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Individualized dosing of tyrosine kinase inhibitors – are we there yet?

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ABSTRACT Tyrosine kinase inhibitors (TKIs) are registered at a fixed oral dose, despite their large variability in pharmacokinetics (PK). Given that the evidence for a relation between drug exposure and treatment outcome is growing, this one-dose-fits-all approach can unintentionally lead to under- and overexposure. Dose individualization could lower this variability and thereby beneficially effect treatment outcome. In this article, we explore whether TKIs used for solid tumors meet the criteria for dose individualization. Despite limitations such as retrospective analysis, current data suggest that the following C_{trough} levels could be used: imatinib 1100 ng/mL, sunitinib when continuously dosed 37.5 ng/mL, intermittent 50 ng/mL and pazopanib 20 µg/mL. A comprehensive review of the literature also shows that prospective trials investigating the influence of dose individualization on treatment outcome are warranted.

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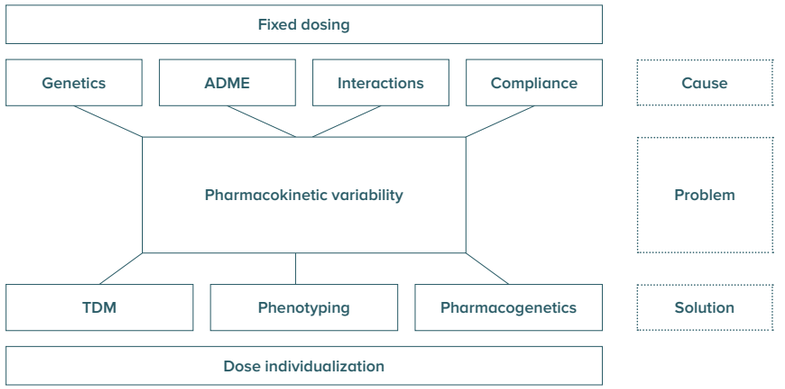
Introduction

With the increased understanding of cancer pathophysiology, tyrosine kinases have become important targets for anticancer drug design. Tyrosine kinases activate signal-transduction pathways that are crucial for growth, activation, differentiation, and death of cells [1]. Insights into dysregulation of these pathways in cancer led to the development of tyrosine kinase inhibitors (TKIs). With the introduction of TKIs, a new category of rationally designed targeted anticancer agents has emerged.

Fixed dosing is usually a good option for drugs with a broad therapeutic window, small inter-patient variability in exposure, and limited toxicity [2]. However, most TKIs show a large variability in their exposure (pharmacokinetics; PK) and treatment outcome (pharmacodynamics; PD). Different causes for variability in PK are summarized in Figure 1. In addition, the evidence for a relation between drug exposure and response for TKIs is growing fast [3-7]. Consequently, fixed dosing could potentially result in sub- or supratherapeutic exposure with decreased therapeutic effects in some patients or increased incidence and severity of toxicity in others.

Figure 1 Variability of tyrosine kinase inhibitor pharmacokinetics



Abbreviation: ADME, absorption, distribution, metabolism, and excretion.

Several studies have focused on reducing the inter-patient variability in exposure by dose individualization [8-11]. Some general criteria for dose individualization include: repeated administration, no easier assessable biomarkers to determine the response (e.g. blood pressure or rash), an available quantitative bioanalytical assay, and a validated dose-adaptation strategy. Dose proportional PK is helpful for the development of such strategies [12]. All these criteria are in general applicable to TKIs. However, the most important criteria that should be met to prove the added value of dose individualization are a narrow therapeutic window and a proven exposure-response relation [12]. A narrow therapeutic window is applicable for all anticancer agents, including TKIs. Moreover, it is important that variability in PK within patients (intra-patient) is small compared with the variability between patients (inter-patient) [12]. In this review, we evaluate whether TKIs used for the treatment of solid tumors meet the criteria necessary for dose individualization. We emphasize the evidence for exposure-response relations and the inter- and intra-patient variability in PK.

Search

A PubMed search was performed using different synonyms of the keywords 'pharmacokinetics' and 'variability', and the names of the individual TKIs registered by the European Medicines Agency (EMA) up until February 2014 (Table 1). In addition, reference lists were screened for other relevant studies and registration information from the EMA and U.S. Food and Drug Administration (FDA) was used. Results were limited to studies in humans and English full-text articles published until the 24th of February 2014. An overview of PK properties of the selected TKIs is shown in Table 2. Evidence for correlations between exposure-efficacy and exposure-toxicity is summarized in Tables 3 and 4, respectively. Table 5 describes the inter- and intra-patient variability in PK.

