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Challenging the Value of Minimal Residual Disease in Predicting Outcome of Patients With Chronic Lymphocytic Leukemia

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Improvements in treatments for patients with chronic lymphocytic leukemia (CLL) can allow therapeutic eradication of any detectable disease by even the most sensitive methods. Intuition dictates that patients who do not have any detectable minimal residual disease (MRD) after treatment should have a longer progression-free survival (PFS) than those who have residual disease after therapy. Clinical studies evaluating for MRD after therapy and assessing its relationship with PFS provided evidence that clearance of MRD may supplant other metrics for assessing the response to therapy. For example, patients who have undetectable MRD (uMRD) after chemoimmunotherapy (CIT), but who achieved only a partial response by International Workshop on Chronic Lymphocytic Leukemia criteria,[1] had a longer PFS than patients who had achieved a complete response, but had detectable MRD after therapy.[2] Similar observations subsequently were made for patients treated with venetoclax and anti-CD20 monoclonal antibodies (mAb).[3,4] Moreover, the relative level of MRD detected after therapy appeared to correlate inversely with the length of disease remission. This has led to the assumption that clearance of detectable MRD may be among the most consequential surrogate markers for a prolonged PFS after fixed-duration (FD) therapy.

For this reason, work has focused on defining practical means for detecting MRD (Fig 1). Many clinical pathology laboratories can certify that a sample contains fewer than 1 CLL cell in 10,000 cells (ie, $<10^{-4}$ or MDR4) using flow cytometry to analyze cells stained with a panel of fluorochrome-conjugated antibodies, each specific for any one of the six cell surface proteins (eg, CD19, CD20, CD5, CD43, CD79b, and CD81). Flow cytometry actually can determine with confidence that there are fewer than 1 in 100,000 CLL cells in any given sample (ie, $<10^{-5}$ or MRD5),[5] but this understandably requires high-level expertise and attention to collecting data on millions of cells and not just a few hundred thousand. There generally is good concordance between flow cytometry and molecular sequencing analysis for the immunoglobulin heavy (IGH) complementarity determining region 3 (ie, the variable, diversity, and joining genes [VDJ] rearrangement) that is idiosyncratic for the leukemia cell population. However, sequencing analysis for the VDJ rearrangement generally is more sensitive than flow cytometry and can determine whether there are fewer than one in a million CLL cells in a sample (ie, $<10^{-6}$ or MRD6). However, such sequencing methods require molecular characterization of the VDJ rearrangement in pretreatment CLL cells; moreover, some VDJ rearrangements are difficult to sequence for a variety of reasons (eg, high guanine-cytosine content). Both techniques are limited by the numbers of cells available for analysis and can be affected by uneven distribution of residual disease in sampled tissue compartments; for example, sampling the blood for MRD within 3-6 months after having had anti-CD20 mAb therapy typically lowers the sensitivity for detecting MRD in the blood compared with the marrow. Assessing the cell-free DNA (cfDNA) in plasma for CLL-associated VDJ rearrangements is a newer method that has the advantage of being able to analyze for residual disease across multiple compartments and, in theory, could assess the total body MRD after therapy with a sensitivity that appears at least similar, if not greater, than that of flow cytometry.[6] However, some of the limitations noted for detecting clonal VDJ rearrangements in DNA extracted from leukocytes also apply to assays for MRD in cfDNA; moreover, for unexplained reasons, detection of MRD in some patients (eg, those with del(11q)) appeared more readily achieved using flow cytometry than through analysis of cfDNA for idiosyncratic clonal VDJ rearrangements; this did not appear to be the case for patients lacking del(11q), suggesting that the sensitivity of this approach for monitoring MRD may be influenced by factors associated with the leukemia cell's cytogenetics.

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THE TAKEAWAY

In the article that accompanies this editorial, Munir et al[10] describe the relationship between 1-year progression-free survival (PFS) and the level of minimal residual disease (MRD) in patients with chronic lymphocytic leukemia (CLL) who were given fixed-duration therapy with either ibrutinib and venetoclax or chlorambucil and obinutuzumab. Patients with detectable MRD at 3 months after completing therapy with ibrutinib and venetoclax generally retained the same level of MRD 9 months later and did not have PFS at 1 year that was lower than that of patients who had undetectable MRD; such was not the case for patients treated with chlorambucil and obinutuzumab. Therapy with ibrutinib and venetoclax may mitigate the value of post-treatment MRD in predicting shorter PFS of patients with CLL.

