On precision dosing of oral small molecule drugs in oncology

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April 28, 2020

Abstract

Personalization of oral small molecule anticancer drug doses based on individual patient blood drug levels, also known as therapeutic drug monitoring or TDM, has the potential to significantly improve the effectiveness of treatment by maximizing drug efficacy and minimize toxicity. However, this option has not yet been widely embraced by the oncology community. Some reasons for this include increased logistical complexity of dose individualization, the lack of clinical laboratories that measure small molecule drug concentrations in support of patient care, and the lack of reimbursement of costs. However, the main obstacle may be the lack of studies clearly demonstrating that monitoring of oral small molecule anticancer drug levels actually improves clinical outcomes. Without unequivocal evidence in support of TDM-guided dose individualization, especially demonstration of improved survival with TDM in randomized controlled trials, wide acceptance of this approach by oncologists and reimbursement by insurance companies is unlikely, and patients may continue to suffer as a result of receiving incorrect drug doses. This article reviews the current status of therapeutic drug monitoring of oral small molecule drugs in oncology and intends to provide strategic insights into the design of studies for evaluating the utility of TDM in this clinical context.

Introduction

Precision oncology approaches have enabled matching of the best available anticancer drug to each individual patient's particular tumor type. Nevertheless, treatment even with such targeted agents is often short-lived or unsuccessful. One factor that may significantly contribute to failure of treatment, despite successful selection of the correct drug, is the failure to select the correct drug dose.

Oral small molecule anticancer drugs are typically prescribed at fixed drug doses regardless of patient weight, age, or gender. Differences in bioavailability, metabolism, and adherence further increase pharmacokinetic (PK) variability from patient to patient. This means that, despite being prescribed the same dose of the drug, individual patients may have significant differences in the resultant blood drug levels (*i.e.* drug exposure), with some being under-dosed and others over-dosed.

One efficient way to optimize drug dosing is through therapeutic drug monitoring (TDM) of patient blood drug levels. TDM is most effective for the subset of drugs for which the inter-patient variation in systemic drug exposure (*e.g.* blood drug levels) is high relative to the therapeutic index (concentration range of adequate efficacy and minimal toxicity), and for which the exposure is strongly correlated with clinical response. For such drugs, a flat-fixed dose will be optimal for only a fraction of patients. Numerous oral small molecule anticancer drugs that are already in clinical use have been shown to exhibit such high inter-patient PK variabilities and strong pharmacokinetics-pharmacodynamics (PK-PD) relationships, and seem to be strong candidates for benefiting from TDM as described in several excellent reviews on this subject.[1–5]

Candidate drugs for TDM can be actively identified throughout various phases of drug development, which includes the post-marketing phase. For newly approved drugs and those in clinical development, critical

analysis of PK and PD data may provide clues to potential benefits of dose individualization. PK and PD data is typically available for every anticancer drug on the market or in late phases of clinical development, but the type of analysis of this data for the purpose of further drug development differs widely from company to company. Regulatory authorities usually only require non-compartmental analysis of PK data, and the relationships with therapeutic and adverse drug effects are often explored only with correlative analysis. Alternatively, PK and PKPD modeling and simulation can provide additional insights into the often complex relationship between dose and effects and, in fact, there are several efforts from the regulatory authorities to encourage the use of modeling and simulation in drug development.[6,7]Consequently, the results from such additional analyses can be quite useful for selection of optimal dose regimens for further clinical studies, identification of candidates for TDM and, ultimately, for patient care.

Drug dosing regimens are typically established during early phase trials involving a small number of participants, with dosing decisions based on population level data rather than individual level data. Late phase trials often do not even include a PK component, which in the context of establishing dosing for optimal drug exposure may be a missed opportunity. Compared to early phase trials, phase 3 studies are usually much larger and longer (involving hundreds to thousands of participants over months to years), and are therefore better suited for accurate characterization of inter- and intra-patient PK variability as well as for determination of the relationships between systemic exposure, relevant clinical outcome parameters, and side effects. The PK and PD results that could be obtained in such studies (*e.g.* PK variability and exposure-efficacy/toxicity relationships) would inform the need for optimization and perhaps individualization of drug dosing for subsequent studies and for patient care.