Axitinib

Correlation between exposure and efficacy

Recently, a study that used pooled data of 168 patients with metastatic renal cell carcinoma (mRCC) showed that patients with an area under curve $(AUC)_{0\text{-}24} \geq 300$ ng·hr/mL after 4 weeks of treatment had significantly ($P = 0.003$) longer progression-free survival (PFS) and significant ($P < 0.001$) longer overall survival (OS) compared with patients with an $AUC_{0\text{-}24} < 300$ ng·hr/mL [13]. Moreover, with every 100 ng·hr/mL increase in $AUC_{0\text{-}24}$, a 1.5-fold increase in probability of partial response (PR) was found ($P < 0.001$) [13]. In another study, 49 patients with mRCC were grouped into four quartiles based on their day 1, 1-2 hour post-dose axitinib levels. Patients in the third quartile ($C_{1\text{-}2}$ 45.4 - 56.4 ng/mL and $AUC_{0\text{-}12}$ 154-620 ng·hr/mL) showed the best 5-year clinical outcome with longer OS, PFS, and higher overall response rate (ORR) [14]. The better outcomes in the third quartile compared with the fourth quartile were explained by the higher incidence of grade ≥ 3 toxicities leading to early discontinuation and interruptions in the fourth quartile. Another pooled analysis found a median OS of 69 weeks for patients with an $AUC_{ss} \leq 605$ ng·hr/mL versus 88 weeks for patients with an $AUC_{ss} > 605$ ng·hr/mL, but this difference was not significant ($P > 0.05$)

[15]. However, this analysis did show that patients with diastolic blood pressure (dBP) ≥ 90 mmHg had longer OS compared with patients with dBP < 90 mmHg, which was also shown in other analyses [13,16-19].

A double-blind placebo-controlled randomized phase II study prospectively evaluated the effect of axitinib dose titration on treatment outcome in 203 patients with mRCC [20]. Patients started with axitinib 5 mg twice daily (BID) for 4 weeks. Patients with BP ≤ 150/90 mmHg, no grade 3/4 axitinib-related toxicities, no dose reductions, and ≤ 2 anti-hypertensive treatments, were randomized to receive axitinib 5 mg BID plus dose titration up to a total of 10 mg axitinib BID or dose titration with placebo. Patients not eligible for titration continued with axitinib ≤ 5 mg BID. Patients who were eligible for dose titration showed two times lower axitinib exposures compared with patients not eligible (AUC_{0-24} 176 versus 432 ng·hr/mL). Furthermore, the axitinib dose titration group showed significantly ($P = 0.019$) more objective responses compared with the placebo titration group. Patients not eligible for titration (those with initial higher initial axitinib exposure) had comparable objective responses to the axitinib dose titration group. This demonstrates a positive relation between axitinib exposure and response, although there was no difference in PFS or OS between the axitinib and placebo dose titration arm.

Correlation between exposure and toxicity

In the before-mentioned study, patients eligible for titration had over two times lower axitinib exposures compared with patients not eligible for dose titration because of dose-limiting toxicities (DLT), including hypertension, suggestive of a correlation between exposure and toxicity [20]. However, in a PK-PD analysis on axitinib-related BP increase, the correlation between exposure and dBP change was only weak (r^2 values < 0.10) [13,15]. Therefore, dBP could be useful as a predictive biomarker to optimize axitinib therapy. However, dBP is potentially also not merely a reflection of higher axitinib exposure. Therefore, the most adequate biomarker (drug exposure or BP) needs to be established. Thyroid-stimulating hormone changes have also been suggested as a biomarker of axitinib exposure [21,22]. The axitinib drug approval report from the FDA states that pooled exposure-safety analysis from three phase II trials and a pivotal phase III trial, showed a significant ($P < 0.001$) exposure dependent increase in hypertension, proteinuria, fatigue, and diarrhea [23]. However, an analysis of 128 patients with metastatic colorectal cancer (mCRC) did not find any correlation ($P > 0.05$) [18].

Inter- and intra-patient variability in exposure

Axitinib shows large inter-patient variability in PK with coefficients of variation (CV%) ranging from 17% to 94% for the AUC and 17% to 113% for the apparent oral clearance (CI/F) [21,22,24-26]. The intra-patient variability is modest, with CV% values for C_{trough} and CI/F of 20-22 CV% and for AUC of 20-33 CV% [25,27]. Population PK analysis found that age, ethnicity, and body weight could partly explain inter-patient variability, although effect

Table 1 Overview of indications and targets of TKIs for the treatment of solid tumors

