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POINT OF VIEW

Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine

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Abstract

Purpose While in the era of precision medicine, the right drug for each patient is selected based on molecular tumor characteristics, most novel oral targeted anticancer agents are still being administered using a one-size-fits-all fixed dosing approach. In this review, we discuss the scientific evidence for dose individualization of oral targeted therapies in oncology, based on therapeutic drug monitoring (TDM).

Methods Based on literature search and our own experiences, seven criteria for drugs to be suitable candidates for TDM will be addressed: (1) absence of an easily measurable biomarker for drug effect; (2) long-term therapy; (3) availability of a validated sensitive bioanalytical method; (4) significant variability in pharmacokinetic exposure; (5) narrow therapeutic range; (6) defined and consistent exposure-response relationships; (7) feasible dose-adaptation strategies.

Results All of these requirements are met for most oral targeted therapies in oncology. Also, prospective studies have already shown TDM to be feasible for imatinib, pazopanib, sunitinib, everolimus, and endoxifen.

Conclusions In order to realize the full potential of personalized medicine in oncology, patients should not only be treated with the right drug, but also at the right dose. TDM could be a suitable tool to achieve this.

Keywords Therapeutic drug monitoring · Individualized dosing · Personalized medicine · Precision medicine · Oral targeted therapies

Introduction

Many new oral targeted therapies have become available in oncology over the past two decades. As a result, the treatment paradigm has partly shifted from a one-size-fits-all approach into precision medicine, in which the right drug is selected based on molecular characteristics of the tumor.

Dose finding of these new oral targeted therapies, however, has simply been copied from classical intravenous cytotoxic drugs. In traditional phase I dose escalation studies, which generally enroll only few patients (median sample size of 26 patients [1]), doses are increased until dose-limiting toxicities occur. This maximum tolerated dose (MTD), at which typically only 3–6 patients have been treated, is then used in all further studies, leading to a one-size-fits-all fixed dosing strategy [2]. However, pharmacokinetic characteristics of these new oral targeted therapies suggest individualized dosing would be far more rational.

Although one might think drug selection based on molecular diagnoses makes any further dose individualization superfluous, it seems logical to combine these two approaches to realize the full potential of personalized medicine (Fig. 1). Currently, all patients are treated at a standard fixed dose, resulting in low pharmacokinetic exposure and thus suboptimal treatment in a substantial proportion of patients. This subtherapeutic treatment is

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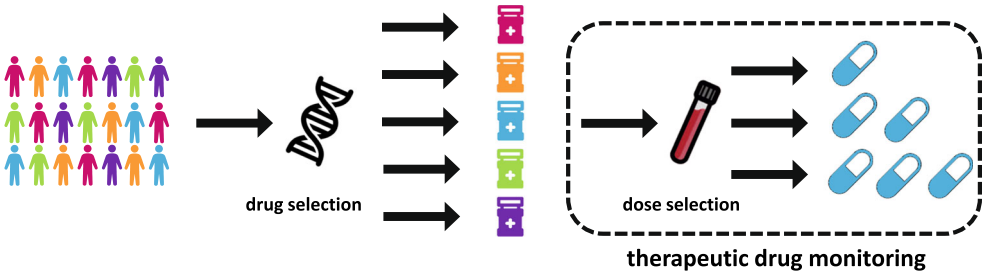


Fig. 1 Schematic overview of how precision medicine can be combined with dose individualization by therapeutic drug monitoring

senseless, especially with these expensive drugs. Therefore, we believe that the current fixed dosing paradigm should be left. Therapeutic drug monitoring (TDM), which is individualized dosing based on measured plasma concentrations of the drug, can be used to select the right dose for each individual patient. In case of pharmacokinetic exposure below the predefined efficacy threshold and acceptable toxicities, pharmacokinetically guided interventions will be performed. These could include absolute dose increments or alternative interventions to increase pharmacokinetic exposure (i.e., concomitant intake with food in case of a clinically relevant food effect [3] or splitting intake moments in case of saturable absorption [4]). Although TDM is widely applied in clinical practice for many drug classes, such as antibiotics, anticonvulsants, and immunosuppressants, it is still being very limitedly applied in oncology.

