COMMENTARY

Therapeutic Drug Monitoring of Oral Oncology Drugs: Another Example of Maslow's Hammer

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While therapeutic drug monitoring is a potentially attractive strategy that can be utilized by clinical pharmacologists to optimize drug dosing, the costs and risks must be balanced against the potential benefits. However, there is great uncertainty regarding the optimal population dose for most oncology drugs, given the lack of randomized dose-ranging phase II trials. Therefore, efforts to individualize dosing are for the most part premature for such agents.

Therapeutic drug monitoring (TDM) is one of the various strategies available for individualizing drug dosing, which is potentially useful in the context of narrow therapeutic drugs for which there is a well-defined range of therapeutic concentrations. In the United States, such assays are regulated by the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) as an in vitro diagnostic device, as well as by the Centers for Medicare and Medicaid Services (CMS) for reimbursement using the Current Procedural Terminology codes for therapeutic drug assays. With that said, neither FDA nor CMS approval are necessary to utilize TDM for dosing of any drug.

However, like many potential diagnostic tests, the big question is whether TDM of oral oncology drugs is useful or harmful. For many older drugs, there is a well-defined therapeutic index and TDM is part of the standard of care. In oncology, there has been minimal use of TDM for cytotoxic chemotherapy, as these agents are generally administered intermittently, and toxicity has been used to guide dosing—based on the presumption that the maximally tolerated dose is the optimal dose. Over the last 20 years, there has been increasing use of non-cytotoxic drugs for the treatment of cancer, many of which have putative-specific molecular targets and are administered chronically like drugs for other chronic diseases. In this context, Geraud *et al*. have now proposed a quantitative scoring system to best identify those newer agents for which TDM is potentially useful.[1]

These molecularly targeted drugs include both tyrosine kinase inhibitors (TKIs), as well as other small molecules that reversibly inhibit or covalently bind to specific targets. For some agents, the target is a mutant protein absent in normal tissue, analogous to the development of antimicrobial drugs targeting nonhuman proteins. In this context, the optimal dose will often be well below the maximally tolerated dose.[2] In fact, this presumption led to the creation of Project Optimus by the FDA Oncology Center of Excellence, as well as a draft Guidance regarding the optimization of oncology drug dosing prior to approval. One impetus for this initiative has been the observation that many oral oncology drugs have been approved at excessive doses (often developed based on the mistaken belief that "more is better"), resulting in unnecessary toxicities (and costs).[3]

So, for those drugs that are labeled at excessive doses, how can TDM be superior to simply prescribing a lower dose to all patients? A second question is "How can one individualize dosing when the optimal population dose has not been established?" I think the answer to both these rhetorical questions is that it cannot. Thus, I believe that the promotion of TDM for oral oncology drugs is premature and not supported by the current evidence.

Geraud *et al*.[1] have proposed four criteria for optimal TDM candidates: (i) high interpatient pharmacokinetic variability, (ii) feasible dose-adaptation strategy, (iii) established exposure-response relationship, and (iv) established exposure-safety relationship. They also acknowledged the importance of intrapatient variability but were not able to evaluate this key criterion because of the lack of available data for most oral oncology TKIs. And while they acknowledged that one of the general criteria for TDM is the "absence of an easily measurable clinical or biological marker for drug effect," it is not clear that this was further considered. Using only the four criteria described above, they evaluated 67 FDA-approved oral drugs and

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identified five drugs they considered most appropriate for TDM: sunitinib, sorafenib, cabozantinib, nilotinib, and abemaciclib. The references used to address the four criteria for all drugs are included in the publication's supplemental materials.

I was particularly surprised to see sorafenib, a first-generation multitargeted tyrosine kinase inhibitor, as the second highest-ranking drug. We previously performed several clinical pharmacology studies of sorafenib's pharmacodynamics, aiming to increase its antiangiogenic effects believed to be mediated through its inhibition of the vascular endothelial growth factor receptor (VEGFR2). We evaluated a downstream biomarker of VEGFR2 inhibition and increase in blood pressure, and concluded that there was no apparent exposure-response relationship.[4]

Geraud *et al.*[1] cite only two publications regarding sorafenib, as well as the FDA review. While the latter confirmed an expected dose-toxicity relationship, it does not report any exposure-response analyses. While the authors of the two cited publications of small series of hepatocellular cancer (HCC) patients found relationships between clinical outcomes and total sorafenib exposure, a publication of a larger series (not cited by Geraud *et al.*) refuted these findings.[5]

Another concern is reliance on exposure-response analyses on data sets of patients treated at a single dose. Such analyses can be highly flawed due to confounding of drug clearance and measures of efficacy. This is most obvious in the context of monoclonal antibodies, if the efficacy end point is survival, as antibody clearance is highly correlated with markers of short survival, such as low serum albumin.[6] Thus, cancer patients with low albumin administered any monoclonal antibody drug will have high clearance, low exposure, and short survival, regardless of the pharmacological effects of the monoclonal antibody.