TKI	Indication	Targets	REF
Axitinib	mRCC	VEGFR 1-3	[259]
Dabrafenib	melanoma	BRAF	[260]
Erlotinib	NSCLC, pancreatic cancer	EGFR	[261]
Gefitinib	NSCLC	EGFR	[262]
Imatinib	ALL, CEL, DFSP, CML, GIST, HES, MDS/MPD	Bcr-Abl, cKIT, PDGFRα,β	[263]
Lapatinib	HER2+ breast cancer	EGFR, HER2	[264]
Pazopanib	mRCC, STS	cKIT, PDGFRα,β, VEGFR 1-3	[163]
Regorafenib	CRC, GIST	BRAF, cKIT, PDGFRα,β, RAF, RET, TEK, VEGFR 1-3	[265]
Sorafenib	HCC, mRCC	cKIT, FLT3, PDGFRβ RAF-kinases, VEGFR 1-3	[266]
Sunitinib	GIST, mRCC, pNET	cKIT, CSFR, FLT3, PDGFRα,β, RET, VEGFR 1-3	[267]
Vandetanib	MTC	EGFR, RET, VEGFR 2	[268]
Vemurafenib	melanoma	BRAF	[269]

Abbreviations: ALL, acute lymphoblastic leukemia; Bcr-Abl, fusion protein; BRAF, B-rapidly accelerated fibrosarcoma oncoprotein; CEL, chronic eosinophilic leukemia; c-KIT, mast/stem cell growth factor receptor; CML, chronic myeloid leukemia; CRC, colorectal cancer; CSFR, colony stimulating factor receptor; DFSP, dermatofibrosarcoma protuberans; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER2+, human epidermal growth factor receptor mutation positive; HES, hypereosinophilic syndrome; MDS/MPD, myelodysplastic/myeloproliferative diseases; mRCC, metastatic renal cell carcinoma; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PDGFR, platelet derived growth factor receptor; pNET, pancreatic neuroendocrine tumor; RAF, receptor accessory factor; RET, rearranged during transfection; STS, soft tissue sarcoma; VEGFR, vascular endothelial growth factor receptor.

Table 2 Pharmacokinetic parameters of the TKIs

TKI	Dosage	Bioavailability	T_{max} (hr)	Protein binding	T½ (hr)	REF
Axitinib	5 mg BID	58%	2-6	99%	2-5	[21,24,27]
Dabrafenib	150 mg BID	95%	2	>99%	8	[29]
Erlotinib	100-150 mg QD	59%	3	95%	36	[51,270]
Gefitinib	250 mg QD	59%	3-7	90%	48	[271]
Imatinib	400-800 mg QD	98%	2-4	95%	18	[263]
Lapatinib	1000-1500 mg QD	N/A	3-4	99%	24	[272]
Pazopanib	800 mg QD	14-39%	2-4	98.8%	31	[163,273]
Regorafenib	160 mg QD: 3/1	N/A	3-4	>99%	20-40	[174]
Sorafenib	400 mg BID	N/A	3	>99%	25-48	[274]
Sunitinib	50 mg QD: 4/2, 37.5 mg QD	N/A	6-12	~95%	40-60	[267]
Vandetanib	300 mg QD	N/A	6	93%	480	[275]
Vemurafenib	960 mg BID	N/A	4	>99%	57	[255]

Abbreviations: 3/1, three weeks on therapy followed by 1 week off therapy; 4/2, four weeks on therapy followed by 2 weeks off therapy; BID, twice daily; N/A, not available; QD, once daily.

