Review Article

Precision dosing of targeted anticancer drugs—challenges in the real world

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Abstract: The prerequisites for the successful implementation of therapeutic drug monitoring (TDM) include high inter-subject variation, low inter-occasion variation, narrow therapeutic index and a strong link between plasma drug concentrations and clinical effects. The degree to which targeted anticancer drugs meet these criteria is not the only consideration in implementing precision dosing. Methodological, logistical, funding and cultural barriers also provide challenges to the successful implementation of approaches to individualised therapy. This review considers the barriers to the routine use of TDM, using examples from both conventional (cytotoxic) anticancer, but also considering more recent data and examples more relevant to chronic, oral administration of targeted therapies. Based on these examples and the associated principles for the implementation of precision dosing, proposals may be made for a more rational, real-world approach to the best use of precision medicines.

Keywords: Oral dosing; kinase inhibitors (KIs); therapeutic drug monitoring (TDM); individualisation

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Current evidence for the role of therapeutic drug monitoring (TDM) in cancer

The International Association of Therapeutic Drug Monitoring and Clinical Toxicology define TDM as a "multi-disciplinary clinical specialty aimed at improving patient care by individually adjusting the dose of drugs for which clinical experience or clinical trials have shown it improved outcome in the general or special populations. It can be based on a priori pharmacogenetic, demographic and clinical information, and/or on the a posteriori measurement of blood concentrations of drugs (pharmacokinetic monitoring) and/or biomarkers (pharmacodynamic monitoring)" (1).

Targeted anticancer drugs, by which we mean agents designed to act at a specific protein identified in tumour cells in a biopsy from an individual patient, are excellent candidates for TDM. These medicines are administered chronically, usually by oral administration, often have defined inhibitory concentrations for their targets and, despite their "targeted" nature, have the potential to cause debilitating or treatment-limiting side-effects (2). As commonly applied, in this review article we will consider TDM to refer to an adjustment of dose based on a posteriori measurement of drug concentrations and other biomarkers in blood, when correlated with efficacy or toxicity. Dose calculation based on body size (weight or surface area) could be described as implementing a dose adjustment.

With the exceptions of carboplatin (renal function) and 6-mercaptopurine [thiopurine methyltransferase (TPMT) activity or genotype], there are few widely-accepted examples in cancer treatment of dose adjustment based on a priori measures (3). TDM is a tool that can be used to

investigate possible adverse effects or inadequate response to a medicine by detecting and confirming changes in exposure to drugs or metabolites, especially when these effects may present in an atypical manner (4). Such adverse effects may be more common when the use of novel therapies is extended beyond well-defined trial populations to include older patients with a range of comorbidities. TDM also has a role in assessing adherence to a prescribed dose regimen (5).

A critical part of establishing the utility of TDM in practice is high-quality evidence of safety and effectiveness. A challenge with the current evidence base for TDM is that many studies are observational in design, few have an appropriate control group and many are under-powered for clinical endpoints (6). While there has been a number of well-designed concentration-controlled trials (7) which have demonstrated that pharmacokinetic (PK)-guided dosing can improve outcomes when compared to empiric dosing (8), these trials are sparse in the literature and difficult to translate into practice. A further gap in the literature is evidence to support the cost-effectiveness of TDM in practice. However, a systematic review by Touw *et al.* (9) investigated the value of using TDM as a therapeutic intervention and found that the current evidence is limited, with only a few examples of TDM application being cost-effective (10), and then only under specific circumstances.

Most cytotoxic (non-targeted) anticancer drugs are characterized by a narrow therapeutic index, high toxicity profile and large degree of inter-patient PK variability, all of which are necessary conditions to justify TDM (11). However, while necessary, these characteristics are often not sufficient and there are currently relatively few examples where TDM has been used in routine care for anticancer drugs, either conventional cytotoxic therapy or newer targeted agents. Thus, the current role of TDM in cancer treatment is still limited, lacking sufficient level of evidence or tools for implementation despite supporting evidence (12).

Reviewing the data for current cancer therapeutics where TDM is implemented routinely is useful to understand the required levels of rigorous evidence and any barriers to implementation. This information provides a background to the extension of this approach to other drugs, including targeted anticancer drugs.

