Olverembatinib in chronic myeloid leukemia: is less actually better?

Maria Agustina Perusini and Dennis Dong Hwan Kim

Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, and Department of Hematology, Faculty of Medicine, University of Toronto, Toronto, Canada

Correspondence: D.D.H. Kim
dr.dennis.kim@uhn.ca

Received: May 27, 2025.
Accepted: June 10, 2025.
Early view: June 19, 2025.

https://doi.org/10.3324/haematol.2025.288065

In this issue of *Haematologica*, Zhang *et al.* present a multicenter retrospective analysis entitled "*Optimizing olverembatinib dose in chronic phase chronic myeloid leukemia*", which evaluates different starting doses of olverembatinib in patients with chronic-phase chronic myeloid leukemia (CML) in whom prior tyrosine kinase inhibitor (TKI) therapy had failed. The study compares two dosing strategies: 30 mg every other day (QOD) *versus* 40 mg QOD.[1] Olverembatinib, a third-generation BCR-ABL1 inhibitor with potent activity against the T315I mutation and compound mutations, has been approved in China at a 40 mg QOD schedule based on earlier phase I/II data.[2] However, the real-world evidence presented by Zhang *et al.* invites critical reflection, suggesting that an approach starting with a lower dose might achieve similar efficacy with improved tolerability, ultimately refining dosing paradigms in CML management.

The study enrolled 282 patients across 36 Chinese centers, pooling data from clinical trials and routine clinical practice. Baseline characteristics were largely balanced, aside from a slightly higher proportion of prior TKI responders in the 30 mg QOD group. Propensity score matching was employed and mitigated this imbalance, strengthening the robustness of the comparative analyses. Nevertheless, inherent limitations of the retrospective design of the analysis, such as unmeasured confounding and selection biases, must be kept in mind when interpreting the findings.

The primary outcomes are provocative: cytogenetic, molecular, and survival endpoints were comparable between the two dosing groups. Crucially, patients starting at 30 mg QOD experienced significantly fewer dose reductions or treatment discontinuations due to adverse events (18% *vs*. 38%, *P*=0.003), and a higher proportion of the patients maintained their initial dose through follow-up (67% *vs*. 47%, *P*=0.009). Notably, despite fewer dose modifications, the overall adverse event rates remained similar in the two groups, suggesting that a lower dose mitigates toxicity without compromising disease control. Table 1 provides a summary of the key outcomes.

These findings challenge the prevailing notion that "more drug equals better outcomes" in CML treatment and align with broader regulatory shifts, including the U.S. Food and Drug Administration's increasing emphasis on optimizing the minimum effective dose to enhance long-term safety.[3] They support a prevailing concept of a biologically optimal dose in CML practice.[4,5] In CML, for which therapy often spans decades, striking the right balance between efficacy and tolerability is paramount. The real-world dataset presented by Zhang *et al.* underscores the importance of questioning fixed-dose assumptions that have historically guided TKI therapy.

The analogy with the OPTIC trial for ponatinib is instructive. OPTIC implemented a response-adapted dosing strategy, initiating therapy at 45 mg daily and reducing it to 15 mg upon achieving *BCR::ABL1*^{IS} ≤1%.[6] This approach preserved efficacy while significantly reducing vascular toxicity – a paradigm shift in TKI management. Whether a similar response-adapted strategy could be safely applied to olverembatinib remains an open question, particularly given the uncertainty surrounding the reversibility of its adverse events.

The pharmacokinetic data reported by Zhang *et al.* bolster the biological plausibility of lower dosing of olverembatinib. Patients in the 30 mg QOD cohort had lower plasma concentrations (before dose [C_0] and 6 hours after dosing [C_6]), yet these remained within the presumed therapeutic window. However, extrapolating from pharmacokinetic parameters to long-term outcomes demands caution. Chronic CML therapy introduces complex variables – adherence patterns, shifts in pharmacodynamics over time, clonal evolution – that pharmacokinetic snapshots cannot fully predict. Longer follow-up is essential to ascertain the durability of responses and the potential emergence of late toxicities at lower exposure levels.

Clinical experience already underscores the importance of

Table 1. Comparative summary of clinical outcomes for olverembatinib 30 mg QOD *versus* 40 mg QOD in the propensity score matched population.