Table 3 Correlations between exposure and efficacy of TKIs

TKI	Tumor type	N	PK parameter	Outcome	Correlation	Significance	REF
Axitinib	mRCC	168	AUC_{0-24} ≥ versus < 300 ng·hr/mL	OS	37.4 versus 15.8 months	*P* < 0.001	[13]
			AUC_{0-24}	PFS	13.8 versus 7.4 months	*P* = 0.003	
				PR	1.5 fold increase in probability of a PR for every 100 ng·hr/mL increase in AUC_{0-24}	*P* < 0.001	
		49	C_{1-2}: 45.2-56.4 ng/mL AUC_{0-12}: 154-620 ng·hr/mL	OS	NR versus 20.3-27.7 months	N/A	[14]
				PFS	28.3 versus 7.5-11.8 months	N/A	
				ORR	81.8% versus 16.7-53.8%	N/A	
		109	AUC_{ss} ≥ versus < 605 ng·hr/mL	OS	88 versus 69 weeks	*P* > 0.05	[15]
		112	Dose titration versus no titration	ORR	54% versus 34%	*P* = 0.019	[20]
Erlotinib	NSCLC	56	C_{trough} C_{trough} ≥ versus < 4.6 nmol/mL	OR	5.22 versus 4.00 versus 3.44 nmol/mL for PR, SD and PD respectively	*P* > 0.05	[33]
				OS	HR: 1.424 (95%-CI: 0.677-2.996)	*P* = 0.351	
				PFS	HR: 1.765 (95%-CI: 0.852-3.657)	*P* = 0.127	
		16	Ratio C_{trough} D8/D2 > median versus < median	PFS	11.2 versus 5.6 months	*P* = 0.044	[34]
	HNSCC	18	C_{trough} C_{trough}	OS	OS was related to magnitude C_{trough} of OSI-420	*P* = 0.019	[35]
				TTP	TTP was related to magnitude C_{trough} of erlotinib and OSI-420	*P* = 0.042 and 0.036	
		42	C_{trough} OSI-420	OS	HR: 1.387 (95%-CI: 1.135-1.695)	*P* = 0.0014	[36]
		47	C_{5-10} erlotinib and OSI-420	OS	HR: 1.054 (95%-CI: 1.008-1.103) and 1.422 (95%-CI: 1.166-1.735)	*P* = 0.021 *P* = 0.0005	
Gefitinib	NSCLC	44	Ratio C_{trough} D8/D3 < versus ≥ 1.587	PFS	HR: 0.452 (95%-CI: 0.237-0.862)	*P* = 0.0158	[74]
		30	C_{trough} ≥ versus < 200 ng/mL	OS	14.6 versus 4.7 months	*P* = 0.007	[75]
	HNSCC	20	C_{trough}	Response	1,117 versus 520 ng/mL for patients with PR + SD versus PD	*P* = 0.0103	[76]
Imatinib	GIST	73	C_{trough} ≥ versus < 1,110 ng/mL	TTP	> 30 versus 11.3 months	*P* = 0.0029	[4]
	GIST KIT exon 11	39	C_{trough} ≥ versus < 1,110 ng/mL	OOBR	100% versus 67%	*P* = 0.001	
	GIST	38	AUC_{0-24} unbound	CR + PR	2.6 fold increase in probability of CR+PR for every doubling of unbound AUC_{0-24}	*P* = 0.026	[102]
Pazopanib	mRCC	10	C_{trough} ≥ versus < 15 µg/mL	PR + SD	83% versus 0%	N/A	[163]
	NPC	19	AUC_{0-24}	reduction v2	ΔT v2 decreased linear with AUC_{0-24} (r = 0.54)	*P* = 0.021	[164]
	HCC	17	C_{trough} > 20 µg/mL	decrease K_{trans}	Δ K_{trans} decreased most with C_{trough} > 20 µg/mL	N/A	[165]
	mRCC	205	C_{trough} > versus ≤ 20.6 µg/mL	PFS	49.4 versus 20.3 weeks	*P* = 0.0041	[7]
				RR	45% versus 18%	*P* < 0.0001	
				tumor shrinkage	37.8% versus 8.8%	*P* < 0.0001	
Sorafenib	melanoma	27	AUC_{max} ≥ versus < 100 µg·hr/mL	tumor control	86% versus 50%	*P* = 0.04	[177]
				PR+SD	80% versus 33%	*P* = 0.02	
				PFS	21 versus 10 weeks	*P* = 0.005	
	HCC	36	C_{max} ≥ versus < 4.78 µg/mL	OS	12.0 versus 6.5 months	*P* = 0.0824	[178]
Sunitinib	mRCC	146	AUC_{0-24} ≥ versus < 800 ng·hr/mL	TTP	TTP increased with increasing AUC_{0-24}	*P* = 0.001	[5]
				OS	OS increased with increasing AUC_{0-24}	*P* = 0.010	
				ORR	ORR increased with increasing AUC_{0-24}	*P* < 0.001	
				SD	SD increased with increasing AUC_{0-24}	*P* = 0.002	
	GIST	278	AUC_{0-24} ≥ versus < 600 ng·hr/mL	TTP	TTP increased with increasing AUC_{0-24}	*P* = 0.001	[5]
				OS	OS increased with increasing AUC_{0-24}	*P* = 0.001	
				ORR	ORR increased with increasing AUC_{0-24}	*P* = 0.06	
				SD	SD increased with increasing AUC_{0-24}	*P* < 0.001	
	solid		C_{trough} 50-100 ng/mL	target inhibition	a C_{trough} 50-100 ng/mL is the minimum plasma concentration required to inhibit Flk-1/KDR and PDGFRβ	N/A	[215]
Vemurafenib	N/A	N/A	C_{trough}	PFS	HR: 0.653 (95%-CI: 0.503-0.848)	*P* = 0.0014	[255]
	melanoma	403	Low, medium and high AUC_{0-12}	tumor growth	22% versus 11% versus 9% respectively	N/A	[256]

