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Adherence to ibrutinib remains an unmet clinical need in chronic lymphocytic leukemia.

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More than twenty years ago, the tyrosine kinase inhibitor imatinib, used in the treatment of chronic-phase chronic myeloid leukemia (CML), heralded a new era of targeted oral treatments in hematology (1). For the vast majority of patients, imatinib treatment results in high rates of molecular remission and prolonged survival (1). However, achieving such excellent results necessitates patients to be at least 90% adherent to therapy, which only about two-thirds of patients with CML achieve. Indeed, poor adherence is the predominant reason for the failure to obtain adequate molecular responses (2). As a result, non-compliance to treatment, rather than biological resistance to medication, is the key driver of suboptimal responses in CML (2).

In chronic lymphocytic leukemia (CLL), the most frequent form of leukemia in western countries, a major revolution in treatment approaches occurred about eight years ago with the approval of ibrutinib, a first-in-class oral Bruton tyrosine kinase inhibitor (BTKi). Early results of phase I studies investigating ibrutinib in relapsed/refractory (R/R) disease clearly indicated that ibrutinib was transforming the therapeutic approach to CLL (3). Subsequently, several phase III studies in R/R or treatment-naïve CLL clearly demonstrated that ibrutinib-based therapies outperformed chemo-immunotherapy regimens (3-7). Of note, the overwhelming benefit of ibrutinib was especially noted in the setting of genetically high-risk patients who are known to be poorly responsive to chemo-immunotherapy (3-7). However, due to the general lack of deep therapeutic responses and persistent minimal residual disease with ibrutinib and related agents, the BTKi therapeutic paradigm requires indefinite treatment with patients exposed to the therapy for prolonged periods of time with potential ongoing treatment-related toxicities (8).

Ibrutinib is a nonselective covalent BTKi associated with well-described toxicities such as atrial fibrillation, infection, pneumonitis, bleeding, and arthralgia (9). Such toxicities may result in therapy discontinuation or interruption which are correlated with shortened progression-free survival (PFS) (10). Barr et al. (11) investigated the impact of ibrutinib dose adherence on patient outcomes in CLL patients recruited into the phase 3 RESONATE study. Dose intensity (DI) was assessed for the first eight weeks of treatment (DI-8 weeks) as well as for the entire duration of the treatment (DI-overall). Patients with DI > 95% had fewer PFS events than patients with DI less than 95% in both groups. The observation period of this study was, however, restricted to the first nine months of therapy and thus did not capture most subsequent disease-progression events (11). In the UK CLL Forum study, treatment breaks of more than 14 days during the first year of ibrutinib therapy were associated with a lower chance of survival (12). Patients with early, temporary, treatment breaks generally had a poor performance status and were four times more likely to subsequently permanently discontinue ibrutinib during the first year, suggesting host-related issues relating to patient fitness as a confounder (12). However, despite the results of these studies, the

impact of ibrutinib dose modifications on clinical outcomes remains unclear. A recent comprehensive review including fourteen clinical trials and fifteen "real-world practice" studies outlines the numerous confounders that potentially affect ibrutinib dose changes and outcomes, rendering it difficult to draw any definitive dosing recommendations at this time (13).

In this issue of Leukemia & Lymphoma Collins et al (14) present the results of a retrospective, multicenter study wherein the authors assessed ibrutinib adherence and the impact of adherence on real-world clinical outcomes of CLL patients over the complete duration of ibrutinib treatment. . The proportion of days covered (PDC) computation was used to calculate ibrutinib adherence rates. The mean PDC for the 100 patients in the primary analysis was 95% (range: 65 – 100%). Of note, patients who maintained PDC>95% for each of the first six months experienced fewer PFS events (n=1) compared to those with PDC < 95% (n=5,p=0.03)(14). In this respect, it is important to realize that despite the rapid expansion and development of oral targeted therapies for CLL treatment, there are substantial concerns about the availability of standardized methods for monitoring the adherence to these agents. Although the PDC calculation has been validated as an effective method to assess adherence and favorably compares to DI, the results of the present study, mainly based on the PDC calculation, are not easily comparable with those of previously published studies (12-13,15). Nonetheless, the paper by Collins et al (14) indicates the urgent need to harmonize methods of adherence assessment to oral CLL therapies. This could potentially lead to more clinical research into the effects of ibrutinib adherence on patient outcomes and provide more comparative data.

The results of the study by Collins et al (14) suggest that close adherence to the ibrutinib therapy in the first six months significantly reduces the risk of progression events but unavoidably translates into an increase of adverse events. The authors speculate that the starting dose of ibrutinib corresponding to 420mg per day may not be appropriate for all patients. A single study established that after one cycle of ibrutinib at the licensed dose of 420 mg per day doses, patients with CLL can be dose reduced without loss of biological activity (16). At the current time though, in absence of confirmatory data, caution should however be exercised in the arbitrary reduction of starting dose of ibrutinib. At present, we have limited information on how best to select patients who are likely to develop ibrutinib-related side effects and who may therefore benefit from dose reduction. Furthermore, the cumulative illness rating scale (CIRS) recently validated as a predictor of survival in patients treated with ibrutinib only partially impacted the ibrutinib-related patient outcomes (17). Thus until now, we do not have sufficiently reliable predictors of ibrutinib toxicity that may guide clinicians to identify those patients at higher risk of ibrutinib-related side effects.

