

THERAPEUTIC DRUG MONITORING FOR THE CANCER PATIENT: CHALLENGES AND OPPORTUNITIES

S. Angelini¹, E. Cecchin², V. Conti^{3,4}, F. Dal Piaz³, A. Filippelli³, P. Hrelia¹, I. Landini⁵, P. Menna⁶, E. Mini⁵, S. Nobili⁷, A. Soledad Poetto⁸, G. Ravegnini¹, R. Roncato², G. Minotti⁶ on behalf of the Cancer Pharmacology Working Group of the Italian Society of Pharmacology

¹ Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy

² Experimental and Clinical Pharmacology, National Cancer Institute – IRCCS, Aviano (PN), Italy

³ Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi (SA), Italy

⁴ Unit of Clinical Pharmacology, AOU San Giovanni di Dio e Ruggi d’Aragona, Salerno, Italy

⁵ Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence, Italy

⁶ Unit of Clinical Pharmacology, Department of Medicine, Campus Bio-Medico University, Rome, Italy

⁷ Department of Neurosciences, Imaging and Clinical Sciences, G. D’Annunzio University of Chieti-Pescara, Chieti, Italy

⁸ Experimental and Clinical Pharmacology Unit, National Cancer Institute - IRCCS, Aviano (PN) and Doctoral School in Pharmacological Sciences, University of Padua, Padua, Italy

E-mail: g.minotti@unicampus.it

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SUMMARY

Therapeutic Drug Monitoring (TDM) is a valuable option to improve the efficacy and safety of cancer drugs. Here, members of the Cancer Pharmacology Working Group of the Italian Society of Pharmacology describe and discuss some paradigms of TDM, moving from best known examples (TDM for fluoropyrimidines) to new opportunities as applied to last generation targeted drugs (TDM for tyrosine kinase inhibitors and monoclonal antibodies). Advances in sampling and TDM-oriented genotyping are also discussed. Based on these paradigms, this Working Group concludes that TDM should be widely exploited in both investigational and real world settings, contributing to the optimal usage of drugs.

Key words

Therapeutic Drug Monitoring; Cancer; Pharmacology; efficacy; safety.

Impact statement

Therapeutic Drug Monitoring (TDM) has gained popularity over the years in the light of its value in improving the efficacy and safety of cancer treatment with traditional cytotoxics; however, broader applications of TDM to targeted drugs and mAbs are now available as are novel and easier-to-do methods of blood sampling. The importance of combining TDM with patient genotyping can revolutionize therapeutic strategies in many settings. It is the time for pharmacologists, clinicians and expert groups of scientific societies to cooperate and foster the widest possible exploitation of TDM in oncologic settings.

INTRODUCTION

In this opinion paper members of the Cancer Pharmacology Working Group of the Italian

Society of Pharmacology describe what therapeutic drug monitoring (TDM) can do for the cancer patient treated by drugs characterized

by a narrow therapeutic index or liable to potentially harmful drug-drug interactions. Few paradigms will be described, moving from TDM for conventional chemotherapeutics to genotyping, new sampling methodologies, or TDM for monoclonal antibodies (**figure 1**).

TDM FOR FLUOROPYRIMIDINES

Fluoropyrimidines (FPs) like 5-fluorouracil and its oral prodrug, capecitabine, and the camptothecin, irinotecan (IRI), remain the backbone of combination chemotherapy of many different solid tumors and in different therapeutic settings. In contemporary oncology the dosage of FPs or IRI is calculated on the basis of patient's body surface area (BSA), however, this has been shown to be an insufficient predictor of systemic drug exposure (1). TDM has therefore been considered as an important strategy to improve the efficacy and safety of anticancer drugs with a narrow therapeutic index (2). In the early times of FPs-based chemotherapy 10-40% of patients experienced severe and, in rare cases (0.2-0.5%), even lethal toxicity (3, 4). Pharmacokinetic studies then revealed that 5-FU systemic exposure was highly variable among patients (4, 5). Further complexity was introduced by possible correlations between toxicity and clinical outcomes, such that dose reductions aimed at preventing toxicity would

in principle jeopardize the oncologic efficacy of 5-FU (6). TDM-guided adjustment of 5-FU dose is therefore essential to achieve a proper balance between toxicity and activity and may eventually help reduce adverse events while also improving response rates as compared with patients exposed to unadjusted 5-FU regimens (7). International and national guidelines and, recently, also EMA recommend measuring the activity of dihydropyrimidine dehydrogenase (DPD, major catabolic enzyme of FPs) before FPs treatment or, in alternative, to perform genotyping of DPYD, the gene encoding DPD. As a surrogate measure of activity, the level of uracil in the blood can be determined (8-11). In specific cases, when a genotype-predicted status of poor metabolizer is detected (more than one DPYD defective allele), FPs use at a strongly reduced dose is allowed only if combined with early TDM (10) to immediately discontinue therapy if the plasma levels are too high.