Abbreviations: AUC, area under the concentration-time curve; C_{1-2}, concentration 1-2 hours post-dose; C_{5-10}, concentration 5-10 hours post-dose; CR, complete response; dBP, diastolic blood pressure; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; K_{trans}, volume transfer coefficient: an indicator of vascular response; PFS, progression free survival; mRCC, metastatic renal cell carcinoma; mRCC, metastatic renal cell carcinoma; N/A, not available; NPC, nasopharyngeal carcinoma; NR, not reached; NSCLC, non-small cell lung carcinoma; OR, objective response; ORR, objective response rate; OS, overall survival; OSI-420, active metabolite erlotinib; OOBR, overall objective benefit rate (complete response + partial response + stable disease); PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease; TTP, time to progression; V, varying.

sizes were small, making dose adjustment based on these covariates unnecessary [13,28].

Dose individualization
The above-mentioned individualization study shows that titration based on toxicity facilitates optimization of plasma exposure and is associated with a greater proportion of patients with mRCC achieving a response. Therefore, toxicity-driven dose adjustment is beneficial to optimize and individualize axitinib therapy [20].

Conclusion
Axitinib has substantional inter-patient, with relatively modest intra-patient PK variability. Several studies showed a clear exposure-response relation and BP also seems a potential biomarker to select patients in need of dose adjustment. Surprisingly, conflicting data are presented on the correlation between exposure and BP. Therefore, the most adequate biomarker (drug exposure or BP) needs to be established. However, the current available data from the axitinib dose titration trial provide evidence for a toxicity-driven individualized axitinib dosing approach.

Dabrafenib
Correlation between exposure and efficacy and toxicity
There are currently no data that explore the relation between dabrafenib exposure and efficacy or toxicity.

Inter- and intra-patient variability in exposure
The inter-patient variability in PK is large, with CV% for AUC, C_{trough}, and Cl/F of 38-68%, 119% and 58%, respectively [29,30]. Weight, age, and gender were not considered clinically relevant in explaining the large inter-patient variability [29,31,32]. No data on intra-patient variability are available.

Dose individualization
There are currently no studies investigating dose individualization strategies for dabrafenib.

Conclusion
Dabrafenib shows high inter-patient variability in exposure. However, data regarding the intra-patient variability are lacking and, most importantly, there are no proven correlations between drug exposure and response. These main prerequisites need to be met before dose individualization of dabrafenib can be considered.

Erlotinib
Correlation between exposure and efficacy
A study in 56 patients with stage IV non-small cell lung cancer (NSCLC) showed that C_{trough} levels after 7 days of therapy were 5.22 nmol/mL in patients with PR, 4.00 nmol/mL in patients with stable disease (SD), and 3.44 nmol/mL in patients with progressive disease (PD), although, statistically, this was not significantly different ($P > 0.05$) [33]. In addition, the cut-off value of 4.6 nmol/mL for C_{trough} associated with skin toxicity (patients with skin toxicity had better treatment outcome) could not predict OS ($P = 0.351$) and PFS ($P = 0.127$) [33]. In another phase II study in 19 patients with NSCLC, C_{trough} levels were measured on day 2 and 8 of treatment [34]. The C_{trough} day 8:C_{trough} day 2 ratio represented the accumulation of erlotinib over time. A larger ratio was considered to reflect low metabolism and thereby higher erlotinib exposure. In this analysis, a higher ratio was associated with longer PFS ($P = 0.004$). However, an effect of this ratio on OS could not be shown. Although erlotinib is not registered for the treatment of head and neck squamous cell cancer (HNSCC), two studies showed a correlation in this patient population. In a phase II study in 18 patients with HNSCC, time to progression (TTP) was related to C_{trough} levels of erlotinib ($P = 0.042$) and its active metabolite OSI-420 ($P = 0.036$) [35]. A correlation with OS was only found for OSI-420 C_{trough} levels ($P = 0.019$). Another study in patients with HNSCC evaluated three sampling windows; C_{trough} window (20-25 hours post-dose, n = 42), C_{max} window (2-5 hours post-dose, n = 77) or $C_{5\text{-}10}$ (5-10 hours post-dose, n = 47]. The median $C_{5\text{-}10}$ of both erlotinib and OSI-420 ($P = 0.021$ and $P = 0.0005$), as well as C_{trough} of OSI-420 ($P = 0.0014$) predicted improved OS [36].

