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Without Therapeutic Drug Monitoring, There Is No Personalized Cancer Care

JH Beumer[1,2]

The relevance of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) can be an important tool in addressing the following concerns.

- After selecting the correct patient and the correct drug, we often fail to confirm the correct exposure.
- The majority of cancer patients have exposures outside the therapeutic window, and most are underdosed.
- Failure of phase III trials is due not to excess toxicity but to low efficacy, partly as a result of underdosing.

TDM and exposure–response relationships

TDM is the measurement and interpretation of drug concentrations in biological fluids so as to determine the correct drug dosage for an individual patient.[1] The technique requires that dose be correlated with exposure and that exposure be correlated with pharmacodynamic (PD) response. Exposure metrics include the pharmacokinetic (PK) parameters: area under the plasma concentration–time curve, time above threshold concentration, maximum concentration, and trough. Area under the plasma concentration–time curve is often used, but trough will probably be a more widely assessed metric in the future thanks to its practicality with respect to daily-dosed, long-half-life tyrosine kinase inhibitors (TKIs). PD responses that can be correlated with exposure are efficacy and toxicity. A single dose may result in a range of exposures (PK variability), and a single exposure may result in a range of responses (PD variability) (**Figure 1**). Previously established exposure–response relationships can be the basis for determining the therapeutic target window. By creating a distribution of doses, TDM can correct for most of the PK variability, consequently reducing the variability in responses.

A current guidance from the US Food and Drug Administration describes exploration of the relationship between exposure and response at a population level that may include mere dose–response relationships. For TDM, first a PD response is shown to correlate with exposure in individuals, often retrospectively. Next, a prospective study should validate the effect of TDM intervention on patient outcome.

Why we ultimately misdose patients: dose determination in oncology

Doses in oncology are often established by means of the 3+3 modified Fibonacci study design. The maximum tolerable dose (MTD) is the discrete dose at which at least one of six patients (~17%) experiences dose-limiting toxicity (DLT). Assuming an exposure–response relationship with little PD variability, the patients experiencing DLT have a high exposure, above the maximum tolerable exposure (MTE) (**Figure 1**). Interpatient PK variability is commonly between 25 and 70% coefficient of variation (CV).[2] Assuming a conservative PK variability of 35% CV and a minimally effective exposure (MEE) at two-thirds of the MTE, only 45% of patients fall within the therapeutic window. Approximately 17% of patients are being overdosed and will discontinue therapy before deriving benefit. Yet the largest proportion of patients that fall outside the therapeutic window—38% of all patients—is underdosed, experiences subtherapeutic exposure, and is unlikely to derive benefit. It follows that with greater PK variability or a narrower therapeutic window, the proportion of patients being underdosed increases further. These patients probably represent a large proportion of nonresponders in phase III trials of TKIs. Missing the target therapeutic window has the same effect as not having the target present: the therapeutic effect is diluted and statistically lost. For example, erlotinib will be clearly effective in patients selected for epidermal growth factor receptor (EGFR) mutation–positive status, but in unselected non–small cell lung cancers this effect would be diluted by patients who are EGFR mutation–negative. Likewise, any significant treatment benefit for patients who have exposures within the therapeutic range may be lost as a result of the absence of

[1]Molecular Therapeutics and Drug Discovery Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA; [2]Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. Correspondence: JH Beumer (beumerj@gmail.com)

