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Clinical Challenges in the Era of Targeted Therapies: Double Refractory Chronic Lymphocytic Leukemia

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Abstract

Double refractory chronic lymphocytic leukemia (DR-CLL) is defined as disease progression during or after exposure to both Bruton tyrosine kinase (BTK) inhibitors and BCL2 inhibitors. It represents a critical therapeutic challenge. Patients with DR-CLL exhibit poor outcomes, with median overall survival of approximately 2.2 years following progression. Current treatment options are limited, and responses to available agents are often short-lived. Several innovative approaches are under active investigation, to address this unmet need including noncovalent BTK inhibitors, CAR-T cell therapy, bispecific antibodies, and novel targeted combinations. There is urgency for developing durable and accessible treatment approaches for this high-risk population.

Keywords: Chronic lymphocytic leukemia; Double refractory; Double Exposed; Venetoclax; Bruton tyrosine kinase degrader

Abbreviations: CLL: Chronic Lymphocytic Leukemia; BTKi: Bruton Tyrosine Kinase Inhibitor; ncBTKi: Non-Covalent BTK Inhibitor; uMRD: Undetectable MRD; R/R: Relapsed/Refractory; PD: Progressive Disease; ORRs: Overall Response Rates; SLL: Small Lymphocytic Leukemia

Introduction

Treatment resistance and toxicity are leading clinical challenges in chronic lymphocytic leukemia (CLL) [1]. Development of small molecule agents targeting key proteins in BCR-signaling and intrinsic apoptotic pathways in the last 10–15 years have significantly improved clinical outcomes of CLL. Current treatment algorithms with cBTKi- and venetoclax-based therapies based on patient characteristics and treatment responses can bring long-term survival to patients with this incurable disease [2]. BTKi monotherapy does not typically result in undetectable MRD (uMRD) but the use of covalent BTKi (cBTKi) in combination with anti-CD20 monoclonal antibody (mAb) results in higher rates of uMRD compared with monotherapy.

Several randomized clinical trials showed that venetoclax-based combination regimens result in higher rates of uMRD ($<10^{-4}$, uMRD4 or $<10^{-6}$, uMRD6 in blood or bone marrow) than chemoimmunotherapy [3]. Limited data exist on outcomes of patients exposed to both BTKis and B-cell lymphoma 2 inhibitors (BCL2is) [1]. Double-refractory (DR) CLL is very different from double-exposed (DE) CLL (1). DR CLL is defined as having progressive disease (PD) during active treatment with continuous BTKi- and continuous BCL2i-containing therapy, given sequentially or in combination. DE CLL refers to the discontinuation of BTKi and/or BCL2i due to reasons other than PD such as intolerable side effects, patient preference, or reaching the end of a planned treatment course [1].

Mechanisms of resistance to covalent BTK inhibitors and venetoclax

The best characterized and most common secondary mechanisms of resistance to cBTKi in CLL are mutations of the C481 residue in BTK, located at the drug binding site, and of the BTK effector PLCG2 [4]. Recent studies reported acquired BTK mutations including T474I gatekeeper mutations on the treatment with non-covalent BTK inhibitors (ncBTKis) [2]. Resistance to venetoclax is largely mediated by acquired mutations in the BH3-binding domain of BCL2, the target of venetoclax. Resistance to venetoclax can also be mediated by G101V mutated BCL2 and

overexpression of the pro-survival proteins BCL-XL and MCL-1. These proteins are also upregulated in response to CD40 activation by T cells in the CLL microenvironment. G101V BCL-2 mutations were rare in double refractory patients [4].