Although some studies have shown a prognostic advantage in assessing for MRD5 ($<10^{-5}$) rather than MRD4 ($<10^{-4}$) for patients treated with CIT (eg, chlorambucil and obinutuzumab, as described in the article that accompanies this editorial),[2,7,8] there appears to be growing acceptance of MRD4 as a practical threshold for defining MRD in patients with CLL after therapy, including newer targeted therapies. Could MRD4 be considered a useful prognostic marker for predicting the relative PFS after therapy? Perhaps, but there are some caveats. For example, among patients who have uMRD after treatment with fludarabine, cyclophosphamide, and rituximab, those who had CLL with mutated immunoglobulin heavy chain variable (IGHV) region genes had a longer PFS compared with patients with unmutated IGHV CLL,[9] indicating that achieving uMRD after CIT does not have the same prognostic implications for all patients.

In the article that accompanies this editorial, Munir et al[10] provide another potential caveat to solely using MRD to predict PFS after therapy. They performed an analysis of the GLOW study in which treatment-naïve patients were randomly assigned to receive either FD chlorambucil and obinutuzumab or 3 months therapy with ibrutinib followed by 12 months of combined therapy with ibrutinib and

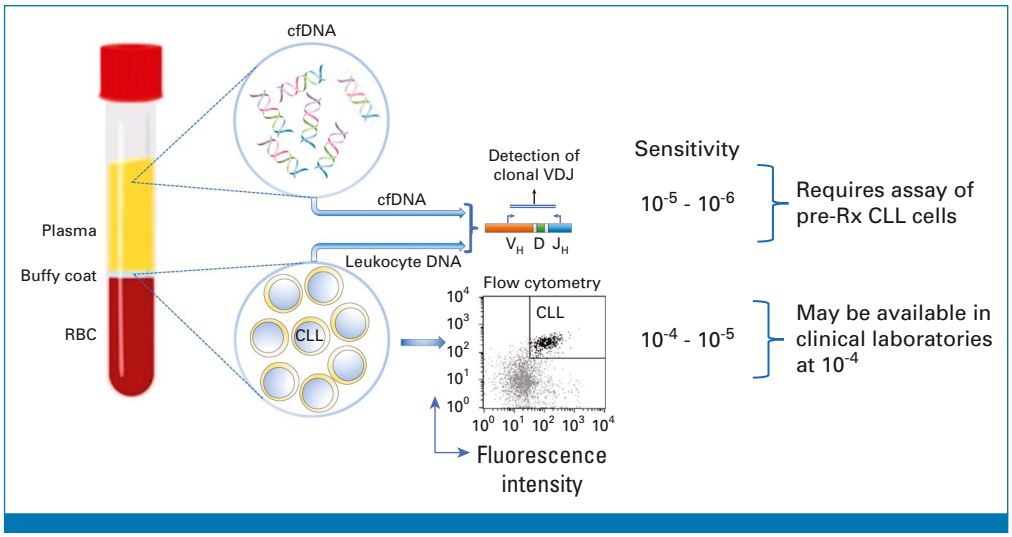

FIG 1. Methods for detecting minimal residual disease in patients with CLL. Centrifugation separates a heparinized blood sample on the left into plasma (top layer), red blood cells (bottom layer), and a buffy coat (middle) containing blood leukocytes, as indicated on the left. The blood leukocytes can be harvested (depicted in the bottom circle) for analyses using flow cytometry to detect leukemia cells having the right constellation of surface proteins (bottom dot plot) or for preparing leukocyte DNA, which can be assessed for clonal leukemia VDJ rearrangements, which juxtapose the Ig V_H, D, and J_H. cfDNA can be found in plasma (top circle); such cfDNA also can be assessed for leukemia-specific VDJ rearrangements. The assays on DNA collected from leukocytes or plasma require analysis of leukemia cells before therapy to determine its idiosyncratic VDJ rearrangement. The general sensitivity for these assays for detecting leukemia cells ranges from one CLL cell in 10^5 to 10^6 cells (for leukocyte-DNA-based assays) to one in 10^4 to 10^5 cells using flow cytometry, which may be available in clinical laboratories at a sensitivity of 10^{-4}. cfDNA, cell-free DNA; CLL, chronic lymphocytic leukemia; D, diversity segment; I_g, immunoglobulin; J_H, Ig-heavy-chain joining segment; R_X, therapy; VDJ, variable, diversity, and joining genes; V_H, heavy chain variable region.

