistance could severely limit future treatment lines. Studies are currently underway to explore pirtobrutinib in the frontline setting.

Newer BCL-2 inhibitor therapies such as lisaftoclax and Bgb-11417 are being explored in R/R CLL. Lisaftoclax has a daily ramp-up over 5 days, which is faster than the current ramp-up schedule for venetoclax of 5 weeks, whereas Bgb-11417 had an over 8-week ramp-up period, or daily over an entire month, in its initial study.[36, 37] In a small study, lisaftoclax showed about 64% response rate in R/R CLL as monotherapy with activity even in patients resistant or intolerant to BTK inhibitors.[36] As more research and long-term data become available, these new BCL-2 inhibitors may differentiate themselves and potentially become CLL treatment options. However, venetoclax remains the preferred agent owing to its extensive clinical experience and well-tolerated profile.

Though not yet FDA-approved for CLL, chimeric antigen receptor T-cell therapy (CAR T-cell) shows potential in preventing long-term disease and treatment-free time and could be accessed through clinical trials. However, the outcomes with chimeric antigen receptor T-cell therapy in CLL have not been as remarkable as in other lymphoma types, in part due to the inherent dysregulation of the immune system in CLL leading to exhausted T-cells decreasing CAR-T cell activation after transduction.[38] Further research is ongoing to evaluate the role of CAR-T cells in CLL including bispecific T-cell engagers, antibody drug conjugates, as well as BTK degraders.

Conclusion

The landscape of CLL management has undergone transformational changes, shifting from traditional chemotherapy to targeted therapies. This pivotal advancement offers patients extended remissions and a better quality of life. Clinicians must keep pace with these evolving treatment modalities while considering individualized patient preferences and potential side effects.

Therapeutic choices, particularly between BTK inhibitors and venetoclax-based regimens, are increasingly made through a collaborative, shared decision-making process that weighs various factors, such as side effect profiles, treatment adherence, and the patient's unique circumstances. This highly personalized approach, coupled with an expanding therapeutic toolkit, not only signals significant progress within the field of hematology but also ensures that effective treatment options are accessible across a diverse range of CLL complexities.

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