This article discusses some important considerations for evaluating the utility of TDM for new oral anticancer drugs during clinical trials as well as during patient care. Similar to other types of clinical interventions, studies evaluating TDM of oral small molecule oncology drugs are likely to progress through several stages of increasing complexity, with additional levels of evidence in support of the intervention being gathered at each stage. To help conceptualize this progression as it relates to TDM of oral small molecule oncology drugs, we have subjectively categorized it into four stages (Figure 1) that are detailed in the following sections. We first focus on measuring systemic drug exposure to assess inter- and intra-patient PK variability, followed by correlating drug exposure to efficacy and toxicity, then evaluating whether TDM can effectively optimize drug exposure, and finally testing whether the implementation of TDM-guided precision dosing, *i.e.* adjusting an individual's drug dose based on measured blood drug concentrations, might improve clinical outcomes indeed.

Assessing Variability in Systemic Drug Exposure

Some drugs (*e.g.* intravenously administered medications with well-known pharmacokinetics) have relatively consistent and predictable dose-exposure relationships. The blood levels of such drugs can be estimated reasonably well and measuring them may not provide additional valuable information. Here, TDM is of limited relevance, except perhaps for cases of medication non-compliance or failure of organs involved in drug metabolism and excretion. For many orally administered medications, on the other hand, numerous additional variables such as bioavailability and first-pass metabolism widen the range of possible blood level concentrations and make predicting systemic drug exposure from the dose much more difficult. Thus, the earliest evidence in support of TDM for a new oral anticancer drug would be derived from observation of a large range of not otherwise predictable blood drug levels between patients on the same treatment regimen (Figure 1, Stage 1).

There are several ways of measuring the systemic exposure to a drug. Examples include comprehensive sampling of numerous time points to determine area under the concentration (AUC) time curves as well as parsimonious or limited sampling strategies such as trough (C_{min}) levels, peak levels, or a combination thereof. For routine monitoring of oral drugs that are taken once or twice daily in an outpatient setting, measuring the drug concentration in a single sample collected prior to the next dose (*i.e.* trough level

monitoring) is often the only practical option. Even during phase 2 and phase 3 trials, blood sampling is restricted and, if possible, sparse sampling strategies (*e.g.* trough concentrations) should be used to study PK and PK/PD. We will therefore only focus on trough level monitoring.

The relationship between a trough level and the systemic exposure, as determined by area under the concentration (AUC) time curves, can often be obtained from phase 1 and phase 2 clinical studies.[8–10] Although most early-phase trials collect the data to derive this correlation, it may not be explicitly reported. Using phase 1 and 2 study data, one can get a reasonable idea if trough level monitoring could be used as a proxy for the more comprehensive AUC analysis. It is important to keep in mind that a clinical drug development PK study is usually much more controlled in terms of drug intake and sample collection than routine patient care and that parameters obtained in such studies may not translate to real world patients. Therefore, there may be added value from assessing the relationship between trough levels and AUC in a patient care setting. Factors that may confound the relationship between $C_{min}$and AUC include PK drug-drug interactions, alterations in PK as a result of (auto-)induction, and inhibition of metabolizing enzymes and transporters, as well as inaccuracies in determining the triad of time of drug intake, time of sample collection, and half-life of a drug. All components of this triad are relevant for an accurate assessment of the systemic exposure and all may differ from patient to patient.[11] Nevertheless, it is intriguing that less-than-perfect correlation between trough levels and systemic exposure can still be useful for assessing systemic exposure. Indeed, even for some of the most monitored drugs that utilize trough levels, such as cyclosporine and tacrolimus, the correlation coefficient between trough levels and systemic exposure is in the 0.7-0.8 range.[12,13]

For effective TDM, in addition to being able to measure systemic exposure (*e.g.* trough levels), one must also be able to predict how changes in dosing will change the drug exposure. Consequently, the dose-exposure relationships must be well-characterized. To this end, serial sampling of drug exposure in the same individual over time provides crucial information and should be incorporated into precision dosing studies whenever possible.[14] First, it enables evaluation of intra-individual exposure variability over time. This helps estimate how well the systemic exposure can be predicted from dose alterations. Second, it improves estimation of the total systemic exposure over the course of treatment. Finally, it allows for determination of additional parameters, such as the maximum or minimum blood drug concentrations, which may also be relevant for predicting drug efficacy, resistance, and toxicity.

The inter- and intra-individual PK variability and the strength of correlation between trough levels and AUC are important considerations for calculation of sample sizes in clinical studies. These parameters should guide not only the number of study participants but also the number of samples per individual as well as the sampling frequency.

