Minimal residual disease (MRD) detection in chronic lymphocytic leukemia (CLL) is evolving as an important concept in patient treatment algorithms due to the availability of drug combinations capable of inducing complete responses (CR). Such achievement raises the concept of time-limited therapy in an incurable disease outside of bone marrow transplant.

While ibrutinib (Imbruvica), a Bruton tyrosine kinase inhibitor (BTKi), has improved progression-free survival (PFS) and overall survival (OS), including in patients with poor prognostic features, CRs are rare, with deeper responses improving over time. Therefore, ibrutinib is maintained until disease progression or intolerance.

Venetoclax (Venclexta) is a game changer for the CLL treatment arsenal, with data showing high rates of undetectable MRD (uMRD) in peripheral blood and bone marrow samples as reported in both the CLL14 and MURANO clinical trials for frontline and relapsed/refractory CLL patients, respectively, including those with poor prognostic features (Al-Sawaf et al., 2020; Kater et al. 2019). Venetoclax is a BCL2 inhibitor that restores apoptosis independent of del17p/TP53 mutations. Collectively, these data suggest that certain subsets of patients may be eligible for time-limited therapy once uMRD achieved. Advanced practitioners (APs) should be cognizant of how MRD is defined, measured, and may be applied to therapeutic decision-making in the clinical management of CLL.

**Key Points**

- Minimal residual disease (MRD) has become an important indicator of response in CLL.
- Advanced practitioners should be able to educate patients on what MRD is, specifically when considering therapy of limited duration on venetoclax-based regimens.

**MRD METHODS**

The most applied MRD methods, with differing levels of sensitivity, are flow cytometry, polymerase chain reaction with allele-specific oligonucleotide primers for immunoglobulin heavy chain genes, and next-generation sequencing (NGS). Undetectable MRD is defined as less than 1 CLL cell in 10,000 leukocytes or $< 10^{-4}$ (Fürstenau, De Silva, Eichhorst, & Hallek, 2019). Next generation sequencing–based approaches have higher sensitivity rates, down to $10^{-5}$ or $10^{-6}$. One limitation to consider is that CLL is a multicompartment disease involving the bone marrow, peripheral blood, and extramedullary sites, such as skin and lymph nodes.
marrow, lymph nodes, spleen, or other secondary lymphoid tissue. Therefore, sampling tissue, assay, and level of sensitivity are important considerations when interpreting MRD status. Such techniques not only hold promise for detecting MRD but may also lead to improved outcomes by providing response assessment and prognostic information.

MRD DATA
MRD data in CLL have largely been derived from chemoimmunotherapy regimens, such as with fludarabine, cyclophosphamide, and rituximab (FCR), where data have demonstrated that patients achieving uMRD showed a significant improvement in PFS and OS compared with those with persistent MRD (Thompson et al., 2018). Pretreatment prognostics retain significance, as time to MRD reemergence in uMRD patients with unmutated IGHV was shorter compared with mutated IGHV (Thompson et al., 2016).

Venetoclax-based regimens capable of inducing CRs have paved the way for clinical trials examining both the time to achievement and attainment of uMRD in both frontline and relapsed/refractory CLL settings. The phase II iFCG trial utilizing ibrutinib, FCR, and obinutuzumab (Gazyva) has shown uMRD after 12 cycles in 91% and 63% of patients in bone marrow samples with $10^5$ and $10^6$ sensitivity, respectively (Jain et al., 2019a). Undetectable MRD achievement after 12 courses served to randomize patients to continue or discontinue ibrutinib. Grade 3/4 adverse events included neutropenia in 58% of patients and thrombocytopenia in 40% of patients. The frontline combination of ibrutinib and venetoclax reported uMRD rates increased to 75% (n = 49) by 24 months in bone marrow samples (Jain et al., 2019b). In the relapsed/refractory setting, ibrutinib and venetoclax combinations are showing impressive rates of uMRD in 68% of bone marrow samples (n = 34) by 24 months (Jain et al., 2019c).

The Advanced Practitioner Perspective
Evolving data with venetoclax-based regimens are showing promise for time-limited therapy. This has implications for AP practice, as we have a pivotal role in the discussion of therapeutic goals of care with patients. Moreover, APs often partake in treatment selection aimed at inducing a deep response while minimizing the exposure to AEs and financial toxicity, and decreasing the potential risk of developing resistance mutation(s) during indefinite therapy. Advanced practitioners should continue to follow maturing clinical trial data exploring the utility of MRD in practice whether as an indicator of response or detector of early relapse before clinical or laboratory manifestations arise.

Disclosure
Dr. Nodzon has consulted for AbbVie, AstraZeneca, and Genentech.

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