venetoclax. Patients were assessed for MRD using flow cytometry and molecular sequencing analysis on leukocyte-extracted DNA for CLL-associated VJD rearrangements at 3 and 12 months after the end of therapy (EOT), abbreviated as EOT+3 and EOT+12, respectively. As anticipated, higher proportions of patients treated with ibrutinib and venetoclax had greater clearance of MRD at EOT+3 and maintained higher levels of uMRD at EOT+12 than did patients treated with chlorambucil and obinutuzumab. Surprisingly, however, most ibrutinib-venetoclax–treated patients with detectable MRD at EOT+3 maintained the same level of MRD at EOT+12. This was not the case for patients treated with chlorambucil and obinutuzumab, who more commonly progressed to levels of MRD at EOT+12 higher than they had at EOT+3. Moreover, the value of detecting MRD at EOT+3 appeared to have little relevance to predicting PFS at EOT+12, as all patients treated with ibrutinib and venetoclax had comparably high PFS (eg, >93%) at EOT+12, independent of their IGHV mutation status or whether they had detectable MRD at EOT+3. This was not apparent for patients treated with chlorambucil and obinutuzumab; for such patients, the clearance of detectable MRD at EOT+3 was a clear predictor of superior PFS at EOT+12. As such, the study by Munir et al[10] challenges the widely held notion that detection of MRD after therapy necessarily portends a relatively short PFS.

As noted by the authors, there are limitations to this study, including the relatively short follow-up, potential for imbalances in baseline characteristics between groups, and small numbers of patients in some subgroups. However, it should be noted that in the FD cohort of the CAPTIVATE study, in which patients were treated with ibrutinib and then ibrutinib and venetoclax, as in the GLOW study, the best uMRD4 rates at EOT were 77% (blood) and 60% (marrow); nonetheless, the collective 24-month PFS and overall survival rates were 95% and 98%,[11] respectively, indicating that patients who had detectable MRD after FD therapy with ibrutinib and venetoclax generally were doing as well as those who had uMRD4, at least for 2 years after therapy, blurring the relationship between MRD and PFS. This challenges the notion that detection of MRD can be considered the sole indicator of an inferior response to therapy that is predictive of a relatively poor PFS, even when patients are stratified by their relative risk for disease progression, for example by their leukemia cell's IGHV mutation status. Instead, the PFS of patients with detectable MRD after therapy also may be governed in part by the type of therapy, questioning the use of MRD as the sole surrogate end point for assessing the relative response to treatment in registration studies of new drugs or drug combinations. Additional time will be required to bring the relationship between MRD and PFS into clearer focus and to determine whether combined therapy with ibrutinib and venetoclax is truly a game changer that can mitigate the value of assessing for MRD after therapy in predicting the duration of PFS of patients with CLL.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Hallek M, Cheson BD, Catovsky D, et al: iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 131:2745-2760, 2018
2. Kovacs G, Robrecht S, Fink AM, et al: Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: Comprehensive analysis of two phase III studies of the German CLL study group. J Clin Oncol 34:3758-3765, 2016
3. Kater AP, Seymour JF, Hillmen P, et al: Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO phase III study. J Clin Oncol 37:269-277, 2019
4. Kersting S, Dubois J, Nasserinejad K, et al: Venetoclax consolidation after fixed-duration venetoclax plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (HOVON 139/GiVe): Primary endpoint analysis of a multicentre, open-label, randomised, parallel-group, phase 2 trial. Lancet Haematol 9:e190-e199, 2022
5. Rawstron AC, Fazi C, Agathangelidis A, et al: A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: An European Research Initiative on CLL study. Leukemia 30:929-936, 2016
6. Furstenau M, Weiss J, Giza A, et al: Circulating tumor DNA-based MRD assessment in patients with CLL treated with obinutuzumab, acalabrutinib, and venetoclax. Clin Cancer Res 28:4203-4211, 2022
7. Feugier P, Aurran T, Mahe B, et al: Long-term follow up of the CLL2007FMP trial evaluating fludarabine and cyclophosphamide in combination with either rituximab or alemtuzumab in previously untreated patients with chronic lymphocytic leukemia. Haematologica 103:e304-e306, 2018
8. Letestu R, Dahmani A, Boubaya M, et al: Prognostic value of high-sensitivity measurable residual disease assessment after front-line chemoimmunotherapy in chronic lymphocytic leukemia. Leukemia 35:1597-1609, 2021
9. Thompson PA, Tam CS, O'Brien SM, et al: Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood 127:303-309, 2016
10. Munir T, Moreno C, Owen C, et al: Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. J Clin Oncol 41:3689-3699, 2023
11. Tam CS, Allan JN, Siddiqi T, et al: Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: Primary analysis of the CAPTIVATE FD cohort. Blood 139:3278-3289, 2022

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