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Comment on 'Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: a prospective multicenter study' by Dr Steffie L. Groenland et al.

We congratulate Steffie L. Groenland et al.[1] on their recent publication; this is a milestone in the personalization of oncology drug therapy. The well-documented study allows us to consider several aspects for the further development of the method.

With the help of pharmacokinetic (PK) measurements, they adjusted the dosing of oral targeted therapies in a prospective multicenter study. Compared with historical data, the primary outcome was to halve the proportion of underexposed patients. Although the trial did not reach its primary endpoint, in patients where the interventions were applied, it was successful in 74.3% of cases, suggesting that this therapeutic drug monitoring (TDM)-based method is feasible.

Some points may facilitate the development of the method. First, Groenland et al.[1] observed quite a significant intra-patient variability in PK values that were also observed previously.[2] Despite the pharmacokinetically guided intervention, they measured PK values under the predefined limit (lower exposure) in about a quarter of patients at each measurement point, which stayed constant throughout the study. However, ∼35% of patients switched between the low- and high-exposure groups at each measurement point without any intervention. This observation underlines the importance of regular PK control for oral targeted therapies, as they stated, throughout the treatment period. However, it is also crucial to focus study design in the future on exploring the causes of intra-patient variability, including, but not limited to, adverse effects, drug—drug interactions, and food.[3]

Second, it is a prospective feasibility study without a control arm. We need to determine the advantage of the TDM method over general practice. The success of the TDM method differs in the cases of investigated drugs. Moreover, four cohorts were closed for various reasons, such as enzalutamide PK values were appropriate in almost all patients or side-effects exceeded the TDM application with sorafenib. In the present study, the determination of overdosing and the need for dose reduction were judged by the presence or lack of side-effects. It was assumed that C_{min} and C_{max} are indicative of reaching adequate and toxicity-related drug levels, respectively.[4] The early detection of high C_{max} may give the possibility to actively prevent serious side-effects (active and preventive side-effect management) and consequent treatment interruption or discontinuation.[5] To answer these questions, we need randomized trials comparing TDM-based and tolerance-based dosing. Furthermore, we will need to determine specific patient cohorts and drugs most suitable for TDM-based dosing.

Third, Groenland et al.[1] emphasized the importance of simplifying the method and making it suitable for general practice. For this purpose, random blood sampling was adopted, and C_{min} values were obtained by extrapolation and estimation. Further considerations should be given as to whether the adherence of predose sampling would mitigate intrapatient variability of PK values in future investigations.

We sincerely congratulate our Dutch Pharmacology Oncology Group colleagues for this crucial trial. We hope that it allows for TDM-based dosing in oncology and will facilitate investigations in this field.

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DISCLOSURE

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