Correlation between exposure and toxicity
Besides the correlation between erlotinib exposure and efficacy, several studies have reported on associations between the occurrence and severity of rash and clinical outcome. In a phase II study in 57 patients with NSCLC, the median OS for patients with ≥ grade 2 rash was 19.6 months versus 8.5 for grade 1 rash, and 1.5 months for patients without rash [37]. Comparable results were shown in other trials [33,35,36,38-45]. Surprisingly, in the studies that showed correlations between PK and treatment outcome and/or toxicity and treatment outcome, PK parameters were not always related to toxicity [33-36]. This indicates that skin toxicity is not merely a reflection of high erlotinib exposure. The largest analysis performed to determine the correlation between exposure and toxicity is that of the pivotal BR.21 trial in 339 patients with NSCLC. In this analysis, a correlation between $AUC_{0\text{-}24}$ and C_{max} and rash was demonstrated. However, because of a large overlap in PK parameters between patients with and without toxicity, the correlation was considered not relevant [46]. Several smaller analyses have also shown correlations between

TKI	Tumor type	N	PK parameter	Outcome	Correlation	Significance	REF
Axitinib	mRCC	73	AUC_{0-24}	hypertension, grade 3-4 toxicity, dose reductions and ≤ 2 AH-treatments	432 versus 176 ng·hr/mL for patients with and without toxicity	N/A	[20]
	solid	10	AUC_{0-12}	ΔTSH level	ΔTSH increased linear with AUC_{0-12} (r = 0.72 and r = 0.80)	*P* = 0.018 *P* = 0.005	[21,22]
	mRCC	233	AUC_{0-24}	hypertension, proteinuria, fatigue and diarrhea	probability for toxicities was AUC_{0-24} dependent	*P* < 0.001	[23]
	mCRC	128	AUC_{ss}	diarrhea, fatigue and hypertension	no correlation	*P* > 0.05	[18]
Erlotinib	NSCLC	339	AUC_{0-24} and C_{max}	rash	severity of rash increased with AUC_{0-24} and C_{max} (r = 0.14 and r = 0.13)	*P* = 0.01 *P* = 0.02	[46]
		84	C_{trough}	grade 3-4 toxicities	incidence of grade 3/4 toxicities increased with C_{trough}	*P* = 0.007	[45]
			C_{trough} ≥ versus < 1.21 µg/mL	grade ≥ 2 rash	OR: 2.83 (95%-CI: 1.10-7.29)	*P* = 0.031	
				grade ≥ 2 diarrhea	OR: 3.79 (95%-CI: 1.09-13.2)	*P* = 0.037	
			C_{trough}	ILD	~1000 versus ~3300 ng/mL for patients with and without ILD	*P* = 0.014	
		28	AUC_{0-24}	rash	54.2 and 59.1 vs 36.2 µg·hr/mL for patients with grade 2 and 3 or grade 1 rash	*P* = 0.046	[47]
			C_{max}	rash	1.99 and 1.86 vs 1.29 µg/mL for patients with grade 2 and 3 or grade 1 rash	*P* = 0.044	
	brain	46	AUC_{0-24}	skin toxicity	severity of skin toxicity increased with AUC_{0-24} probability for skin toxicity was AUC_{0-24} dependent	*P* = 0.06 N/A	[48]
	HNSCC	42	AUC_{0-24}	skin toxicity	severity of skin toxicity increased with AUC_{0-24} probability for skin toxicity was AUC_{0-24} dependent	*P* = 0.014 N/A	[49]
	NSCLC, HNSCC and ovarian	80	AUC_{0-24}	grade ≥ 2 rash	1.18 fold increase in probability of grade ≥ 2 rash for every 10 µg·hr/mL increase in AUC_{0-24}	*P* = 0.082	[50]
			C_{trough}	grade ≥ 2 rash	1.75-fold increase in probability of grade ≥ 2 rash for every 1 µg/mL increase in C_{trough}	*P* = 0.040	
	solid	40	AUC_{0-24}	skin toxicity	18 versus 11.8 µg·hr/mL for patients with and without skin toxicity	*P* = 0.02	[51]
Gefitinib	NSCLC	30	C_{trough} ≥ versus < 200 ng/mL	incidence skin toxicity	85.7% versus 42.9%	*P* = 0.043	[75]
	solid	27	C_{trough}	≥ grade 1 diarrhea	probability for ≥ grade 1 diarrhea was C_{trough} dependent	*P* < 0.05	[80]
Imatinib	GIST	38	AUC_{0-24}	toxicity	2.2 fold increase in probability of toxicity for every doubling of the AUC_{0-24}	*P* < 0.001	[102]
	GIST	30	AUC_{0-24} unbound	% decrease in ANC	Δ ANC decreased linear with AUC_{0-24} (r = 0.56)	*P* < 0.001	[103]
	CML	351	C_{trough} > 1,170 versus < 647 ng/mL	fluid retention, rash, myalgia and anemia	76% versus 53%, 51% versus 32%, 30% versus 20% and 20% versus 8% respectively	N/A	[3]
	CML	240	C_{trough} > 3180 ng/mL	grade 3-4 neutropenia, rash, diarrhea, myalgia and edema	32% versus 17%, 35% vs 12%, 35% versus 17%, 27% versus 17% and 22% versus 5% respectively	N/A	[104]
Pazopanib	solid	54	C_{trough} ≥ versus < 15 µg/mL	hypertension	77% versus 39%	N/A	[163]
	solid	31	AUC_{0-24}	DLT	896 versus 367 µg·h/mL for patients with and without DLT	*P* = 0.039	[167]
					incidence of DLT increased linear with AUC_{0-24} (r = 0.595)	*P* = 0.001	
			C_{trough}	DLT	38.8 versus 29.6 µg/mL for patients with and without DLT	*P* = 0.040	
			C_{trough}	grade 2-3 hypertension	43.7 versus 29.4 µg/mL for patients with grade 2/3 hypertension and normotensive patients	*P* = 0.004	
		22	AUC_{0-72}	sBP	magnitude and duration of elevation in sBP greater for patients with AUC_{0-72} of 1,840 versus 786 µg·h/mL	N/A	[168]
	mRCC	205	C_{trough} 12.6-46 µg/mL	diarrhoea, hair colour change, ALT increase, HFS and stomatitis	≥ 2 fold increase in incidence of toxicities with increase of C_{trough}	N/A	[6]
			C_{trough}	HFS	occurrence and severity increased with C_{trough}	*P* < 0.001	[169]
Sorafenib	solid	72	AUC_{0-12}	grade 3-4 toxicities	61.9 versus 53 µg·hr/mL for patients with and without grade 3-4 toxicities	*P* = 0.017	[179]