As for IRI, this is activated to the potent topoisomerase I inhibitor, SN-38, which in turn is conjugated by UDP glucuronosyltransferase 1A1 (UGT1A1) to SN-38 glucuronide for elimination. Carriers of functional polymorphisms in UGT1A1 have been significantly associated with increased plasma levels of IRI as well as increased risk of diarrhea and neutropenia (12). However, a not so clear relationship has been

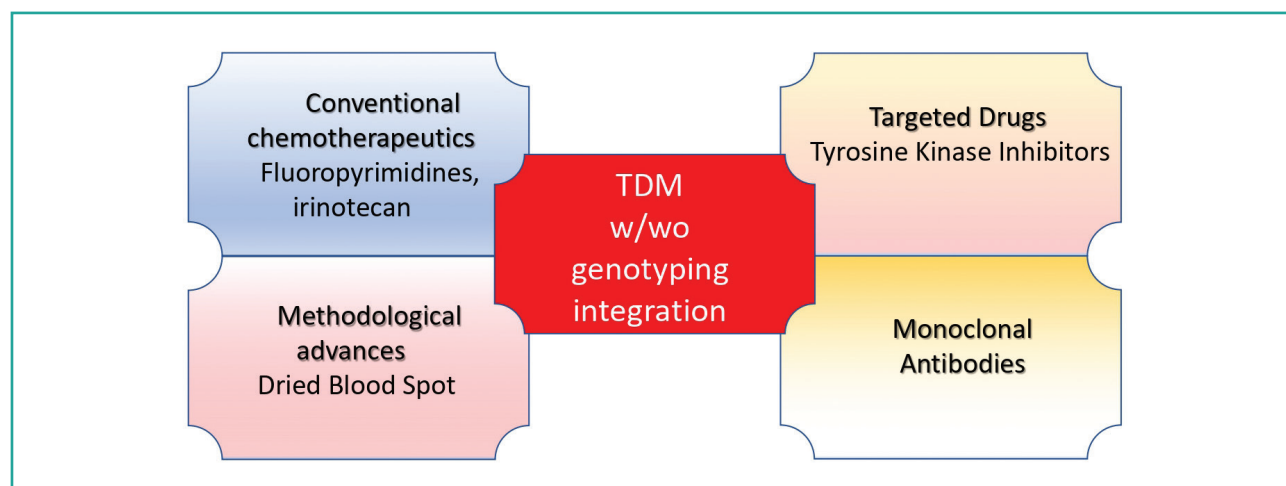


Figure 1. TDM paradigms described in the opinion paper.

established between irinotecan/SN-38 plasma levels and treatment efficacy. Although routine TDM has not been formally established in clinical practice so far, it may still be useful in explorative studies testing non-standard dosages, combination therapies with new anticancer drugs (13), genotype-driven clinical outcomes (14, 15).

TDM FOR TYROSINE KINASE INHIBITORS

TDM offers the opportunity for targeting the therapeutic window also of new generation targeted drugs like tyrosine kinase inhibitors (TKIs). These drugs are formally approved for oral administration at a fixed-flat dose, which was based on early evidence of a poor association between body weight and systemic drug exposure (16). However, fixed-flat doses are accompanied by interindividual PK differences that rest with factors related to drug absorption (patient's compliance, diet, first-pass metabolism), drug activation (CYP450-mediated metabolism), drug elimination (upregulation of key enzymes and transporters) (17, 18). Variability in TKIs exposure, as reflected by the area under the plasma concentration-time curve (AUC) or by steady-state trough concentration ($C_{\text{trough,ss}}$), may cause important effects on treatment efficacy and toxicity. High inter-patient PK variability has in fact been observed (e.g., up to 23-fold for the $C_{\text{trough,ss}}$ of the EGFR-targeted TKI, gefitinib) (18). These findings suggest that a fixed-flat dose might not be the best way to use TKI and provide a rationale for using TDM in optimizing the balance between efficacy and toxicity (19).