Characteristics Of DR and DE CLL Patients

DR and DE CLL are disease groups with distinct molecular characteristics and clinical phenotypes [5]. Patients with DR CLL are more likely to have high-risk features including unmutated IGHV, TP53 mutations or deletions, and BTK mutations [1]. DR CLL is very different from DE CLL, with patients having double-refractory disease having worse outcomes [1]. The median OS of patients with DR CLL disease whose disease progressed during BTK and BCL2 inhibition was 2.2 years [5]. This was achieved even with the use of cellular therapies, such as CAR-T or allogeneic stem cell (bone marrow) transplants, or the reversibly binding BTKi, pirtobrutinib. DR CLL is a challenging condition to treat. Patients should consider participating in clinical trials, as promising agents are being developed, including BTK degraders [1]. Unlike DR disease, DE CLL was characterized by an indolent course [5], better survival outcomes [1]and often could be monitored without immediate treatment and retained sensitivity to targeted and cellular therapies [5].

Retrospective data from the Dana-Farber Cancer Institute database identify 30 double-refractory patients and 65 double-exposed patients out of over 1000 CLL patients. Median overall survival from time of CLL diagnosis was 12 years for double-refractory patients and 21 years for double-exposed patients. With a median follow-up of 15 years, deaths occurred in 63% of the double-refractory group and 25% of the double-exposed group. The leading cause of death was progressive disease (42%) in the double-refractory group, while in the double-exposed group it was infections (25%). Patients developed double-refractory disease at a median of 7 years after their first therapy [6].

Novel Targeted Therapies for Double Refractory Disease

The treatment of CLL in patients with double refractory disease is a complex and evolving field. Extensive biological research enabled the clinical development of novel targeted agents. The promising preliminary data of ncBTKis and BTK degraders suggest that the use of these BTK-targeted agents may be the next treatment approach for double refractory disease. In addition, novel cancer immunotherapies such as bispecific antibodies (bsAbs) and CAR-T therapies can expand the treatment armamentarium for RR-CLL including double-refractory disease [2]. Current strategies include:

Non-covalent BTK inhibitors (Pirtobrutinib and Nemtabrutinib)

Pirtobrutinib (LOXO-305) is a novel oral ncBTKi, with activity against both wild-type and C481-mutated BTK. In December 2023, pirtobrutinib achieved accelerated FDA approval for the third or later-line treatment of CLL/SLL. Nemtabrutinib (MK-1026, formerly ARQ-531) is another ncBTKi with high potency against both wild-type and C481S-mutated BTK. In a recent analysis of the phase 1/2 BELLWAVE-001 trial, ORRs (overall response rates), mDoR (objective response rate) and mPFS (median progression-free survival) were 58%, 8.5 months and 10.1 months, respectively in those with prior BTKi and venetoclax [2].

BTK Degraders

BTK degraders are another new approach to target BTK and to overcome the resistance to cBTKis and ncBTKis. It acts by the degradation of the BTK protein itself rather than the inhibition of its function. BTK degraders induce catalytic ubiquitination of BTK via recruitment of the cereblon E3 ubiquitin ligase complex, leading to BTK degradation by the proteasome. An interesting finding is that BTK degraders show binding to BTK proteins with T474I gatekeeper mutation. NX-2127 is a novel oral small protein that targets BTK, IKAROS family zinc finger 1 (IKZF1) and IKZF3.

It combines BTK degradation with the immunomodulatory activity of IKAROS. Responses were observed in double-refractory patients and those who progressed on an ncBTKi. NX-5948 is another novel orally administered small molecules that selectively targets and degrades BTK. Preliminary findings from the ongoing phase 1 NX-5948-301 trial in patients with RR B-cell malignancies including CLL showed rapid, robust and sustained BTK degradation. In addition to the previously mentioned BTK degraders, BGB-16673 (NCT05006716 and NCT05294731), ABBV-101 (NCT05753501), and AC676 (NCT05780034 are currently under clinical investigation in B-cell malignancies including CLL [2].