Carboplatin

Carboplatin is widely used in ovarian and other adult cancers and also in paediatric cancers including retinoblastoma and neuroblastoma (13). Carboplatin fulfills the criteria of a clear link between plasma concentration and pharmacological effect (14) and that TDM and subsequent dose adjustment can achieve a targeted plasma concentration (15). The clearance (CL) of carboplatin is closely correlated with renal function (16,17), which is used to calculate the carboplatin dose to achieve a desired target AUC using the so-called Calvert formula expressed as: dose (mg) = area under the curve (AUC) (mg/mL/min) × [glomerular filtration rate (GFR) + 25 mL/min] (17). For carboplatin, TDM has mainly been employed for high-dose protocols, in those with impaired or absent renal function and in neonates (13).

High-dose methotrexate

The antimetabolite methotrexate is used to treat adult and childhood acute lymphoblastic leukaemia (ALL), non-Hodgkin lymphoma (NHL) and osteosarcoma (18). The routine use of TDM for high-dose methotrexate guides the timing of initiation and tailored dose of folinic acid rescue. Patients with plasma concentrations above 10 μM after 24 hours, 1 μM after 48 hours and 0.1 μM 72 hours after methotrexate infusion are considered to be at risk of bone marrow and gastrointestinal toxicity (19-21). Rescue therapy with folinic acid is continued daily with dose adjustment until methotrexate concentration falls below 0.1 μM (18). As such, this TDM approach aims not to modify the administration of the cytotoxic drug itself, but rather to guide the dose and administration of rescue therapy.

A high methotrexate CL, and consequently lower steady-state plasma concentration, results in significantly higher relapse rates in ALL patients (22,23). In a landmark study, a lower steady-state concentration of methotrexate (<16 μM) was associated with 3-fold higher risk of relapse and 7-fold higher risk of specific hematologic relapse (24). In other studies, methotrexate TDM has been used to identify patients at risk of toxicity (25,26).

A randomized, prospective trial compared conventional *vs.* individualized ALL treatment regimens containing methotrexate in children. Those who received individualized therapy, based on measured drug concentrations, had a greater rate of continuous complete remission (27). This is one of the few studies in which the impact of a TDM approach has been assessed in a randomized prospective design, albeit one that involved individualizing doses of

three different drugs. In a similar study in osteosarcoma, pharmacokinetically-guided dose escalation of methotrexate was associated with greater progression-free survival (PFS) and a lower rate of toxicity compared to a control group (28).

13-cis retinoic acid (isotretinoin)

13-cis retinoic acid (13-cisRA) is used for the treatment of minimal residual disease in pediatric patients with high-risk neuroblastoma, and improves 3-year survival from 29% to 46% (29). The standard protocol dose of 160 mg/m^2/day for six 2-week cycles is associated with up to 20-fold variability in C_{max} and AUC (30). The lack of clinical benefit from an alternative regimen of low, but continuous, dosing indicates that dose intensity and plasma drug concentration are important for therapeutic efficacy (31,32). Dose-limiting toxicity is associated with serum concentration of greater than 10 µM (32).

In an adaptive dosing study, the target minimum C_{max} of 2 µM was achieved in 90% of patients. Inter-patient PK variation was also significantly reduced especially for younger patients (<12 kg) who received doses of 5.33 mg/kg (30). TDM of 13-cisRA is now integrated into the European high-risk neuroblastoma protocol. Further studies would be required to confirm the clinical benefit of TDM and to define a specific target exposure range for 13-cisRA.

Busulfan

The alkylating agent busulfan is used as part of conditioning regimens in hematopoietic stem cell transplantation (HSCT) for treatment of hematologic malignancies [e.g., acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML)] and non-malignant disorders (33). Busulfan exhibits a large inter-patient variability in PK and higher plasma exposures (exceeding a C_{ss} of 900–1,025 ng/mL) are associated with an increased risk of severe toxicity, such as sinusoidal obstructive syndrome (SOS) (34-36). Conversely, sub-therapeutic exposure has been associated with graft rejection or relapse (35,37,38). The narrow therapeutic index of busulfan provides a strong argument for TDM (39). Different target ranges have been identified in various studies [e.g., AUC, 950 to 1,520 µM/min (40); AUC, 900–1,350 µM/min (41); C_{ss} >600 ng/mL (42); C_{ss}, 600–900 ng/mL (43)] and uncertainties persist over the optimal method for estimation of AUC.

In a large retrospective cohort of busulfan treatment for allogenic HSCT in children/young adults, the target range for cumulative busulfan AUC was refined to 78–101 mg·h/L (39). This analysis has been implemented in a Bayesian forecasting tool (Insight-Rx), for prediction of busulfan optimal dosing. Adopting this TDM approach in clinical practice may optimise treatment outcome and could be used to design prospective trials to validate the benefit of TDM.