Table 4 [Continued]

TKI	Tumor type	N	PK parameter	Outcome	Correlation	Significance	REF
Sorafenib			AUC_{0-12}	HFSR	high AUC_{0-12} was associated with the occurrence of HFSR	$P = 0.03$	
	melanoma	27	AUC_{0-12}	≥ grade 2 hypertension	82 versus 54 µg·hr/mL for patients with and without hypertension	$P = 0.02$	[177]
				HFSR	76 versus 61 µg·hr/mL for patients with and without HFSR	$P = 0.0008$	
	solid		AUC_{cum}	≥ grade 3 toxicity	OR: 1.07 (95%-CI: 1.01-1.12)	$P = 0.037$	[180]
	RCC and HCC	52	C_{trough}	≥ grade 2 HFS	C_{trough} lower for patients with grade 0-1 HFS versus patients with ≥ grade 2 HFS	$P = 0.0045$	[178]
				≥ grade 2 hypertension	C_{trough} lower for patients with grade 0-1 hypertension versus patients with ≥ grade 2 hypertension	$P = 0.0453$	
	prostate and NSCLC	96	AUC_{0-12}	rash grade	severity of rash increased with AUC_{0-12}	$P = 0.02$	[181]
	HCC	17	AUC_{0-12}	DLT	106.4 versus 56.7 µg·hr/mL for patients with and without DLT	$P = 0.09$	[182]
	NSCLC	42	C_{trough} ≥ versus < median	grade 2-3 diarrhea	patients with C_{trough} > median were more likely to develop diarrhea	$P = 0.04$	[183]
	solid	22	C_{trough}	grade 3 toxicity	7.6 versus 4.4 µg/mL for patients with and without grade 3 toxicity	$P = 0.0083$	[184]
Sunitinib	solid	28	C_{trough} > 100 ng/mL	DLT	most patients with DLT had C_{trough} > 100 ng/mL	N/A	[216]
	mRCC	19	C_{trough} ≥ versus < 90 ng/mL	grade ≥ 2 thrombocytopenia	100% versus 55.6%	$P = 0.033$	[217]
				grade ≥ 2 hypertension	90% versus 22.2%	$P = 0.0055$	
	solid, GIST and mRCC	443	AUC_{0-24}	fatigue	positive correlation between AUC_{0-24} and incidence of fatigue	N/A	[5]
			AUC_{cum28}	ANC	Δ ANC decreased linear with AUC_{cum28} (r = -0.40)	N/A	
			C_{trough}	dBP	Δ dBP increased linear with C_{trough} (r = 0.29)	N/A	
	solid	24	C_{trough} ≥ versus < 180 ng/mL	QTc	15.4 versus 9.6 msec.	N/A	[218]
	pNET, GIST and mRCC	52	Cl/F	grade 3 toxicity	34.4 versus 41.4 L/hr for patients with and without grade 3 toxicity	$P = 0.025$	[219]
			C_{trough}	fatigue	positive correlation between C_{trough} and occurrence of fatigue	$P = 0.007$	
Vandetanib	MTC	223	C_{trough}	grade ≥ 2 diarrhea	positive correlation between C_{trough} and probability of diarrhea	$P = 0.025$	[244]
				grade ≥ 2 fatigue	positive correlation between C_{trough} and probability of fatigue	$P = 0.02$	
Vemurafenib	N/A	N/A	C_{trough}	SCC	positive correlation between C_{trough} and risk of SCC	$P < 0.0001$	[255]
	melanoma	132	C_{trough}	QTc-interval prolongation	positive correlation between C_{trough} QTc-interval prolongation	$P < 0.0001$	[256]

