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Review Article

What Next for Chronic Lymphocytic Leukemia? A Review of Evolving Paradigms, Measurable Residual Disease, and Emerging Immunotherapies

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Chronic lymphocytic leukemia (CLL) has entered an era of unprecedented therapeutic progress, driven by an improved understanding of disease biology and the development of highly effective targeted agents. Over the past decade, the treatment paradigm has shifted decisively away from chemoimmunotherapy towards mechanism-based approaches, most notably Bruton tyrosine kinase inhibitors (BTKi) and BCL2 inhibition. These advances have translated into substantial gains in progression-free and overall survival, redefining expectations for patients with this historically indolent but incurable malignancy (Burger et al., 2015; Shanafelt et al., 2020). Yet, despite these successes, CLL remains characterized by relapse, clonal evolution, and eventual therapeutic resistance, raising critical questions about optimal sequencing, treatment duration, and the potential for durable, treatment-free remission.

The contemporary treatment landscape is dominated by two distinct but increasingly overlapping strategies: continuous inhibition of oncogenic signaling pathways and time-limited therapy designed to induce deep remissions. BTKi, including ibrutinib, acalabrutinib, and Zanubrutinib, are typically administered indefinitely and have demonstrated sustained disease control across multiple patient subgroups, including those with high-risk genomic features. Second-generation agents offer improved tolerability, particularly with respect to cardiovascular toxicity, while maintaining comparable efficacy (Sharman et al., 2020; Tam et al., 2020). In parallel, venetoclax-based regimens, often combined with anti-CD20 monoclonal antibodies such as obinutuzumab or rituximab, have established a fixed-duration approach that yields high rates of deep remission and allows for treatment discontinuation (Fischer et al., 2019; Seymour et al., 2018).

These paradigms are increasingly converging through combination strategies that seek to maximize response depth while limiting treatment exposure. Regimens combining BTKi and venetoclax have demonstrated impressive rates of undetectable measurable residual disease (MRD) and durable remissions in both treatment-naïve and relapsed settings, as exemplified by the CAPTIVATE and GLOW trials (Wierda et al., 2021; Moreno et al., 2022). Such approaches reflect a broader shift towards finite therapy guided by biological response, rather than indefinite disease suppression. Nevertheless, the optimal sequencing of these agents remains uncertain, particularly as an increasing number of patients are exposed to both classes early in their disease course. The emergence of "double-refractory" CLL, defined by progression following both BTKi and venetoclax, represents a growing and clinically challenging population with historically poor outcomes (Mato et al., 2020).

Within this evolving landscape, measurable residual disease has assumed a central role as both a prognostic biomarker and a potential therapeutic guide. Advances in detection methods, including high-sensitivity flow cytometry and next-generation sequencing, now permit identification of residual disease at levels far below conventional morphological thresholds (Thompson et al., 2019). Numerous studies have demonstrated a strong association between MRD negativity and prolonged progression-free survival, particularly in the context of

venetoclax-based therapy, where deep remissions are frequently achieved (Seymour et al., 2018; Fischer et al., 2019). Consequently, MRD assessment is increasingly incorporated into clinical trials as an intermediate endpoint and is beginning to inform treatment decisions, including the duration of therapy and the feasibility of discontinuation.

However, the role of MRD is not uniform across all therapeutic modalities. In patients receiving continuous BTKi therapy, durable disease control can be achieved despite persistent detectable disease, highlighting a divergence between biological eradication and functional suppression of CLL (Shanafelt et al., 2020). Moreover, issues of assay standardization, sensitivity thresholds, and inter-laboratory variability remain unresolved. Ongoing studies, including MRD-adapted treatment strategies such as those explored in the FLAIR trial, will be critical in defining how best to integrate MRD into routine clinical practice (Hillmen et al., 2023). Ultimately, the promise of MRD lies in enabling truly individualized therapy, balancing efficacy with minimization of treatment burden.

Beyond targeted small molecules, immunotherapy is poised to play an increasingly prominent role in the future management of CLL. Chimeric antigen receptor (CAR) T-cell therapy, while transformative in aggressive B-cell malignancies, has yielded more modest and variable results in CLL. Early clinical trials of CD19-directed CAR T cells demonstrated meaningful responses, including durable remissions in a subset of patients, but overall efficacy has been limited by intrinsic T-cell dysfunction and an immunosuppressive tumour microenvironment (Porter et al., 2015; Turtle et al., 2017). These challenges are now being addressed through innovative strategies, including the use of concurrent BTKi to enhance T-cell fitness and CAR T-cell expansion, as well as the development of next-generation constructs with improved persistence and dual antigen targeting (Fraietta et al., 2018).

In parallel, bispecific antibodies have emerged as a compelling “off-the-shelf” immunotherapeutic alternative. By simultaneously engaging CD3 on T cells and CD20 on malignant B cells, these agents redirect endogenous immune effector function without the need for ex vivo manipulation. Molecules such as mosunetuzumab, glofitamab, and epcoritamab have demonstrated significant activity in B-cell lymphomas and are now under active investigation in CLL (Hutchings et al., 2021; Dickinson et al., 2022). Early-phase data suggest that these therapies can induce meaningful responses even in heavily pretreated patients, with manageable toxicity profiles that include cytokine release syndrome and neurotoxicity. Their immediate availability and potential for outpatient administration confer practical advantages over CAR T-cell therapy, although their durability of response and optimal positioning within the treatment algorithm remain to be established.

The therapeutic pipeline in CLL continues to expand, reflecting a broader effort to overcome resistance and further deepen responses. Non-covalent BTK inhibitors, such as pirtobrutinib, have demonstrated activity in patients with resistance mutations affecting covalent BTKi binding, offering an important option in the

relapsed setting (Mato et al., 2021). BTK degraders, trispecific antibodies, and natural killer cell-based therapies represent additional avenues of investigation, each targeting different aspects of tumor biology and immune dysfunction. Collectively, these approaches signal a shift towards increasingly sophisticated and multimodal treatment strategies.

Looking ahead, several themes are likely to define the next phase of CLL management. The integration of MRD into routine care may enable a transition towards time-limited, response-adapted therapy for a broader proportion of patients. Immunotherapies, including CAR T cells and bispecific antibodies, may move earlier in the disease course, particularly for those with high-risk features such as TP53 disruption. At the same time, advances in genomic profiling and disease monitoring will facilitate more precise treatment of selection and sequencing. Perhaps most importantly, the concept of a "functional cure"—defined as sustained, MRD-negative remission in the absence of ongoing therapy—appears increasingly attainable for a subset of patients.

In conclusion, CLL has evolved from a disease managed with largely palliative intent to one characterized by highly effective, targeted, and increasingly individualized therapy. The convergence of MRD-guided strategies, rational combination regimens, and emerging immunotherapies offers the prospect of deeper remissions and prolonged treatment-free intervals. The challenge now lies not in the availability of therapeutic options, but in their optimal deployment, with the ultimate goal of transforming durable disease control into lasting remission.

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