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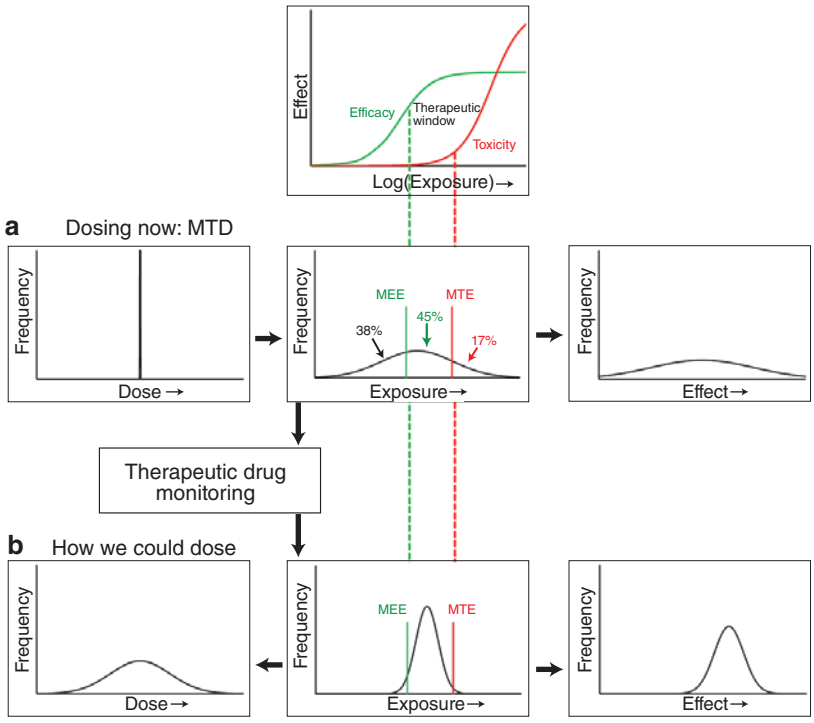

Figure 1 Conventional drug dosing in oncology as compared with dosing with therapeutic drug monitoring (TDM). (**a**) Conventional dosing at a single fixed maximum tolerable dose (MTD) results in a distribution of exposures, through known and unknown pharmacokinetic (PK) covariates, which in turn results in an effect distribution, characterized by a variety of pharmacodynamic covariates. TDM may correct for PK variability by narrowing the distribution of exposures and resulting in a more precise effect. The center graph shows distribution with a coefficient of variation (CV) of 35% (conservative estimate of interpatient PK variability[2]), obtained in a phase I dose-finding study in which up to 17% of patients experience a dose-limiting toxicity and a minimally effective exposure (MEE, green line) at two-thirds of the maximum tolerable exposure (MTE, red line). Only 45% of patients would be treated within the therapeutic window; 38% would be underdosed. With a larger PK variability and narrower therapeutic window, the proportion of patients being underdosed will increase even further. (**b**) The center graph shows distribution of exposure after TDM, with a 10% CV.

response in patients with exposures outside the therapeutic range.

Utilizing TDM to decrease the dose of patients with a supratherapeutic exposure and increase the dose of patients with a subtherapeutic exposure to within the therapeutic window improves treatment outcome through decreased toxicity and increased efficacy.

TDM in oncology

TDM is rarely used in oncology. Although the approach is commonplace in other therapeutic areas (e.g., for antimicrobials, immunosuppressants for organ transplants, and some psychotherapeutics), only a few academic institutions pursue development of TDM in oncology, including the Beumer laboratory at the University of Pittsburgh Cancer Institute.

Proof of principle for TDM in oncology is found in prospective studies of drugs such as 5-fluorouracil, methotrexate, and busulfan that confirm the exposure–response relationships and improved outcome. Exposure–response relationships have been defined to a varying extent for numerous anticancer drugs, including carboplatin, methotrexate, docetaxel, paclitaxel, and, more recently, imatinib, sunitinib, erlotinib, gefitinib, and lapatinib.[3,4] Indeed the TKIs are particularly amenable to TDM because, like antibiotics, they have clearly defined targets and associated half-maximal inhibitory concentrations. As with antibiotics, chronic subtherapeutic exposures will probably result in acquired resistance, emphasizing the importance of confirming appropriate exposure. Exposure–response relationships have been documented for many TKIs, but prospective, confirmatory studies are lacking.

To make TDM practical, only a few samples or a single sample should be needed to evaluate exposure.[4] An advantage with TKIs is their (usually) daily dosing and accumulation upon repeated dosing, enabling the easy quantitation of exposure by a single trough sample. Thus, TKIs present fewer barriers to TDM than do the more classic anticancer agents that are dosed weekly or every 3 weeks and that exhibit complex PK.[3] Some might argue that, because anticancer agents are often used in combination regimens, there is the possibility that exposure–response relationships are modified by these combinations.[1,4] The experience with 5-fluorouracil seems to be proof of principle that exposure–response relationships may hold regardless of concomitantly administered agents.