Previous reviews have summarized the literature for TDM of individual oral anticancer drugs [5–9]. In this review, we will address the scientific evidence for dose individualization by TDM of oral targeted therapies in general. Table 1 provides an overview of approved oral targeted therapies in oncology.

Criteria for rational use of therapeutic drug monitoring

For drugs to be suitable candidates for TDM, the following requirements have previously been proposed [10–14]:

1. absence of an easily measurable biomarker for drug effect;
2. long-term therapy;
3. availability of a validated sensitive bioanalytical method;
4. significant variability in pharmacokinetic exposure;
5. narrow therapeutic range;
6. defined and consistent exposure-response relationships;
7. feasible dose-adaptation strategies.

In the following paragraphs, each of these requirements will be discussed and it will be assessed whether they are met in the case of oral targeted therapies in oncology.

1. Absence of an easily measurable biomarker for drug effect

If more convenient, accurate, and precocious biomarkers for drug response would be available, these would make TDM superfluous. However, while toxicity can easily be measured, for efficacy, these biomarkers are generally not available (yet) and response evaluations with regard to antitumor efficacy are often based on radiological assessments, which are not performed timely enough to be a good biomarker. Imaging is usually performed every 8 to 12 weeks, while ideally dose adjustments should be made at an early stage (i.e., within 14 days). Also, once tumor progression is observed on radiological scans, resistant clones of tumor cells have already emerged and dose adjustments will probably be too late at this moment. Although for some tumor types blood-based tumor markers exist (e.g., cancer antigen 125 in ovarian cancer or carcinoembryonic antigen in colorectal cancer), these are not accurate enough to predict treatment response and to base treatment decisions upon [15]. The same holds true for other potential biomarkers available for oral targeted therapies including diastolic blood pressure for axitinib and skin rash for epidermal growth factor receptor inhibitors such as erlotinib and gefitinib [16–18]. Complete cytogenetic response in case of hematologic malignancies and prostate-specific antigen (PSA) in the case of prostate cancer are the only examples of biomarkers that can accurately predict response to treatment and that are used in clinical practice for this purpose [19, 20]. Apart from these exceptions, the first requirement for TDM is met for most combinations of targeted therapies and tumor types.

2. Long-term therapy

Treatment should be long enough to allow sufficient time for dose adjustments to be made. As the mean treatment duration of targeted therapies is several months, while only few days to weeks are needed to reach steady-state concentrations, there is sufficient time to perform TDM. The time to steady-state concentrations depends on the elimination half-life ($t_{1/2}$) of a drug, which is typically around 20–30 hours for most oral anticancer drugs, although for some compounds, this is markedly longer (e.g., enzalutamide (± 6 days [21]) and endoxifen, which is the

Table 1 Overview of oral targeted therapies in oncology (2019)

Group	Drugs
ALK inhibitors	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
Anti-hormonal drugs	Abiraterone, anastrozole, apalutamide, enzalutamide, exemestane, letrozole, tamoxifen
Bcr-Abl inhibitors	Bosutinib, dasatinib, imatinib, nilotinib, ponatinib
BRAF inhibitors	Dabrafenib, encorafenib, vemurafenib
BTK inhibitors	Ibrutinib
CDK 4/6 inhibitors	Abemaciclib, palbociclib, ribociclib
EGFR inhibitors	Dacomitinib, erlotinib, gefitinib, osimertinib
EGFR/Her2 inhibitors	Afatinib, neratinib, lapatinib
FLT3 inhibitors	Gilteritinib, midostaurin
HDAC inhibitors	Panobinostat, vorinostat
JAK inhibitors	Ruxolitinib
MEK inhibitors	Binimetinib, cobimetinib, trametinib
mTOR inhibitors	Everolimus
NTRK inhibitors	Larotrectinib
PARP inhibitors	Olaparib, niraparib, rucaparib, talazoparib
PI3K inhibitors	Copanlisib, duvelisib, idelalisib
VEGFR inhibitors	Axitinib, cabozantinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, vandetanib