Although the rationale for TDM of TKIs is mainly based on retrospective studies, prospective trials, mainly available for imatinib in BCR-ABL positive leukemias (20, 21) or GIST (22) and for the antiangiogenic drugs, sunitinib (23, 24) and pazopanib (25-27), have confirmed that TDM can, in fact, be useful. Therapeutic windows of 1000-1100 to 3000 ng/ml for imatinib (28-30), 50 to 100 ng/ml for sunitinib (23, 24),

20 to 46-50 ng/ml for pazopanib (25-27), have been proposed on the basis of TDM. Overall, a pharmacokinetically guided individualized dosing successfully increased TKIs $C_{\text{trough,ss}}$ in most of the patients who did not reach the PK target with the starting dose (23, 25).

One more example of TDM value is provided by ponatinib, the only approved TKI active against the BCR-ABL T315I mutation. Ponatinib was approved at the dose of 45 mg/day, which resulted in plasma concentrations significantly higher than those associated with antileukemic activity (40 nM): however, ponatinib caused serious cardiovascular toxicity when used at this dose level (28). Continued TDM may allow for reducing ponatinib dose to 15-30 mg/day, with this regimen causing plasma concentrations of approximately 40 nM while also reducing risk of cardiovascular events (29, 30).

Due to the costs and economic burden of TKIs in real life, a TDM-driven optimal dosing could provide benefits not only in terms of efficacy/safety but also in terms of treatment sustainability. Evidence-based practical guidelines for TKI dose optimization (31) should therefore be proposed and disseminated by joint consensus panels of pharmacological and oncological scientific societies, contributing real world evidence for re-evaluating the benefit-risk profile and cost effectiveness of these drugs (32).

METHODOLOGICAL ADVANCES IN TDM: DRIED BLOOD SPOTS

Having illustrated the clinical advantages that TDM may offer to improve efficacy and safety of traditional cytotoxics/cytostatics or targeted TKIs, we would now move on to describe some methodological advances that can ease TDM in everyday life.

TDM biological matrix choice is based on the studied and proven relationship between drug concentration in the sample matrix and its concentration at the site of action or toxicity (33). Plasma is the most employed biological matrix as plasma exposure to a given drug usually correlates with the efficacy and

toxicity of that drug; however, TDM based on blood sampling requires the set-up of an outpatient clinic where nursing and technical support from blood drawn to plasma separation can be provided (33). These issues, combined with the need for accurate temperature-controlled sample storage, make plasma sampling time-consuming and expensive (33). In recent years alternative matrices and sampling techniques have gained attention because of their wider applicability and convenience in certain therapeutic contexts. Dried Blood Spot (DBS) is one of such advancements and consists in blotting blood obtained by fingerstick on a filter paper and letting it dry (34). After drying, most drugs are demonstrated to be stable, so that DBS samples can be shipped and stored at room temperature (35). Further, being a less invasive and easy to perform home-based sampling technique, DBS could promote cost-effective participation of a huge number of subjects in both clinical monitoring and investigational studies for which TDM is required. DBS would also simplify TDM for pediatric patients and other special populations (like e.g., the elderly or frail) while also making TDM available to patients living in rural areas or low-resources environments) (36).

Being manageable by the patient himself, DBS would not only be easier to perform than blood drawn by venipuncture but would also be more likely to be performed at that defined time when TDM is required for clinical or investigational purposes. This having been said, DBS is not as popular as one would expect to see. There is therefore an urgent need for studies that provide persuasive and large scale evidence of how DBS may contribute to the optimal caring and monitoring of patients, particularly in oncologic settings.

INTEGRATING TDM FOR TKI WITH GENOMIC PROFILING

In summarizing multiple ramifications of TDM in clinical settings we should now address the importance of integrating TDM for TKI with

an individualized genotyping approach, in line with mainstream “personalized medicine”. Gastrointestinal stromal tumor (GIST) represents a valuable setting to describe.

GISTs account for < 1% of all malignancies but represent the most common mesenchymal tumors of GI tract (37,38). Complete surgical resection is the standard of care for localized GIST while locally advanced or metastatic GIST can remarkably benefit from imatinib, the same TKI that revolutionized treatment and prognosis of Ph⁺ chronic myeloid leukemia (39-43). In fact, most GISTs express oncogenic KIT or PDGFRA harbouring receptor tyrosine kinase activating mutations that are druggable by imatinib. On a different note, this was an instructive example of how TKI should always be referred to as multikinase inhibitors that extend their action beyond their prototypic target (in this case, the oncogenic Bcr-ABL fusion protein kinase of leukemias). By having recognized the unprecedented improvements that imatinib introduced in GIST treatment, other TKI should be recognized for their activity in GIST that became resistant to imatinib; these include sunitinib or regorafenib as second or third-line therapeutic options.