A recent study attempted to identify the reasons for non-adherence to oral medicines. These reasons were separated into two categories: modifiable and non-modifiable. Co-payment, age, regimen complexity, and time since diagnosis were classed as non-modifiable factors whilst treatment side effects, forgetfulness, and a lack of information about oral antineoplastic drugs were deemed to be modifiable (18). In the supervision of ibrutinib therapy, it seems that modifiable factors are more prevalent (12-13) with consequential room for improvement in the adherence to ibrutinib therapy. Current oncology practices should continue to develop standard procedures for patient education, the development, and sharing of treatment plans, and routine monitoring of patient adherence to oral antineoplastic therapies. The authors in their current study rightly highlight the central role of the clinical pharmacist in the effective delivery of targeted therapies such as ibrutinib to patients with CLL (14).

Another way to improve the adherence to therapy in CLL could entail the utilization of second-generation, highly selective, BTKi drugs such as acalabrutinib or zanubrutinib (19-20). In the non-inferiority designed ELEVATE RR study, which directly compared ibrutinib and acalabrutinib in R/R CLL patients, treatment discontinuations related to adverse events occurred less frequently in acalabrutinib-treated patients (15%) than in ibrutinib-treated patients (21%)(19). In addition, using zanubrutinib, another oral covalently binding selective BTK inhibitor, early data from the ALPINE study which compared zanubrutinib to ibrutinib treatment in patients with R/R CLL, the rate of adverse events leading to discontinuation was higher for ibrutinib than for acalabrutinib (13% versus 7.8%)(20). Finally, irrespective of which BTKi is used, close monitoring of drug adherence within the first six months of therapy as well as an appropriate multidisciplinary team-based approach aimed at mitigating BTKi-related adverse effects should be offered to patients with CLL in order to optimize the results of therapy. Clinicians supported by pharmacists and clinical nurse specialists with advanced training or certifications should closely cooperate to improve BTKi adherence monitoring. We should also be mindful that good communication between healthcare professionals and patients is crucial to enable our CLL patients to obtain maximal benefit from therapy whilst toxicities are minimized (21).

References

1. O'Brien SG, Guilhot F, Larson RA, et al Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003 Mar 13;348(11):994-1004
2. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol. 2010;28:14:2381-2388.
3. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–223.
4. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373(25):2425–2437.
5. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379(26):2517–2528.
6. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial Lancet Oncol. 2019 Jan;20(1):e10]. Lancet Oncol. 2019;20(1):43–56.
7. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. The New England journal of medicine. 2019;381(5):432-443.
8. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):336-345. DOI: 10.1182/hematology.2020000118.
9. Coutre SE, Byrd JC, Hillmen P, et al Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Adv. 2019 Jun 25;3(12):1799-1807.
10. J Maddocks KJ, Ruppert AS, Lozanski G, et al Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol 2015;1(1):80-87.
11. Barr PM, Brown JR, Hillmen P, et al. Impact of Ibrutinib Dose Adherence on Therapeutic Efficacy in Patients with Previously Treated CLL/SLL. Blood.

2017; 129: 2612 – 2615.
12. UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: the UK and Ireland analysis of outcomes in 315 patients. Haematologica 2016 ;101(12):1563-1572.
13. Hardy-Abeloos C, Pinotti R, Gabrilove J. Ibrutinib dose modifications in the management of CLL. Journal of Hematology & Oncology 2020 13:66-76.
14. Collins J 4th, Stump SE, Healing H, et al Impact of adherence to ibrutinib on clinical outcomes in real-world patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2022 Mar 6:1-8. DOI: 10.1080/10428194.2022.2045597. Online ahead of print.
15. Sattler, E. L. P., Lee, J. S., & Perri, Matthew, I., II. (2013). Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: A review of the literature. Drugs & Aging, 30(6), 383-99.
16. Chen LS, Bose P, Cruz ND, et al A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia. Blood 2018; 132 (21): 2249–2259.
17. Tedeschi A, Frustaci AM, Mauro FR, et al Do age, fitness, and concomitant medications influence management and outcomes of patients with CLL treated with ibrutinib? Blood Adv 2021; 5 (24): 5490–5500.
18. Ross XS, Gunn KM, Suppiah V, et al. A review of factors influencing non-adherence to oral antineoplastic drugs. Support Care Cancer 2020;28(9):4043-4050.
19. Byrd JC, Hillmen P, Ghia P, et al Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. J Clin Oncol 2021;39(31):3441-3452.
20. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: Results of phase III randomized study of zanubrutinib versus ibrutinib in patients with relapsed/refractory CLL/SLL. European Hematology Association,2021, LB 1900.
21. Molica S, Bombaci F, Cuneo A, et al Living with CLL: A quantitative cross-sectional study of Italian patients on behalf of AIL (Associazione Italiana contro le Leucemie-Linfomi e Mielomi). European Hematology Association 2020,EP1743