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COMMENTARY

Is it time to reconsider molecular response milestones in chronic myeloid leukemia?

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It is widespread practice to utilize molecular measurements using real-time qPCR to monitor ongoing responses to tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML). The most popular molecular milestone is major molecular response (MMR), defined as a BCR-ABL transcript level ≤0.1% standardized to the international scale (IS). Failure to achieve MMR has been widely accepted as a warning sign of treatment failure and grounds for therapeutic changes, despite a lack of data clearly showing that acting upon this outcome (i.e., switching or escalating therapy for failing to meet MMR) improves clinically relevant endpoints like overall survival (OS). In the current issue of the *American Journal of Hematology*, Bidikian et al. report long-term survival data on 131 patients with CML who failed to achieve MMR within 2 years of treatment with TKIs.[1] Ten-year OS and CML-related OS were 76% and 88%, respectively, in their cohort, with achievement of a major or complete cytogenetic response (MCyR, CCyR) within 2 years of therapy being predictive of higher survival (10-year CML-related OS of 95%). Their results are in stark contrast with very early reports from the dawn of the TKI era, which show dismal outcomes from failing to meet the milestone. Bidikian et al.'s findings raise doubts about the prognostic value of MMR and the current practice of switching CML patients to more expensive, toxic therapy when MMR milestones are not met.

The use of MMR to optimize therapy for CML was proposed in 2003 by the authors of the IRIS study, which randomized 1106 CML patients to initial therapy with imatinib or interferon alfa + cytarabine.[2] Among patients who achieved CCyR at 12 months, the probability of remaining progression-free was 100% at 24 months for those who achieved at least a 3-log reduction in BCR-ABL transcript levels from baseline at 12 months compared to 95% for those who did not. Based on these results, the study authors defined "major molecular response" as a reduction in BCR-ABL transcript levels of at least three logs. Notably, even at the outset, the prognostic value of MMR was contingent on its relationship to a different surrogate (progression-free survival at 24 months) rather than OS or quality of life.

The gold standard to validate a surrogate endpoint in oncology is to demonstrate a strong correlation in treatment trials between improving the surrogate and improving clinical endpoints. Across cancer, hundreds of these analyses have been performed.[3] Yet, no such study has ever been conducted for MMR, though it remains a popular primary endpoint in CML trials. Without such validation, it is unclear whether early achievement of MMR truly translates to improvements in patient-centered outcomes, including OS and quality of life.

When trial-level evidence supporting surrogate validity is lacking, observational data should at a minimum demonstrate a strong relationship between the surrogate and OS. Doubts about the use of MMR to assess treatment failure have been raised in the past. In a study by Marin et al. on 224 CML patients treated with imatinib at Hammersmith Hospital, failure to achieve MMR at 12 or 18 months was shown to have no impact on 5-year OS (96.4% vs. 93.4%).[4] Kim et al.'s analysis of 200 imatinib-treated patients found that OS probabilities at 84 months were 96% and 95% in the MMR and no MMR groups, respectively.[5] Oriana et al. conducted a pooled analysis of five studies providing data on MMR and OS, demonstrating that the OS advantage of achieving MMR at 12 months is unclear.[6] The benefit of MMR is even less evident in patients who already achieve cytogenetic response. Kantarjian et al. analyzed 276 patients receiving imatinib for chronic-phase CML and demonstrated that the degree of molecular response was not associated with differences in survival in patients with CCyR.[7] Another analysis of the Hammersmith Hospital data yielded similar results, with authors stating that the study "calls into question the use of MMR at a predetermined time point as a surrogate market for outcome of therapy for CML."[8]

The most important concern raised by Bidikian et al.'s analysis surrounds the use of MMR to justify treatment with second-generation TKIs (2G-TKIs) over imatinib. While 2G-TKIs lead to deeper and faster molecular responses than imatinib, they are associated with increased toxicities and costs—in fact, the cheapest 2G-TKI costs more than 30 times the price of generic imatinib. 2G-TKIs have been

widely endorsed by oncologists and formal guidelines. The latest National Comprehensive Cancer Network guidelines (NCCN version 1.2023) recommend 2G-TKIs as first-line therapy for high-risk chronic-phase CML. The 2020 European LeukemiaNet recommendations for CML state that a change in treatment can be accepted if MMR is not achieved by 36–48 months.