ALK, anaplastic lymphoma kinase; *Bcr-Abl*, breakpoint cluster region-Abelson fusion protein; *BRAF*, serine/threonine-protein kinase B-Raf; *BTK*, Bruton's tyrosine kinase; *CDK*, cyclin-dependent kinase; *EGFR*, epidermal growth factor receptor; *Her2*, human epidermal growth factor receptor 2; *FLT3*, FMS-like tyrosine kinase 3; *HDAC*, histone deacetylase; *JAK*, Janus-associated kinase; *MEK*, mitogen-activated protein kinase; *mTOR*, mammalian target of rapamycin; *NTRK*, neurotrophic tyrosine kinase; *PARP*, poly ADP ribose polymerase; *PI3K*, phosphoinositide 3 kinase; *VEGFR*, vascular endothelial growth factor receptor

active metabolite of tamoxifen (± 2 weeks [22])). After four to five times the $t_{1/2}$, steady-state concentrations have been attained.

3. Availability of a validated sensitive bioanalytical method

In order to perform dose individualization based on pharmacokinetic exposure, bioanalytical assays to measure plasma concentrations should be available. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is usually applied for quantification of these drugs and validated assays are available for almost all oral anticancer drugs at a reasonable price. Since LC-MS/MS is a labor-intensive method and many different targeted therapies will be used in routine clinical practice, combining multiple drugs into one bioanalytical assay might be useful [23–25]. To implement TDM into routine clinical practice, an adequate infrastructure for sample collection and shipment should be in place, with a short turn-over and reporting time. In addition, dried blood spot (DBS) sampling could offer a more patient friendly sampling approach, as patients can obtain their blood samples themselves at home instead of having to visit the hospital. Whole blood samples can be collected by a finger prick at a paper DBS card, which can then be send to the laboratory by regular mail. DBS assays are already available for several oral anticancer drugs [26–33]. Also, commercial automated immunoassays could facilitate measurement in routine clinical practice, for example of imatinib [34].

4. Significant variability in pharmacokinetic exposure

The fourth requirement for TDM comprises a marked variability in pharmacokinetic exposure. Otherwise, when pharmacokinetic exposure would be predictable and similar for all patients, there would be no need for dose individualization.

Oral targeted therapies typically exhibit a large interindividual variability in pharmacokinetic exposure in the range of 24–84%, providing a strong rationale for TDM [35–40]. Reasons for this high interindividual variability include differences in absorption, which could be influenced by the poor bioavailability of these drugs, potential food effects, or the use of drugs that alter the stomach pH (i.e., proton pump inhibitors and H_2 receptor antagonists); interactions with concomitant medication (e.g., via cytochrome P450 enzymes such as CYP3A4); pharmacogenetics (i.e., patients harboring polymorphisms of cytochrome P450 enzymes or ABC-

transporters); hepatic and renal function; body composition and patient adherence [2, 41].

While data on interindividual variability are widely available, reports on intra-individual variability are sparse [42]. Poor formulations of most oral targeted therapies result in a low bioavailability and thus a high inter- and intra-individual variability [43, 44]. The intra-individual variability should be judged taking into account the interindividual variability as well. For example, abiraterone has an intra-individual variability of 33%, while the interindividual variability is higher (i.e., 46%) [37]. The same holds true for vemurafenib, which has an intra- and interindividual variability of 28% and 41%, respectively [38]. Unfortunately, these data are not available for all oral targeted therapies. Therefore, Chatelut et al. advocate intra-individual variability should ultimately be characterized before registration of new drugs [42]. Although assessment of the intra-individual variability for registration purposes might be challenging, especially in the context of oncological patients with potentially fluctuating (patho-)physiological states, we do propose that efforts should be made to quantify the intra-individual variability.