Correlating Drug Exposure with Drug Efficacy and Toxicity

Once it is established that the blood levels of a novel oral anticancer drug vary significantly from one patient to another and cannot be practically estimated by means other than direct measurement, the relationship between systemic drug exposure and drug efficacy and drug toxicity should be investigated (Figure 1, Stage 2). Such studies can provide evidence in favor of TDM and define the target (therapeutic) exposure range by demonstrating increased treatment failures at sub-therapeutic exposures and increased toxicity at supra-therapeutic exposures. After all, if low drug levels cannot predict treatment failure and high drug levels cannot predict adverse drug effects, TDM will be of limited value.

Measuring Efficacy

A drug's effect can be measured in various ways. In oncology, efficacy endpoints such as response rates, progression free survival, or overall survival are typically used.[15] These endpoints are commonly derived from histologic and/or radiologic tumor evaluations, but other assessments such as circulating tumor cells, circulating cell-free tumor DNA, microRNA, or protein markers can also be used. In addition, pharmacodynamics

markers (*e.g.* measurable molecules corresponding to drug target inhibition or downstream pathway activity) may be available for some drugs, which may enable close to real-time PD monitoring.[16] Thus, for studying the relationship between drug levels and effect, one or more efficacy endpoints, alone or in combination with PD biomarkers, can be used.[1–3]Measures of drug effect can be represented by dichotomous variables, such as frequency of occurrence, or by continuous variables such as concentrations of tumor markers.

To help decrease methodological heterogeneity in measuring drug response, an international multidisciplinary working group developed RECIST (Response Evaluation Criteria in Solid Tumours) criteria for the evaluation of tumor burden. [17] These criteria describe standardized approaches of solid tumor size measurement, primarily using imaging techniques, and define the outcomes of complete response (CR), partial response (CR), stable disease (SD), and progressive disease (PD). [17]

The duration of time it takes to achieve the chosen efficacy endpoints is also important for study design. The lag in time between when drug exposure is initially assessed and when clinical response can be detected is typically on the order of weeks to months or even years. On these timescales, the initial exposure assessment may no longer accurately represent the total drug exposure over the course of treatment. Thus, in studies with long treatment duration, serial exposure assessments over time may be particularly useful for capturing the overall drug exposure more accurately.

The pre-treatment dynamics of outcome measures is also important to consider. For example, high heterogeneity in the pre-treatment rates of tumor growth and trajectories of biomarker levels between individuals in a study population is likely to result in high inter-individual variability in these measures during treatment. Consequently, the statistical power of the study suffers, requiring increased numbers of participants. As a further example, a small decrease in the rate of tumor growth after treatment initiation may be interpreted as disease progression in a patient with a fast-growing tumor and as stable disease in a patient with a slow-growing tumor. This suggests that several pre-treatment assessments of the patient's baseline tumor size or biomarker levels, as well as the use of a control group, may help more accurately characterize the effect of the drug.

Measuring Toxicity

The side effects that occur during treatment can be a consequence a drug's effect, related to a drug's unwanted but expected off-target effect, or they can be idiopathic. Depending on the mechanism, side effects can manifest relatively quickly, within hours or days, or can take months to develop. Similar to the assessment of drug efficacy discussed above, the prevalence and timing of drug toxicity will impact the study design with respect to the number of participants required, the frequency of toxicity assessments, and the duration of toxicity monitoring.

Drug-related toxicity often correlates with drug dose and typically subsides following dose decrease or interruption. However, the occurrence of adverse drug events may also seem stochastic and they may appear and disappear without temporally related dose adjustments. In this context, variations in drug exposure (at the same prescribed dose) may correlate with toxicity. Thus, serial exposure assessments over time may be particularly helpful for relating fluctuations in drug trough levels to toxicity symptoms, especially in individuals concurrently treated with other drugs prone to interactions or toxicities of their own.