Comparison with other therapeutic areas

TDM to individualise dosing is now more common and routine practice in a range of therapeutic areas such as infectious diseases (44), transplantation (45), cardiovascular disease (26), neurology (26) and mental health (46). There is also compelling evidence for the use of TDM to individualise treatment in vulnerable patient groups such as paediatric and geriatric populations (26).

There is growing evidence of the use of TDM in optimising treatment with biological medicines (47) and combining TDM with model-based dose optimisation (48). This approach has also been applied to managing the switch between an innovator biological and biosimilars (49).

Lack of implementation—despite evidence?

The steps to the clinical implementation of TDM have been laid out clearly (50). There must be a demonstrated relationship between plasma concentration and therapeutic effect (or toxicity), the intervention of TDM should result in plasma concentrations within the therapeutic range and, ideally, an improvement in clinical outcome should be evident following the application of a TDM approach. The last element, in the context of a randomized controlled trial (RCT), blinded where possible, is the most challenging. For many cancer therapeutics, although the benefit of TDM is theoretically very likely to result in clinical benefit, definitive, high quality studies to show patient benefit in terms of toxicity and/or efficacy have not been undertaken [reviewed in (18,51)].

Implementation of routine TDM is challenging, particularly in the absence of such comparative efficacy and toxicity data. Clinicians depend on high quality RCTs of new drugs in order to make decisions on optimal treatment. In the context of RCTs of comparative treatments, information regarding PK and the potential role of TDM are rarely included, still less any recommendation for dose optimisation.

In addition to the examples above, there are other cancer therapies where the evidence for the effectiveness of TDM

is compelling. The reasons for this lack of implementation in the presence of strong evidence are complex. However, they include heterogeneous clinical practice in oncology, concerns that trial data are not relevant to the actual clinical practice population, and lack of logistic support. The latter element may include lack of resources for pathology phlebotomy services, timely analytic and reporting times, high-quality laboratory analytic work and clinician education to understand the interpretation of the results [these and other factors are more fully reviewed in (52)].

Examples of drugs for which there is evidence and yet a lack of uptake of routine TDM in practice are:

5-fluorouracil (5-FU)

Conventional body surface area (BSA)-based 5-FU dosing results in a wide variation of 5-FU systemic exposure (53) which correlates with a broad spectrum of measures of efficacy. Although, 5-FU administration is individualized to the extent of BSA-based dosing, BSA does not correlate well with any PK parameters in adults. PK-based dosing to a target concentration is undertaken in several US centres (54) and there is good comparative data of the mortality benefit of TDM-guided 5-FU dosing (55). Dose adjustment of 5-FU is feasible and can significantly improve clinical outcomes by reducing toxicities and improving efficacy.

Mitotane

Although not widely used in cancer treatment, mitotane is the standard of care after complete surgical resection of adrenocortical carcinoma (56). The FDA label recommends a starting dose of 2 to 6 g daily, with incremental dose increases to 9 or 10 g per day, based on tolerance. The long half-life of mitotane means that steady-state concentrations are achieved only after several weeks. A target therapeutic concentration of 14–20 mg/L is recommended by the European Medicines Agency (EMA), as concentrations above the lower bound of this range are associated with better survival (57). Infrastructure support for TDM is available in the UK, but TDM is not routine in many international centres. In Australia, this service is available in only one centre (58), but is not funded as a routine laboratory service.

Tamoxifen

Although active in its own right in the adjuvant treatment of estrogen receptor-positive breast cancer, much of the activity of the selective estrogen receptor modulator tamoxifen is mediated by a major and more potent metabolite, endoxifen. Formation of endoxifen is catalyzed predominantly by the hepatic enzyme CYP2D6 (59), which is subject to a common genetic polymorphism. There has been a significant focus on the impact of *CYP2D6* pharmacogenetics on outcome following tamoxifen treatment (60,61). There is also evidence for an association between endoxifen exposure and clinical outcome (62). Endoxifen plasma concentrations below 5.97 ng/mL were associated with a higher risk of breast cancer recurrence or a new primary breast cancer (63). A combination of low CYP2D6 activity (poor metaboliser; PM phenotype) and low endoxifen concentration (<14 nM) were associated with a poor outcome (64).