It is important to take the source of variability into account when deciding on the interval of sampling. When the major source of variability is interindividual variability, a single measurement or rare measurements would be sufficient. When the main source of variability is intra-individual variability, it depends on the origin. If the origin of intra-individual variability is random from dose to dose (e.g., due to poor formulation), TDM might not be useful, as a single sample would then be of limited value. If the intra-individual variability is caused by an identifiable reason (e.g., concomitant medication or fluctuations in (patho-)physiological conditions), more frequent sampling might be needed. In this case, the sampling interval should be oriented at the change of the condition (e.g., new concomitant medication). Regardless of the source of variability, it is important to continue sampling throughout therapy, since many factors that can influence pharmacokinetic exposure may vary over time (e.g., drug-drug interactions and compliance).

To conclude, variability in pharmacokinetic exposure of oral targeted therapies is definitely sufficiently high to meet the requisite.

5. Narrow therapeutic range

When the window between therapeutic and toxic concentrations is small, dose titration is important to minimize the risk of either ineffective treatment or unnecessary toxicities. The fact that > 50% of the oral targeted therapies have a recommended dose equal to the maximum tolerated dose (MTD), indicates these drugs have a narrow therapeutic index [45]. An exception to this is drugs with a plateau in the exposure-response curve that are dosed at the flat end of this curve, as might be the case for cabozantinib and pazopanib [46, 47]. At the currently used fixed doses, ± 30% of patients are being under dosed (e.g., for abiraterone, imatinib, pazopanib, sunitinib, and vemurafenib), associated with decreased efficacy, while ± 15% of patients are being over dosed, causing unnecessary toxicities [35, 37, 38, 48–50]. These numbers illustrate the significant proportion of patients being treated outside the therapeutic window in the absence of dose titration.

6. Defined and consistent exposure-response relationships

TDM is only rational if defined and consistent exposure-response relationships have been demonstrated for both efficacy and toxicity. For this purpose, exposure can be interpreted as minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}), or area under the plasma concentration-time curve (AUC). Extensive reviews summarizing the available literature on exposure-response relationships for each specific oral targeted therapy have previously been published [5–9]. For many of these drugs, exposure-response relationships have been demonstrated and pharmacokinetic targets could be identified (e.g., imatinib, pazopanib, and sunitinib [51–54]). For other drugs, pharmacokinetic targets based on exposure-efficacy analyses are not well established yet (e.g., dabrafenib, lenvatinib, and palbociclib [5]), but based on their mechanism of action, exposure-response relationships are to be expected. In these cases, the mean or median exposure could be taken as a reference. In previous analyses, we have demonstrated that targets based on exposure-efficacy analyses amounted to 82% (± 17%) and 85% (± 19%) of the average exposure in the population for kinase inhibitors and oral anti-hormonal drugs, respectively [5–7]. Therefore, targeting the mean or median exposure generally leads to efficacious concentrations (as the real exposure-efficacy threshold is expected to be lower). The fact that the exposure-efficacy threshold is generally lower than the average exposure in the population is not a surprising finding, since the efficacy of these drugs has been proven in phase III trials indicating that the mean exposure should be sufficient to generate an antitumor response.

The magnitude of exposure-response relationships can be illustrated by pazopanib, for which a clear exposure-efficacy relationship exists, with progression-free survival (PFS) being significantly longer in patients with $C_{min} \geq 20.5$ mg/L (52.0 weeks versus 19.6 weeks [53]). The PFS of patients with an exposure below this target is even comparable with placebo (4.2 months) [55], making treatment at an inadequate pharmacokinetic exposure as ineffective as no treatment at all.