Some 20 years after the imatinib splash, GISTs remain an oncologic setting open to new therapeutic agents, such as avapritinib, directed against the D842V PDGFRA mutation. The subset of patients carrying this mutation would be primarily insensitive to all other TKIs. Avapritinib approval thus represents one more example of targeted therapy that is driven by patient genotyping (44). The same holds true for ripretinib, which is on its way to worldwide approval as fourth-line treatment of GIST.

The analysis of KIT and PDGFRA mutations provides a powerful tool for choosing the right drug for the right patient. ESMO-EURACAN Clinical Practice Guidelines strongly support tumor mutational analysis (45). This may also guide dose adjustments in some defined circumstances; for example, KIT exon 9 mutations associate with longer progression free survival if imatinib is given at the dose of 800

mg/day instead of the standard 400 mg/day regimen. Identification of the D842V PDGFRA mutation is also recommended as patients carrying such mutations would be unresponsive to standard TKIs.

TDM FOR MONOCLONAL ANTIBODIES

The use of monoclonal antibodies (mAbs) is steadily increasing in many therapeutic settings, due to the efficacy and selectivity with which these drugs may cure diseases. mAbs also show a satisfactory level of safety if properly monitored by trained personnel. This having been acknowledged, the optimal dose for use in a given patient remains a complex challenge. The PK of antibodies is in fact unique in many respects. mAbs are eliminated through cellular uptake and proteolytic digestion. The interaction with specific receptors, mainly neonatal Fc-receptor (FcRn), can prevent mAbs degradation and promote mAbs recycling, thus significantly increasing their half-life. Since the amount of FcRn degradable proteins other than mAbs is influenced by an array of physiological or pathological factors, the PK of mAbs may show considerable inter-individual variability (46). Moreover, the development of anti-drug antibodies (ADA) and the occurrence of off-target binding influence the plasma concentration of mAbs (47). And finally, co-administration of mAbs with immunosuppressive drugs significantly reduces the formation of ADAs, thus introducing additional variables in mAbs PK (48). It follows that TDM for mAbs would be much needed.

Studies aimed at personalizing the clinical use of mAbs are lacking but interesting potential approaches can be found in the literature. For example, some studies suggest that the efficacy of combination therapy with traditional cytotoxics and the anti-VEGFA antibody, bevacizumab, might benefit from pretreatment evaluation of circulating levels of VEGFA (49-51). In addition, many studies have been published that explored the value of TDM for patients treated with mAbs (52-55). On the basis

of ELISA or high resolution mass spectrometry, these studies clearly demonstrated that TDM can help to avoid or correct inappropriately high or low dosages; at the same time, however, these studies also showed that many technical problems remain to be solved before TDM could be routinely applied to mAbs. For example, only few data are available to confirm that a direct relationship exists between inappropriately high plasma levels of mAbs and risk of untoward side effects. Moreover, target concentration has not been definitely identified for the majority of clinically approved mAbs, although several reports were indeed focused to explore this issue (56, 57). The latter problem is at least in part due to variability in expected outcomes or predefined clinical endpoints (58).

It goes without saying that personalization of mAbs-based therapies calls for research efforts, especially if one appreciates that avalanches of new mAbs will become available in few years and will pose the same problems as those discussed for currently available mAbs.

CONCLUSIONS AND PERSPECTIVES

We summarized few paradigms of TDM in contemporary oncology. Whereas the balancing of efficacy with safety remains the ultimate goal of TDM for the majority of cancer patients, other settings will probably gain importance in few years to come. For example, there are cases where guidelines recommend coadministration of substrates and inhibitors of CYP3A4, something that common sense would recommend against if alternative drugs were available. This is the case of guidelines recommending antifungal prophylaxis with posaconazole, a potent CYP3A4 inhibitor, for patients diagnosed with FLT3-mutated acute myeloid leukemia and requiring treatment with midostaurine, a multikinase inhibitor that is a substrate of CYP3A4. Posaconazole clearly increases patient's exposure to midostaurine (59). In circumstances like this, TDM will be needed to adjust midostaurine dosage in

patients treated with posaconazole but will also serve to explore the efficacy, safety and PK congruence of combination therapies in which other antifungals are probed in place of posaconazole. Again, this emphasizes the importance that TDM may gain in real world life to optimize the benefit/risk ratio of drugs (60).

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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