There are similar potential confounders for many small molecule drugs, such as highly protein-bound TKIs, most of the drugs evaluated by Geraud *et al.*[1] As with monoclonal antibodies, there may be a confounding relationship between low serum albumin and high total drug clearance. This would be expected for those drugs which have very high albumin binding, which includes many TKIs. Patients with significant liver disease often have decreased free drug clearance and decreased protein binding but may not have an increase in total (free plus bound) exposure. Thus, exposure-response relationships without adjustment for potential variability in protein binding may yield false-positive associations. In this context, TDM could actually be dangerous, since some patients would be exposed to excessive free drug concentrations if the dose were increased above the labeled dose based on such spurious analyses.

Even if a drug were to satisfactorily meet all four criteria proposed by Geraud *et al.*, it is dangerous to consider TDM without knowledge of intraindividual pharmacokinetic variability. If the intraindividual variability is high, then dose adjustment based on plasma drug concentrations is unlikely to result in the desired concentration, and in fact could result in life-threatening or fatal toxicity, for those analyzed samples that randomly are at the low end of a patient's typical range. TKIs are of particular concern, given that their inherent amphipathic chemical structure often results in poor oral and highly variable bioavailability.[7] This often results in large food effects that are not ameliorated by administering the drug under modified fasting conditions.

Notably, the five top-ranking drugs recommended for TDM by Geraud *et al.* are all TKIs. Nilotinib is of particular concern, given that it has high intraindividual variability due to a large positive food effect, is labeled to be taken twice daily under modified fasting conditions, and has a clear exposure-safety relationship (with QT prolongation)—resulting in a Black Box warning.[8] (To the best of my knowledge, this is the only FDA-approved agent that includes a Black Box warning regarding coadministration with food.) Geraud *et al.* referenced two publications and the FDA review, with the latter resulting in the Black Box warning. While one of the two publications did indeed suggest an exposure-response relationship[9] (when administered as second-line therapy), the other publication concluded that there was no exposure-response relationship (when administered as first-line therapy[10]). Given the lack of a compelling exposure–response relationship for this highly protein-bound drug with high intraindividual variability, the use of TDM is far more likely to increase the risk of serious adverse events due to QT prolongation (including potentially fatal cardiac arrhythmias) than to substantially improve efficacy.

The potential role of TDM in oncology must be considered in the context of how oncology drug prescribing differs from other therapeutic areas. While off-target toxicities are clearly undesirable, the presence of mild-to-moderate mechanism-related toxicities is not only expected, but desirable (*e.g.*, skin rash from an epidermal growth factor receptor inhibitor, blood pressure increase from an angiogenesis inhibitor). Thus, these simple clinical biomarkers are often used to guide dosing in clinical practice, particularly for the purpose of avoiding serious toxicities. In this context, three of the top five drugs prioritized by Geraud *et al.* meet these criteria: sunitinib, cabozantinib, and abemaciclib. While based on the exposure-response relationships, it is theoretically desirable to maximize dosing, in practice, dosing of these agents is limited by mechanism-related toxicities, not by off-target toxicities. Therefore, it would be difficult to establish the incremental benefit of incorporating TDM into clinical practice for such drugs.

While there are sufficient data to support TDM for imatinib, there is substantially less evidence to support the use—or even clinical investigation—of TDM for other TKIs. The critical first step is to determine intraindividual variability of any drug of interest, as well as the implications of variability in protein binding. Furthermore, exposure-response analyses based on small series of patients treated at a single institution should not be used as the basis for concluding the presence of a reliable exposure–response relationship. While Geraud *et al.*, as well as many readers of this journal, have extensive experience with TDM and an interest in applying their expertise to oral anticancer therapy, TDM appears to be another example of Maslow's hammer, since few TKIs are nails.

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