CYP2D6 is always an adequate predictor of endoxifen plasma concentration (62,65) and TDM based on endoxifen plasma concentrations has been suggested for individualising tamoxifen treatment (66). Endoxifen plasma concentrations can be increased by dose escalation of tamoxifen without an increase in side effects (hot flushes) and irrespective of *CYP2D6* genotype (62). However, more prospective trials are required to precisely define a target concentration range for endoxifen and to validate the clinical benefit of endoxifen TDM.

Why is TDM for targeted agents not in routine clinical use?

Logistical challenges

When considering the options for the implementation of TDM for targeted anticancer drugs, it is necessary to consider the models set out above, as these illustrate the pitfalls and challenges of implementing strategies to optimisation of dose. Recent reviews have comprehensively summarized the evidence for the identification of target concentration ranges for a number of novel targeted agents, mostly kinase inhibitors (KIs). As with many of the examples of successful implementation of TDM in cancer, these drugs are administered by repeated, oral administration, giving the opportunity for dose-adjustment based on a trough steady-state concentration. Evidence and opportunity are not sufficient, however, for a successful implementation of TDM.

There are a variety of logistical challenges to the routine implementation of TDM for cancer, even for those drugs for which there is already evidence of benefit. These issues include:

(I) Competition for funding. Approaches to optimise the use of established drugs are viewed unfavourably compared to the development of novel genetic technologies or treatments;
(II) There is no commercial incentive for the pharmaceutical industry to fund or support research into the use of established or off-patent therapies;
(III) Although biochemistry and pathology labs are equipped and staffed to support analytical techniques, there is little funding for assay validation and rapid turn-around times;
(IV) Measures of plasma concentrations do not provide sufficient information without support for clinical and pharmacological interpretation, including statistical analysis, to implement TDM decision making;
(V) Analytical methods for small-volumes using robust sampling techniques, e.g., dried blood spot (DBS), are required. These techniques facilitate the acquisition and transfer to the analytical facility of samples in a stable state, allowing participation at a distance for all patients;
(VI) While pharmacometric methods to predict optimal blood sampling times and to interpret, in context, the results of plasma measurements of drug concentration have been developed, the availability and validation of user-friendly, web-based tools are not well-established or accepted. Models for commercialization and certification of pharmacological tools for TDM are still in their infancy (e.g., Bestdose, DoseMe, Rightdose, InsightRx) and are subject to regulatory approval.

Methodological challenges

Lack of a clear PK/pharmacodynamic (PD) relationship

In order to definitively demonstrate the clinical benefit of TDM for targeted drugs, a prospective randomized trial of conventional or label dosing *vs.* PK-guided dosing would be necessary (12). The design of such a study is often difficult due to the lack of clear PK-PD relationships, providing a challenge for the implementation of TDM.

For some tyrosine KIs (TKIs) such as sorafenib, sunitinib, erlotinib, dasatinib, pazopanib, lapatinib, gefitinib, nilotinib and mTOR inhibitor such as everolimus, evidence is emerging for PK-PD relationships and TDM may potentially be useful, but data are often heterogeneous and need to be clarified. For other KIs such as axitinib, afatinib, bosutinib, crizotinib, regorafenib, cabozantinib, ibrutinib, vandetanib, and BRAF inhibitors such as dabrafenib and vemurafenib, no significant relationship has been observed and level of evidence for or against TDM is still to be evaluated.

The therapeutic target plasma concentration ranges for many KIs have been reviewed recently, as this issue comes under increasing scrutiny (67).

A number of specific issues have emerged that complicate and confound the routine implementation of TDM for targeted agents. Although some of these are familiar from previous attempts to implement TDM for cytotoxic drugs, others are more closely linked to the specific pharmacology of novel, targeted therapies.

Tumour-specific PK-PD relationship

The nature of the PK-PD relationship for any one drug may vary with tumour type, providing a further challenge to the implementation of TDM.

For example, in gastrointestinal stromal tumor (GIST) patients, the steady-state trough level of imatinib associated with clinical benefit was 1,100 ng/mL (68). In CML and GIST patients treated with imatinib as monotherapy, a target C_{min} range of 520–1,390 ng/mL and AUC of 29–48 mg·h/L was suggested. Clinical benefit has not been validated in other tumour types or with combination regimens (69).

However, defining a target range may be challenging due to different tumour mutational status. GIST is often characterised by activating gene mutations in the receptor tyrosine kinase KIT (70,71), and occasionally platelet-derived growth factor receptor α (PDGFRA) (71). Tumour kinase genotype has been identified as a predictive factor of response to imatinib (72-74). Those patients with a *c-Kit* exon 9 mutation receive a higher starting dose of 800 mg/day imatinib (73). Patients with *c-Kit* exon 11 mutations showed better clinical response compared to patients harboring exon 9 mutation (74) or to patients with no detectable mutations in *c-Kit* or *PDGFRA* (73,74).