As pharmacologists and caregivers we have a duty to provide the best possible care, and as a society we must be ever more cognizant of cost–benefit considerations. Optimizing established (off-patent) drugs with TDM may well be more cost-effective than using newer, more expensive drugs at a fixed dose. It may appear that there are no obvious benefits for pharmaceutical companies to invest in TDM, but failure of phase III trials is due not to excess toxicity but to lack of efficacy, which can be attributed to underdosing. TDM will probably lead to increases in the average dose and duration of therapy such that there is more opportunity for efficacy, delaying the switch to alternative therapies. Regulatory incentives aimed at drug developers and health-care providers may need to be put in place to generate market forces that reward exploration of PK exposure–response relationships in general and TDM in particular. As mentioned, daily TKI regimens lend themselves to single-trough sampling, which is easily incorporated into late-phase studies. If not requested by the US Food and Drug Administration or undertaken by the pharmaceutical industry, the pursuit of such correlative end points should be part of the mission of cooperative groups. Finally, patient advocacy groups have a

unique role in demanding personalized therapy, and insurance companies could demand assurances that therapies they reimburse are within a target range and are likely to result in optimal patient benefit and minimal toxicity. Without TDM, there can be no personalized cancer care.

Exposure is the best biomarker for response

TDM will allow personalized cancer care. There is an urgent need to identify the drugs and their exposure measures that are useful as targets and to perform prospective, randomized studies confirming that implementation of TDM is associated, on an individual patient level, with reductions in toxicity and/or improvements in outcome. After documenting the effect size of the outcome improvements, we can evaluate the cost-effectiveness of such interventions, a process involving various stakeholders with a common goal: improving personalized patient care.

In indications other than oncology, doses can be adjusted to achieve target levels of biomarkers that are quickly affected and easily monitored. Statins, antihypertensives, and antidiabetic agents can be dose-adjusted to achieve reductions in serum cholesterol, blood pressure, and serum glucose, respectively. Unfortunately, such biomarkers have been difficult to identify in oncology, despite significant resource allocations. Dosing-to-toxicity approaches have been pursued[5] but are uncommon, and with anticancer agents they may cause toxicities that are not readily reversible. In clinical practice, dose modifications are usually reductions and are a consequence of observed toxicity. Lack of efficacy leads to next-line regimens rather than prompting a dose increase. Because of the often-small therapeutic window in oncology, there is limited appetite for exceeding the approved dosage, even in the obvious absence of benefit—an approach quite the opposite from that in other therapeutic areas. The use of a single dose for all patients, disregarding interpatient PK variability of between 25 and 70% CV (ref. 2), is shortsighted.

The value of TDM in oncology is undeniable: pharmacological principles dictate it, and examples prove it. There is no justification for not applying TDM routinely in oncology, after appropriate evidence has been generated in each specific application. TDM can inform treatment decisions by correcting for a major part of treatment outcome variability. However, there remains the variability in PD susceptibility, and ultimately it is the patient who needs to be treated, not the concentration value.

Exposure is a biomarker, and in many cases it will prove to be the best available biomarker for toxicity and response.

Personalized medicine: what it is and what it should be

Despite recent advances that allow patients with an identifiable target to be selected for treatment with the best drug for that target, in oncology we simply fail to check that the drug has hit the target (range). We shoot sophisticated ammunition at a well-defined target without the benefit of a "spotter." The National Cancer Institute defines personalized medicine as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease" (http://www.cancer.gov/dictionary?CdrID=561717). Radical improvements have been made through the use of such agents as BCR-ABL inhibitors in chronic myeloid leukemia, BRAF/MEK inhibitors in melanoma, and ALK inhibitors in certain non–small cell lung cancers. Dramatic advancements have been achieved in interrogating tumor tissues and subcategorizing cancer types by molecular characteristics, regardless of anatomical location. However, without the benefit of TDM, vast resources spent selecting patients and developing drugs may be wasted. It is clear from the proof-of-principle examples in oncology highlighted above, and readily exemplified in areas outside oncology, that TDM can decrease toxicity and improve outcome. A TDM assay can be considered an on-treatment companion diagnostic. At our institution, significant investments are made in Clinical Laboratory Improvement Amendments–certified capabilities to develop TDM applications. Personalized medicine should be more than dosing a patient with the right drug; it should be dosing a patient with the right drug at the dose required to achieve the right exposure.

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CONFLICT OF INTEREST

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