Outcomes	30 mg QOD	40 mg QOD	*P*	Favors
Molecular response at 12 months, % of patients				
MMR	36	42	0.49	Equal
MR4	22	25	0.28	
Cytogenetic response at 12 months, % of patients				
MCyR	67	69	0.89	Equal
CCyR	56	61	0.80	
Overall survival at 12 months, % of patients	95	92	0.60	Equal
Dose reduction/discontinuation due to TRAE, % of patients	18	38	0.003	30 mg QOD
Maintained initial dose, % of patients	67	47	0.009	30 mg QOD

QOD: every other day; MMR: major molecular response; MR4: four-log reduction in molecular *BCR:ABL1*; MCyR: major cytogenetic response; CCyR: complete cytogenetic response; TRAE: treatment-related adverse events.

flexible TKI dosing.[7] Dose modifications are common across frontline and later-line settings, whether with dasatinib, bosutinib, or ponatinib, often balancing toxicity management with disease control.[8-10] In this light, starting olverembatinib at a lower dose with the flexibility to escalate based on suboptimal response is both logical and consistent with real-world practice patterns.

Yet, important limitations temper the generalizability of the findings. The cohort was relatively young and ethnically homogeneous, and the retrospective design inherently carries the risk of residual confounding despite statistical adjustments. Moreover, the median follow-up of approximately 25-28 months may not fully capture late-emerging adverse events or resistance patterns, especially in a disease in which therapeutic horizons are measured in years. Prospective, randomized trials are needed to definitively validate adaptive dosing approaches with olverembatinib. Encouragingly, forthcoming studies aiming to start at 30 mg QOD with escalation for non-responders are already in planning, and their outcomes will be critical to informing clinical guidelines.

Ultimately, Zhang *et al.* contribute to an evolving conversation: that in the management of CML, precision and individualization – rather than intensity – may yield better long-term outcomes. Their study adds to the growing evidence that fixed-dose, maximum-tolerated strategies may be suboptimal in a chronic disease in which maintaining patients' quality of life and adherence is as important as achieving deep molecular responses.

In conclusion, the data presented by Zhang *et al.* suggest that a 30 mg QOD starting dose of olverembatinib may offer comparable efficacy to the approved 40 mg QOD schedule. Whether these findings will catalyze a shift in clinical practice remains to be seen, but the foundation for a more nuanced, patient-centered approach to olverembatinib dosing is firmly laid.

Disclosures

MAP has no conflicts of interest to disclose. DDHK has received honoraria from Novartis and Ascentage, and has received research grants from Novartis, Ascentage and Enliven.

Contributions

MAP and DDHK contributed equally to the work.

References

1. Zhang X, Yang Y, Liu B, et al. Optimizing olverembatinib dose in chronic phase chronic myeloid leukemia. Haematologica. 2025;110(12):2986-2996.
2. Jiang Q, Li Z, Qin Y, et al. Olverembatinib (HQP1351), a well-tolerated and effective tyrosine kinase inhibitor for patients with T315I-mutated chronic myeloid leukemia: results of an open-label, multicenter phase 1/2 trial. J Hematol Oncol. 2022;15(1):113.
3. U.S. Food and Drug Administration. Dose Optimization Guidance. 2023.
4. Copland M. Is there a role for dose modification of TKI therapy in CML? Curr Hematol Malig Rep. 2019;14(4):337-345.
5. Fassoni AC, Baldow C, Roeder I, Glauche I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. Haematologica. 2018;103(11):1825-1834.
6. Jabbour E, Apperley J, Cortes J, et al. Correction: dose modification dynamics of ponatinib in patients with chronic-

phase chronic myeloid leukemia (CP-CML) from the PACE and OPTIC trials. Leukemia. 2024;38(10):2291.
7. Senapati J, Sasaki K, Issa GC, et al. Management of chronic myeloid leukemia in 2023 - common ground and common sense. Blood Cancer J. 2023;13(1):58.
8. Hughes TP, Clementino NCD, Fominykh M, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. Leukemia. 2021;35(6):1631-1642.
9. Jabbour E, Sasaki K, Haddad FG, et al. Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: a propensity score analysis. Am J Hematol. 2022;97(11):1413-1418.
10. Kota V, Brummendorf TH, Gambacorti-Passerini C, et al. Efficacy and safety following bosutinib dose reduction in patients with Philadelphia chromosome□positive leukemias. Leuk Res. 2021;111:106690.