To overcome resistance, newer generation kinase inhibitors have been designed that block their target irreversibly (e.g., osimertinib, ibrutinib, and afatinib) [56–58]. It still has to be elucidated how this affects exposure-response relationships,

but based on their irreversible mechanism of action, it could be expected that these agents are relatively overdosed due to the MTD paradigm currently still used in dose finding studies. Since these drugs bind their target covalently, inhibition endures even after the drug has been cleared from the systemic circulation. Therefore, the efficacy threshold could be lower than the mean pharmacokinetic exposure at the recommended dose. So far, for none of these agents clear exposure-response relationships have been identified. For example, for osimertinib, a retrospective analysis of 780 subjects showed no association between exposure and response [59].

At the time new oral targeted therapies are approved, in most cases, insufficient data is available to draw conclusions on exposure-response relationships, while typically hundreds of patients have been treated with these drugs in the dose-finding and pivotal studies. However, data on pharmacokinetic exposure is often not structurally being collected in all patients. It is of great value to incorporate these pharmacokinetic analyses in the early stages of clinical development of these new drugs to ensure patients can be treated at a dose giving them adequate exposure.

Thus, for many oral targeted therapies defined and consistent exposure-response relationships exist, for others it can be reasonably expected while awaiting conclusive data, while for some exposure-response relationships might not be expected based on their irreversible mechanism of action and relatively high dose administered.

7. Feasible dose-adaptation strategy

For drugs to be suitable candidates for TDM, feasible dose-adaptation strategies should exist, leading to target attainment without additional toxicities. Prospective clinical studies have already shown TDM to be feasible for pazopanib [48, 49], sunitinib [48, 50], imatinib [48, 60], everolimus [61], and endoxifen [62]. Table 2 provides a summary of the results of these studies. In clinical practice, the dose-adaptation strategies used in these prospective studies could be applied (i.e., the same pharmacokinetic target and dose levels could be used). Also, algorithms describing dose-adaptation schedules for other oral targeted therapies have been published previously [6]. Figure 2 provides a schematic overview of pharmacokinetically guided dose individualization, in which pazopanib is used as an example. Patients start treatment at the standard fixed dose. At regular time intervals, pharmacokinetic sampling is performed (e.g., 4, 8, and 12 weeks after start of treatment, and every 12 weeks thereafter). In case of pharmacokinetic exposure below the predefined target and acceptable toxicities, the dosage can be increased with one dose level.

Dose-adaptation strategies should take into account the MTD of the drug, or—when the MTD has not been reached—the highest dose tested in phase I dose escalation trials, when deciding on the maximum dose level. Although it could be argued that pharmacokinetically guided dose escalation above the MTD could be safe as well (since this dose escalation will only be done in patients with a low pharmacokinetic exposure), this should only be considered with careful monitoring of side effects.

Pharmacokinetically guided interventions do not necessarily have to include absolute dose escalations, as for some oral targeted therapies, other options to increase pharmacokinetic exposure are available as well. For oral targeted therapies with a clinically significant food effect (e.g., abiraterone, lapatinib, and pazopanib), careful concomitant intake with food could be used as a first step in case of low pharmacokinetic exposure [3]. Besides, for drugs with a saturable absorption profile (e.g., pazopanib and everolimus), splitting intake moments could provide a cost-neutral solution to attain adequate pharmacokinetic exposure [4, 63].

Another important consideration is the fact that progressive disease is irreversible. Therefore, it is important to attain an adequate pharmacokinetic exposure in each individual patient as soon as possible. In addition, it could be argued that dose reductions should only be made in case of intolerable toxicities, and not solely based on pharmacokinetic exposure (i.e., patients with high pharmacokinetic exposure, but without any side effects). On this aspect, TDM in oncology differs significantly from other disciplines, where it is often aimed at preventing toxicities as well due to its small therapeutic window.

To summarize, the feasibility of dose-adaptation strategies has been prospectively studied for several oral targeted therapies [48–50, 60–62]. All of these studies have shown TDM to be feasible, at least for a subset of patients. For other oral targeted therapies, possible dose-adaptation strategies have been described in literature or could be set up taking into account the mentioned considerations, while awaiting additional prospective studies [6].