Variations in PK/PD may also arise when the relationship between drug concentrations in plasma and those in tumour varies between tumour types or between individuals with the same tumour type. This may be particularly the case for imatinib, which is used to treat both solid tumours and leukaemias. An approach to measuring intra-tumoral drug concentrations has recently been proposed (75).

End-points for PD

With very few exceptions, PD end-points with a direct link

to clinical benefit are rare in oncology. An exception would be the evaluation of the efficacy of imatinib and second-generations TKIs such as nilotinib, dasatinib and bosutinib in the treatment of CML. Detection of the Philadelphia chromosome positive, and more specifically the BCR-ABL fusion gene, is used to define a cytogenetic or molecular response to treatment (76). Such PD endpoints are useful surrogates for defining PK target concentrations and provide a direct link to clinical outcome (77).

However, such clearly-defined prognostic markers are uncommon for solid tumours and very disease-specific (69).

Intra-individual variation in PK and PD

While inter-subject variation makes a strong argument for the application of TDM, the potential for dose individualization is undermined when there is a large degree of intra-patient or between occasion variation in PK.

In a TDM study of pazopanib (78) the degree of intra-patient variability (24.7 CV%) was comparable to the inter-patient variability (27.3 CV%), such that dose individualisation could not be predictive.

Such intra-patient variation in PK may arise from many factors related to drug absorption, distribution, metabolism and elimination. For orally-administered drugs in particular, fasting/fed states, fat content of food affecting drug solubility, acid suppressive drugs and other features of drug absorption may cause profound differences in plasma concentration. Drug interactions at the level of drug transporters and metabolizing enzymes in the gastrointestinal (GI) tract, liver and kidney, also contribute to variations in bioavailability and drug elimination on different occasions for the same individual.

With an increasing shift from parenteral cytotoxic drugs to orally-administered, targeted therapies, patient compliance may be the key factor in determining fluctuations in drug exposure (79,80). Outpatient, continuous treatment also means more inconsistent exposure to concomitant medications, including over-the-counter drugs, resulting in a variable magnitude of interactions on different occasions.

Food-drug interactions

Food alters gastric pH, gastric emptying rate and gastrointestinal fluid composition, all of which influence solubility and extent of absorption of drugs, including many targeted agents (81). For example, exposure to bosutinib (C_{max} and AUC) significantly increased, up to 2-fold, when taken with food compared to the fasting state (82). Bosutinib is recommended to be taken with food (76).

Similar effects have been reported for pazopanib (83), nilotinib (84), and lapatinib. Despite the augmentation of absorption with food, it is actually recommended that these drugs be taken on fasting state (85), in order to minimise inconsistencies.

Conversely, some KIs such as afatinib and sorafenib are recommended to be taken in the fasting state because a high fat meal reduces C_{max} and AUC (86-88).

Drug interactions

Because of their effect on stability and solubility, drugs which increase pH in the stomach can also affect the absorption of orally-administered drugs. Oral absorption of many KIs such as dasatinib, erlotinib, gefitinib, lapatinib, and pazopanib is significantly reduced by concomitant use of acid-suppressive treatment (89-91).

Most KIs including afatinib, axitinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib and vemurafenib, are substrates of ATP-binding cassette (ABC) transporter (ABC transporters) (92). ABCB1 or P-glycoprotein and ABCG2 (breast cancer resistance protein or BCRP) are responsible for efflux of substrates in organs such as intestine, liver and kidney (93). Concurrent use of drugs which inhibit (e.g., ritonavir, verapamil, cyclosporine, everolimus) or induce (e.g., rifampicin) ABCB1 have reported PK drug interactions with a number of KIs (93). For example, prior administration of ritonavir, a potent inhibitor of ABCB1 and ABCG2, increased AUC by 48% and C_{max} by 39% for a 20-mg dose of afatinib. In contrast, rifampicin is a potent inducer of ABCB1, and if administered for 7 days before a 40-mg dose of afatinib, decreased AUC by 34 % (94).

Co-administration with inhibitors or inducers of drug metabolizing enzymes results in altered AUC or C_{max} (93). Administration of ketoconazole or grapefruit juice, both CYP3A4 inhibitors, increased AUC, C_{max} and half-life of lapatinib in healthy individuals (95). Conversely, administration of carbamazepine, a CYP3A4 inducer, decreased lapatinib AUC and C_{max} (95).