Novel BCL2 Targeted Therapies

Novel BCL2is are currently under development. Very limited clinical data exists on progression of patients treated with venetoclax. Lisaftoclax is a highly selective and potent BCL2i. Phase 2 trial findings revealed that 12% of patients with R/R CLL/SLL patients progressed despite treatment with a BTKi and/or venetoclax [2]. The ORRs to lisaftoclax treatment was 65% as monotherapy and 98% when combined with acalabrutinib, and 87% when combined with rituximab. Sonrotoclax (BGB-11417) is a highly selective novel and potent BCL2i with a favorable pharmacokinetics profile and a broad therapeutic index. Preliminary data for CLL/SLL in phase 1 BGB-11417-101 trial, showed an ORRs of 67% for sonrotoclax monotherapy and 95% when given in combination with zanubrutinib. LOXO-338 is a novel orally bioavailable small molecule inhibitor of BCL2i designed to achieve selectivity over BCL-XL. The phase 1 LOXO-BCL-20001 trial is currently evaluating LOXO-338 monotherapy [2].

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Chimeric Antigen Receptor-T Cell Therapy

In the DR CLL patients, chimeric antigen receptor-T (CAR-T) cell therapy appears to be a potential therapeutic option. Adverse events such as cytokine release syndrome (CRS) and neurotoxicity must be taken into consideration. CAR-T cell therapy demonstrated substantial efficacy yielding encouraging outcomes and high ORR in relapsed CLL patients who failed prior treatment with ibrutinib and/or venetoclax [2]. On March 14, 2024, lisocabtagene maraleucel (liso-cel) received accelerated approval for use in CLL or SLL patients after at least 2 prior treatments, including a BTK inhibitor and a BCL2 inhibitor; approval was based on the results of the TRANSCEND CLL 004 trial [7]. Anti-CD19 CAR-NK cell therapy represents another promising immunotherapeutic approach that has been explored in hematologic malignancies including relapsed or refractory CLL patients. Chimeric antigen receptor- natural killer (CAR-NK) might be advantageous over CAR-T cell therapy. Most patients achieved CR with a manageable less pronounced severity of complications compared to CAR-T cell therapy [2].

Checkpoint Inhibitor

Atezolizumab, a programmed-cell death ligand 1 (PD-L1) checkpoint inhibitor, is being evaluated in a phase 1/1b clinical trial (NCT02500407) involving patients with R/R B-NHL or CLL.

Bispecific T-cell Engager

Epcoritamab (GEN3013; DuoBodyR-CD3A~CD20) is a CD20 × CD3 IgG1 bispecific antibody potentially useful in DR CLL. Preliminary findings indicate a favorable safety profile and activity even among high-risk patients (86% of whom carried del 17p or TP53 mutations, with a median number of six prior therapies).

Another agent is mosunetuzumab (Lunsumio)-an investigational fully humanized bispecific T-cell engaging antibody that targets CD20 on B cells and CD3 on T cells. Mosunetuzumab activates T-cells more effectively in preclinical investigation. It is investigated both as a monotherapy or combined with atezolizumab (NCT02500407 and NCT05091424) as a potential treatment option for various B-cell malignancies, including CLL [2].

Allogeneic Hematopoietic Stem Cell Transplantation (AlloHCT)

AlloHCT is a well-tolerated and durable treatment option, especially in high-risk CLL patients. The patient's fitness is a constricting factor. AlloHCT might be considered in double-refractory fit patients. No significant differences in PFS and OS were observed according to the therapy directly given prior to the alloHCT. The venetoclax–prior-alloHCT group demonstrated a much-reduced incidence of 12-month relapse relative to that observed in ibrutinib–prior-alloHCT participants (20% vs. 9.3%) [8].

Conclusion

Standardized salvage regimens have shown limited efficacy in the management of DR CLL and patient outcomes decline rapidly following progression. Novel agents and immunotherapeutic strategies show encouraging results, but durability of response and toxicity management remain significant obstacles. Future research must emphasize enrollment in clinical trials, integration of biomarker-guided treatment selection, and rational combination approaches to overcome resistance pathways.

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