The approach to capturing and quantifying adverse drug effect data must also be considered. Self-administered patient questionnaires (patient reported outcomes or PROs) may be used to supplement clinical assessments.[18] Toxicity may be represented as dichotomous (either present or not), categorical (based on severity) or even continuous (*e.g.* elevation in blood pressure) variables. In addition, the National Cancer Institute (NCI) provides Common Terminology Criteria for Adverse Events (CTCAE) to help standardize the description and grading of adverse events.[19,20]

Of note, drug toxicity itself can sometimes be used to guide dose optimization. Such "dosing to toxicity" strategies have long been used for chemotherapy but may also have a role in dosing of oral targeted small

molecule drugs.[16] A relevant review on the susceptibility to adverse drug reactions was recently published in this journal.[21] The described susceptibility factors included the type of immunological reaction, genetics, age, sex, physiological changes (such as pregnancy), exogenous factors (such as interacting drugs), and diseases. Notably, the authors highlight that there may be significant inter-patient variability in the dose-response curves not only for drug benefits but also for harm, providing an illustration of how some (hypersusceptible) patients may experience toxicity at drug concentrations insufficient for efficacy.[21] Importantly, this is one context in which TDM has a clear advantage: using a dosing to toxicity approach for hypersusceptible patients results in continued treatment with drug doses that are ineffective, while TDM informs a change in therapy.

Standardization of Assays and Methods

For the vast majority of new drugs there are no FDA-approved quantitative assays. Instead, new drugs are typically quantified by assays developed in individual laboratories, known as laboratory developed tests (LDTs). The required levels of quality assurance for these tests vary widely, in part depending on the laboratory's local and other regulations (*e.g.* CLIA, GLP). In addition, LDTs developed in different labs may employ distinct methodologies (*e.g.*immunoassays, liquid chromatography-tandem mass spectrometry, etc.). Taken together, this can lead to significant inter-laboratory and sometimes even intra-laboratory differences in results. External proficiency testing programs can help minimize such differences but, more often than not, such programs do not exist for new drugs. Therefore, it is important to be aware that lab-to-lab differences in the measurement of drug levels may be a significant contributor of noise in TDM studies. Utilizing the same laboratory with a thoroughly validated method for all drug level measurements for a precision dosing study may be a worthwhile consideration.

The same holds true for methods and approaches for quantifying drug effects. The challenges associated with bioanalytical measurements of pharmacodynamics biomarkers are analogous to those for drug assays. Similarly, there may be significant inter-institution and even intra-institution variability in imaging or anatomical techniques used for tumor assessments. Again, this variability may be a considerable source of noise in TDM studies.

In order to improve experimental reproducibility as well as applicability and translatability of results, attempts should be made to standardize the assays and methods. As mentioned above, RECIST criteria can help standardize solid tumor size measurements and NCI's CTCAE can help standardize assessments of drug toxicity.[17,19]Similarly, guidance from the NCI also exists for the development and incorporation of biomarkers studies in drug trials.[22]The standardization of assays for oral small molecules for cancer is lagging, although some proficiency testing programs have recently become available.[23]

Study Design Considerations for Exposure-Response Relationships

In contrast to biomarker studies, which can obtain useful data through retrospective analysis of repository samples collected during routine patient care, TDM studies aiming to investigate the correlation of drug levels with effects and toxicity will likely require prospective collection of samples. This is because the relative timing of drug intake and blood sampling is critically important to interpreting the obtained drug level results. In samples without associated data on timing of last drug intake (most repository samples), the drug levels may represent trough, peak, or intermediate time points. In addition, exposure-response relationship studies are typically observational (no dose adjustment based on results) rather than interventional, because dose adjustment after blood level measurement but before response measurement would confound interpretation of results. A large number of examples of such studies for oral small molecule anticancer drugs have been summarized in numerous reviews.[1–5]

Although the necessity to conduct such studies prospectively presents certain challenges (*e.g.* obtaining preliminary data for a grant proposal and long accrual times), prospective studies tend to be less prone

to certain types of biases such as recall bias and non-recorded confounders. Other types of bias, such as selection bias, can still occur in prospective studies.[24,25]

As discussed above, numerous choices are available with respect to the frequency and duration of exposure sampling as well as the timing, prevalence, and quantification of clinical endpoints and toxicity. Consequently, study design and power calculations should take into account the temporal relationships between drug levels and efficacy and toxicity as well as the anticipated frequency of measured outcomes and adverse events. Although there are numerous resources to guide power calculations for PK studies, the literature on power calculations for TDM studies seems to be lacking.[26,27]

Data from the exposure-response relationship studies can be described using various forms of regression analysis or more simply by comparing the outcomes of patients stratified by, for example, C_{min} quartiles or deciles.[25,28–30]Ultimately, the goal of such studies is to define a therapeutic exposure range below which there is increased risk of lack of efficacy and above which there is increased risk of toxicity.[1–5]