Dose adjustments may be taken into account for regular concomitant medications, but variations from as required (PRN) or over-the-counter (OTC) medications or changes in dose regimens (dose or frequency) present challenges for maintaining a consistent plasma level of the drug intended for TDM.

"Flat" empiric dosing

With the advent of oral, continuous administration of targeted KIs, in the absence of evidence-based guidelines for tailored dosing of cancer medications in today's complex patients, flat dosing with no adjustment of dose for any patient characteristic is the norm. There are arguments for and against flat dosing. For biological therapies, a single flat dosing level is becoming the standard for the pharmaceutical industry (e.g., pembrolizumab). For pharmacies, it is easier to stock a single dose unit size, and easier for reimbursement agencies to consider. However, the scientific justification for a fixed dose in all patients is not always clear. For example, the plasma concentrations of both sunitinib (96) and pazopanib (83) vary in a population of patients (up to 10-fold) after the same dose, even when renal and hepatic function are "normal".

Small steps forward

Despite these uncertainties, the application of TDM for several targeted agents has advanced, with a strong case for further implementation:

Imatinib

The potential benefit of using TDM to guide imatinib dosing is indicated by the large variability in the relationship between dose and concentration (97), mostly due to variability in CYP3A4 activity (98) which mediates the key metabolic pathway, and in ABCB1, which determines both efflux from the gut wall and active secretion in the bile (99,100). Trough concentrations after administration of the 400 mg standard dose can vary from 109 to 4,980 ng/mL (97). Furthermore, the relationship between plasma concentration and clinical outcome has been clearly demonstrated for imatinib (68,101), aided by the unequivocal PD marker of molecular response.

An imatinib trough concentration at steady-state above 3,000 ng/mL is associated with significantly higher rates of toxicity—rash, neutropenia and oedema—and should be avoided (101,102). Despite the degree of inter-subject variation (69), and reported strong PK-PD relationship, implementation of TDM for imatinib has not gained wide acceptance, and key barriers to uptake were identified in a prospective study (103). The most prominent of these seemed to be lack of uptake by practitioners.

Pazopanib

Pazopanib is a TKI that inhibits the vascular endothelial growth factor receptor (VEGFR), PDGFR, fibroblast growth factor receptor (FGFR) and stem cell receptor (c-Kit) with demonstrated efficacy in renal cell carcinoma and soft tissue sarcoma and emerging data on efficacy in other tumour types (104). Like other TKIs (105), there is evidence of inter-patient variability in PK leading to the risk of suboptimal dosing when administered using empirical fixed dose regimens (106).

Pazopanib is predominantly excreted in the faeces with a small fraction (about 10%) metabolised by CYP3A4 and other CYPs (106). A feature of pazopanib PK is low and variable bioavailability, which appears to be dose-dependent and significantly affected by the concomitant administration of food and changes in gastric pH (83). These factors lead to significant inter- and intra-patient variability.

In a study of the efficacy of pazopanib in renal cell carcinoma, a clear relationship was demonstrated between plasma concentration and outcome, with patients who achieved a steady-state trough concentration of pazopanib above 20.5 mg/L having a longer PFS and great tumour shrinkage (104,107). However, these higher plasma concentrations of pazopanib were also associated with adverse effects such as hypertension, diarrhoea, increase in serum activity of hepatic enzymes and stomatitis (104). Similar observations have been reported in small studies involving other tumour types (thyroid cancer and advanced solid tumours) [see review (106)].

The variable PK, narrow safety margin and evidence of exposure-response relationship indicate that pazopanib would benefit from pharmacokinetically-guided dosing. This has been examined in two small studies, one of 13 patients (108,109) and another with 30 patients (109). Both studies demonstrated the feasibility of optimising pazopanib systematic exposure using TDM-based dose adjustments.

Conclusions

The cited examples with imatinib and pazopanib where TDM has been implemented and evaluated highlight the potential, but also the recurrent challenges, for the routine use of TDM for targeted agents. However, as these agents are used in cancer therapy in an increasing portfolio of indications, the possibilities of long-term survival, and the need to optimise quality of life provide an imperative for optimal dosing. The high cost of targeted agents, and the increasing use of indications based on tumour molecular pathology rather than anatomical site also provide positive incentives for ensuring the optimal dose is used in each

patient, in the context of real world clinical treatment.

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