Notably, large phase III RCTs of 2G-TKIs have demonstrated no benefit in OS or quality of life of these agents over imatinib despite higher rates of MMR. The 10-year follow up of the ENESTnd study comparing imatinib and nilotinib reported increased rates of MMR in patients treated with nilotinib compared to imatinib (36.4% vs. 21.2%).[9] The median time to MMR was also improved with nilotinib. However, survival rates between the three treatment arms of the study were very similar: The 10-year OS was 87.6% in nilotinib 300 mg 2× daily, 90.3% in nilotinib 400 mg 2× daily, and 88.3% in imatinib 400 mg 2× daily. Nilotinib failed to improve survival over imatinib even in patients with high Sokal scores. Similar findings were observed at the 5-year follow-up of the DASISION trial on dasatinib versus imatinib: 5-year OS was 91% and 90% in the dasatinib and imatinib arms, respectively, even though rates of MMR were higher with dasatinib (76% vs. 64%).[10] Furthermore, according to Bidikian et al.'s retrospective analysis, frontline imatinib was not associated with a significant decrease in OS in patients without MMR.

Bidikian et al. noted that while achievement of MCyR or CCyR within the first 2 years of TKI therapy was associated with a higher OS, outcomes of those who achieved a minor or no cytogenetic response were not as catastrophic as suggested by other analyses: 10-year CML-related OS was 95% in those who achieved at least MCyR versus 80% in those who did not. Although cytogenetic responses have been considered the gold standard for monitoring therapy response, patients without CCyR may still have good outcomes. While CCyR is a more reliable surrogate outcome than MMR, the question of the optimal endpoint in CML still remains.

As the popularity of molecular monitoring in CML grows, an increasing body of evidence suggests that achieving treatment responses beyond MCyR does not guarantee additional clinical benefit. Moreover, failing to achieve this endpoint can no longer be used to imply dismal outcomes; rather, outcomes are still favorable in this group. Thus, the criteria used to guide therapeutic strategy in CML must be reassessed. It is time to abandon pursuing early molecular response benchmarks for the sake of increased treatment costs and toxicities for patients with no ultimate difference in outcomes. Patience—allowing the patient a little more time with imatinib when responses are slow—remains the prudent strategy for the practicing hematologist.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Bidikian A, Jabbour E, Issa GC, Short NJ, Sasaki K, Kantarjian H. Chronic myeloid leukemia without major molecular response after 2 years of treatment with tyrosine kinase inhibitor. *Am J Hematol*. 2023;94(4):639-644. doi:10.1002/ajh.26836
2. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003;349(15):1423-1432. doi:10.1056/NEJMoa030513
3. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. *JAMA Intern Med*. 2015;175(8):1389-1398. doi:10.1001/jamainternmed.2015.2829
4. Marin D, Milojkovic D, Olavarria E, et al. European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. *Blood*. 2008;112(12):4437-4444. doi:10.1182/blood-2008-06-162388
5. Kim D, Goh HG, Kim SH, et al. Comprehensive therapeutic outcomes of frontline imatinib mesylate in newly diagnosed chronic phase chronic myeloid leukemia patients in Korea: feasibility assessment of current ELN recommendation. *Int J Hematol*. 2012;96(1):47-57. doi:10.1007/s12185-012-1093-y
6. Oriana C, Martin H, Toby P, et al. Complete cytogenetic response and major molecular response as surrogate outcomes for overall survival in first-line treatment of chronic myelogenous leukemia: a case study for technology appraisal on the basis of surrogate outcomes evidence. *Value Health*. 2013;16(6):1081-1090. doi:10.1016/j.jval.2013.07.004
7. Kantarjian H, O'Brien S, Shan J, et al. Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia. *Cancer*. 2008;112(4):837-845. doi:10.1002/cncr.23238
8. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *JCO*. 2008;26(20):3358-3363. doi:10.1200/JCO.2007.15.8154
9. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021;35(2):440-453. doi:10.1038/s41375-020-01111-2
10. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the Dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol*. 2016;34(20):2333-2340. doi:10.1200/JCO.2015.64.8899

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