Discussion

In this concise review article, we discussed the conditions that should be fulfilled for oral targeted therapies in oncology to be suitable candidates for TDM. Apart from some exceptions (e.g., osimertinib or cabozantinib), for most oral targeted therapies all of these requirements are met, providing a strong rationale for TDM.

A practical advantage is that most oral anticancer drugs are administered at a once or twice daily basis, making the timing of sampling more convenient compared with intermittent dosing (e.g., classical chemotherapy or immunotherapy). TDM targets are generally based on trough concentrations (C_{min}). While ideally trough samples would be drawn, this is not always possible in routine clinical practice. In this case, samples could be drawn at a random time point and C_{min} can be

Table 2 Summary of results of prospective studies on the feasibility of TDM for oral targeted therapies in oncology

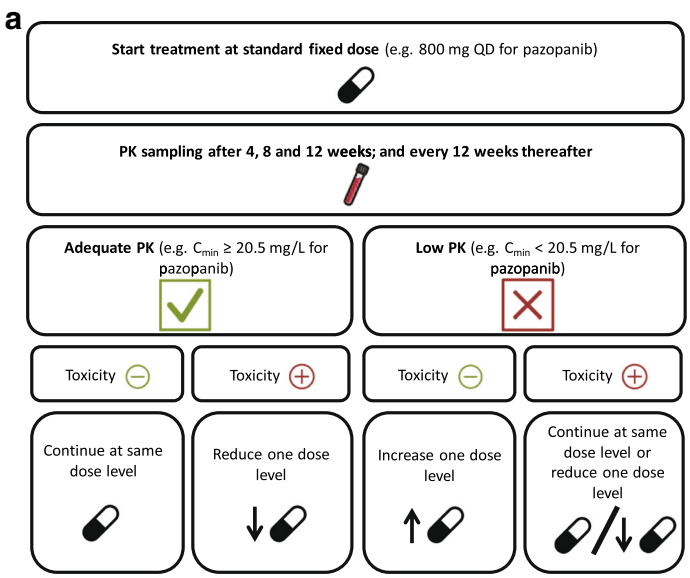
	Fox et al [62]	Lankheet et al [48]	Verheijen et al [49]	Lankheet et al [50]	Gotta et al [60]	Krueger et al [61]	De Wit et al [72]
Drug(s)	Endoxifen	Imatinib Sunitinib Pazopanib	Pazopanib	Sunitinib	Imatinib	Everolimus	Pazopanib
Evaluable patients (no.)	122	109	30	29	28	28	13
Inadequate PK exposure (no. (%))	78 (63%)	68 (62%)	17 (57%)	15 (52%)	17 (61%)	NR	1 (8%)
PK-guided intervention (no. (%))	68 (87%)	41 (60%)	10 (59%)	14 (93%)	NR	NR	1 (100%)
Successful PK-guided intervention (i.e., target attainment with acceptable toxicity) (no. (%))	65 (96%)	35 (85%)	7 (70%)	5 (36%)	NR	NR	NR

NR, not reported; *PK*, pharmacokinetic; *TDM*, therapeutic drug monitoring

estimated using several algorithms like the method proposed by Wang et al [64] or by Bayesian forecasting. In addition, a number of powerful pharmacokinetic computer tools are available for this purpose [65].

Even though convincing evidence supports dose individualization of oral targeted therapies, TDM is still being scarcely applied in daily clinical care. One of the reasons for this is that randomized controlled trials (RCTs), demonstrating the added value of TDM on clinical treatment outcomes, are lacking. However, it is highly unlikely that these RCTs could ever be performed. First, high numbers of patients would be needed, while most oral targeted therapies are indicated for rare tumor types or for a small subset of patients. For example, a randomized phase 3 study of TDM in patients with gastro-intestinal stromal tumors (GIST) treated with imatinib has been terminated prematurely due to slow accrual [66]. Second, it is difficult to secure (sufficient) funding for these types of studies. Furthermore, it is questionable whether it is ethical to fail to perform dose adjustments for some patients, when clear exposure-response relationships exist. Only a few RCTs of fixed dosing versus PK-guided dosing have ever been completed in oncology, all with chemotherapy [67–70].