It should be mentioned that *in vitro* and pre-clinical*in-vivo* experiments may also demonstrate concentration-effect relationships and can be used to supplement the results obtained in clinical studies. [4,5] For solid tumors, blood level measurements may be complemented by *in vivo* studies that also measure drug concentrations in tumor tissue.[31]

Evaluating the Feasibility of TDM

Once drug exposure-response studies successfully define a target therapeutic concentration range or efficacy cutoff, prospective dose-adjustment trials intended to demonstrate that TDM can be implemented should be initiated (Figure 1, Stage 3). The primary outcome of this type of study is the proportion of patients starting the treatment under- or over-exposed who successfully achieve therapeutic blood drug levels following recommendations for dose adjustments.[1–5,32–35] Such TDM feasibility studies may compare the prevalence of therapeutic exposure before and after dose adjustment recommendation in the same group of subjects or, preferably, with a separate control arm.

The data on feasibility of dose individualization generated by such studies is crucial, as it can identify a number of reasons why a dose adjustment recommendation is not actually carried out. A substantial number of physicians will not follow the dosing advice.[24] For example, doctors may be hesitant to increase the dose beyond the highest FDA-approved dose or the maximum tolerated dose established in clinical trials. On the other hand, most oncologists would be rightfully reluctant to reduce the dose in the absence of observable toxicity. Lack of reimbursement for increased doses of these often very expensive drugs may also stifle dose optimization. Finally, medication compliance issues may further reduce feasibility of optimizing drug exposure through dose individualization.

As mentioned above, numerous examples of such studies evaluating feasibility of TDM for oral small molecule anticancer drugs are available and many of them indeed succeed in increasing the proportion of patients with drug levels in the therapeutic range.[1–5,32–35] An example that deserves special mention is the recently described study of the Dutch Pharmacology Oncology Group (DPOG).[33] The primary objective of this ongoing prospective multi-center trial involving 600 patients is to halve the proportion of patients with a drug exposure below the TDM target after 2 potential PK-guided interventions which, for most of the 23 oral anticancer drugs that are being monitored, will be after 12 weeks of treatment. The secondary objectives are to examine tolerability and outcome parameters such as objective response rate, time to progression, progression free survival, etc.

Testing Whether Precision Dosing Improves Clinical Outcomes

TDM feasibility trials can demonstrate that TDM-guided dose individualization is effective in optimizing drug exposure, but they are not designed to prove that TDM actually improves treatment outcomes. Nevertheless, these studies are essential for test-driving dose-adjustment protocols, workflows, and infrastructure, as well as for identifying unforeseen barriers to execution of dose-adjustment recommendations. Consequently, the parameters derived from TDM feasibility trials are critical for informing the design and implementation of subsequent randomized controlled trials (RCTs) for testing whether dose individualization improves treatment outcomes (Figure 1, Stage 4). Based on TDM feasibility trial data, much consideration during the design of the RCT should be given to defining the comparison groups and the criteria for inclusion and exclusion of subjects with respect to the population of patients most likely to benefit from TDM. For example, it may be prudent to select only those individuals who are over- or under-exposed as your study population, *i.e.* those at high risk of treatment failure due to lack of efficacy or toxicity, rather than comparing outcomes for "TDM" vs "no TDM" in all patients receiving the drug.

One possible concern related to conducting a randomized controlled trial comparing TDM with the standard of care (*i.e.* no TDM) is that some may consider it unethical to abstain from increasing the drug dose in control patients with low systemic exposure. The underlying assumption in such an argument is that increasing the drug dose in an under-exposed patient will improve the clinical outcome. Based on this assumption, however, it may further be argued that it would be unethical not to measure drug levels in all patients to identify the underexposed individuals who would benefit from dose increases, and the ethical solution may be to apply TDM universally.[33] A "catch-22" of sorts, this assumption is exactly what the randomized controlled trial in attempting to prove! Without RCTs demonstrating clear benefits of TDM versus no TDM for at least some oral small molecule anticancer drugs, the current oncology practice will not have enough incentive to change and all underexposed patients receiving the standard of care will continue to be prescribed sub-therapeutic doses of these drugs. For example, at our institution there are approximately 550 patients with active imatinib prescriptions. Despite evidence to suggest that approximately 150 to 350 of these individuals may be under-dosed (˜25%-65%),[29,36,37] our laboratory receives fewer than 3 samples per week for imatinib level monitoring.