Therefore, we are currently performing a large multi-center prospective study, in which we investigate the feasibility and efficacy of TDM for 23 different oral targeted therapies in more than 600 patients (www.trialregister.nl; NTR 6866 [71]). Patients starting regular treatment with one of these drugs can be included in this study. For each drug,



b

Dose level	Pazopanib dose
-3	200 mg QD
-2	400 mg QD
-1	600 mg QD
0	**800 mg QD**
+1	400 mg BID
+2	400 mg BID + food
+3	400 mg / 600 mg + food
+4	600 mg BID + food
+5	600 mg / 800 mg + food
+6	800 mg BID + food
+7	800 mg / 1000 mg + food
+8	1000 mg BID + food

Fig. 2 Schematic overview of PK-guided dose adaptation strategy for oral anticancer drugs. **a** Schematic overview of how therapeutic drug monitoring could be applied in clinical practice. **b** Example of proposed dose levels for pazopanib. BID, twice daily; PK, pharmacokinetics; QD, once daily

pharmacokinetic targets and dose levels have been defined and are described in the protocol. Pharmacokinetic sampling and dose adaptations are performed according to the strategy depicted in Fig. 2. Primary outcome is to halve the proportion of patients with pharmacokinetic exposure below the target after 12 weeks (compared with historical data). Secondary outcomes are the safety, feasibility, and efficacy of pharmacokinetically guided dosing and physician adherence to the tailored treatment recommendations. If this study underscores the results of previous retrospective studies and prospective feasibility studies, this will further support the implementation of pharmacokinetically guided dose optimization as the new standard [48–50, 60–62, 72].

As can be seen in Table 2, results of PK-guided dose individualization studies are currently not being reported in a uniform way, making mutual comparisons difficult. Therefore, we propose that future studies should at least report the following:

- Proportion of patients with low pharmacokinetic exposure;
- Proportion of patients in whom PK-guided interventions were applied;
  - Reasons why these were not applied in other patients (e.g., toxicity, physician adherence);
- Proportion of patients in which PK-guided interventions were successful, thus in which adequate PK-exposure was attained without intolerable toxicities.

In this way, study results could be compared more easily and potentially be combined in a meta-analytical approach.

It is essential to convince treating physicians of the importance of TDM, as they need to implement the treatment recommendations into clinical practice. Unwillingness of treating physicians to follow these treatment recommendations was the main reason that a previous randomized controlled trial could not demonstrate the benefit of TDM for imatinib [60].

Apart from the apparent advantages of TDM in optimizing pharmacokinetic exposure to improve treatment outcomes, TDM could serve several other purposes as well. First, it could play a role in detecting nonadherence to therapy. This is especially important in the case of long-term therapy, as compliance drastically decreases over time (e.g., for tamoxifen adherence was only 50% after 4 years of therapy [73]). Second, TDM could be helpful in the management of drug-drug interactions, since pharmacokinetic exposure to many oral targeted therapies is affected by concomitant use of CYP3A4 inhibitors/inducers or gastric acid-suppressive agents [74]. Last, measuring plasma drug concentrations could also support dose titration in patients with renal or hepatic impairment.

Conclusion

The pharmacokinetic characteristics of (most) oral targeted therapies in oncology support dose individualization by therapeutic drug monitoring. To realize the full potential of personalized medicine, we should not only treat each patient with the right drug, but also at the right dose.

Author's contributions Conception and design of this review were performed by SG, AH, and NS; SG wrote the manuscript; RM, JB, AH, and NS critically reviewed the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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