To the best of our knowledge, there is no randomized controlled trial, either published in a peer-reviewed journal or ongoing, that uses a clinical outcome as the primary endpoint and demonstrates the benefit of TDM of targeted oral anticancer drugs. Nevertheless, results from several trials have been published in abstract form only, and thus may need to be considered with caution. Rousselot et al. reported the final results of the randomized OPTIM Imatinib study, which demonstrated that TDM increases the rates of molecular response in patients with chronic myeloid leukemia (CML).[36] Another abstract from the same group reported that TDM of dasatinib resulted in reduced risk of pleural effusions and high molecular response rates in CML.[38] Results of a trial by Gotta et al. were published in a peer-reviewed journal, but this study did not compare TDM versus no TDM. Instead, "routine TDM" was compared to "rescue TDM" for Imatinib in 57 CML patients.[24] The primary endpoint was a combined outcome (failure- and toxicity-free survival with continuation on imatinib) over 1-year follow-up. This dose individualization trial could not demonstrate additional benefit of "routine TDM" using intention-to-treat analysis, due to a small number of study participants and, surprisingly, limited prescribers' adherence to dosage recommendations. However, using as-treated subgroup analysis of "routine TDM" group, 10 of 14 of patients receiving the recommended dosage after one cycle of TDM remained event-free compared to 3 of 13 patients for whom dosage recommendations were not correctly adopted (P=0.033).

Thus, despite numerous studies (primarily in Stages 1-3 of Figure 1) providing evidence to suggest that TDM of oral small molecule anticancer drugs may be beneficial to patients, and perhaps even cost-effective,[39] there seems to be no published study that definitively demonstrates such benefit. Historically, there are examples of drugs, such as calcineurin inhibitors, for which TDM became the standard of care without demonstrated superiority of "TDM" vs "no TDM" in RCTs. However, in the present culture emphasizing evidence-based medicine, having more drugs reach stage 4 of Figure 1 must be the goal, as this will encourage requests for

TDM by medical oncologists as well as increase the chances for reimbursement of costs.

Precision Dosing in Clinical Studies Versus in Routine Clinical Care

It must be emphasized that the levels of treatment oversight as well as the characteristics of the patient populations in clinical studies are significantly different from those in real-world patient care, which is highly relevant for implementation of TDM. In routine patient care, the timing of sample collection for trough levels is unlikely to be exact, and there is increased likelihood of drug-drug and drug-food interactions as well as other factors that could alter the relationships between drug dose, trough levels, systemic exposure, and, subsequently, biomarkers and treatment outcome. Prospective studies comparing TDM with no TDM using clinical outcomes as the primary endpoint will therefore need to be followed up by analysis of real-world patient data.

Comprehensive Approaches to Precision Dosing

Systemic exposure to a drug may be closely related to outcome as well as side effects, but it would be naïve to think that exposure is the only parameter that we should focus on optimizing. As previously mentioned, there are other ways a drug's effect can be monitored and other parameters may modulate the relationship between systemic exposure and effect. Thus, an ideal precision dosing approach goes far beyond the use of TDM reference ranges, TDM software, or even PKPD software with population models and Bayesian forecasting. In reality, we need to be able to monitor, aggregate, and derive conclusions from thousands of data points, and continually adjust treatment recommendations as new data points are collected. This calls for machine learning and artificial intelligence approaches that have started to make their mark on some areas of medicine, although not yet in precision dosing. Current and future technology will make this a reality and help bridge the gap between clinical studies and real-world patient care.[40]

Conclusion

In summary, although numerous studies provide a clear rationale for monitoring drug levels of oral small molecule anticancer drugs, the lack of trials clearly showing significant improvement in outcomes with TDM prevents this approach from being embraced by the oncology community. Well-designed randomized controlled trials comparing drug level monitoring with the standard of care, which are sufficiently powered to demonstrate an effect on survival are desperately needed. Numerous completed and ongoing studies on TDM of oral small molecule anticancer drugs have prepared the precision oncology field for such a trial. The time has come to take the next step.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Figure Legends

Figure 1: Stages of clinical studies with increasing levels evidence in support of TDM of oral small molecule anticancer drugs. (C_{min}, trough level; TDM, therapeutic drug monitoring; RCT, randomized controlled trial; PFS, progression-free survival.)