Abbreviations: AH, antihypertensive; ANC, absolute neutrophil count; AUCcum28, 28-day cumulative AUC; dBP, diastolic blood pressure; CML, chronic myeloid leukemia; DLT, dose limiting toxicities; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; HFS, hand-foot syndrome; HFSR, hand foot skin reactions; ILD, interstitial lung disease; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma; MTC, medullary thyroid cancer; N/A, not available; NSCLC, non-small cell lung carcinoma; p-NET, pancreatic neuroendocrine tumor; sBP, systolic blood pressure; SCC, squamous cell carcinomas; THS, thyroid stimulating hormone

AUC_{0-24}, C_{trough}, C_{max}, and grade 3/4 toxicities, skin toxicity, rash, and diarrhea in NSCLC, HNSCC, ovarian cancer, and brain tumors, as shown in Table 4 [45,47-50].

Inter- and intra-patient variability in exposure

The inter-patient variability in C_{trough}, AUC, and CI/F is 38-76%, 18-156%, and 10-129%, respectively [40,42,47,51-72]. The European Public Assessment Report (EPAR) of erlotinib reports an intra-patient AUC variability of 16-24 CV% measured in healthy volunteers.

Dose individualization

A phase II trial investigated the feasibility of toxicity-driven dosing to a maximal level of tolerable target rash (TR) that required symptomatic treatment with minocycline [73]. Only 21% of the patients who ultimately experienced a TR developed this under dose escalation, whereas most patients experienced the TR under the standard dose of 150 mg once daily (QD). In addition, no increase in anticancer activity was observed in the dose-escalated group.

Table 5 PK inter- and intra-patient variability of TKIs

TKI	Inter-patient variability (CV%)			Intra-patient variability (CV%)			
	C_{trough}	AUC_a	Cl/F (L/hr)	C_{trough}	AUC_a	Cl/F (L/hr)	Ref
Axitinib	N/A	17-113%	17-113%	20-22%	20-33%	20-22%	[21,22,24-26]
Dabrafenib	119%	59%	59%	N/A	N/A	N/A	[29,30]
Erlotinib	38-76%	10-129%	10-129%	N/A	16-24%	N/A	[40,42,47,51-72]
Gefitinib	14-166%	79-90%	79-90%	2-49%	14%	N/A	[75,77,78,81-98]
Imatinib	25-64%	17-88%	17-88%	15-27%	12%	N/A	[4,105-123]
Lapatinib	55-97%	48%	48%	N/A	30-36%	N/A	[147-162]
Pazopanib	11-90%	N/A	N/A	N/A	N/A	N/A	[158,163,165,167,168,170,171]
Regorafenib	57%	N/A	N/A	N/A	34%	N/A	[172,174-176]
Sorafenib	25-104%	13-80%	13-80%	N/A	31-47%	N/A	[92,177-180,184-210]
Sunitinib	34-59%	28-46%	28-46%	N/A	N/A	N/A	[209,216,220-236]
Vandetanib	20-56%	8-55%	8-55%	N/A	8%	N/A	[245-253]
Vemurafenib	N/A	32-54%	32-54%	N/A	N/A	N/A	[255-258]

Abbreviations: %CV, coefficient of variation; AUC, area under the concentration time curve; Cl/F, apparent oral clearance; C_{trough}, minimum plasma concentration level; N/A, not available. [a]AUC_∞ following a single dose or AUC over the dosing interval at steady state.

Conclusion

Erlotinib shows large inter-patient variability and, although based on limited data, the intra-patient variability appears small. Some studies have shown exposure-efficacy and exposure-toxicity relations. Rash is often suggested as a potential early biomarker to select patients in need for dose adjustment, although dosing to rash did not improve clinical activity. Furthermore, in studies that showed correlations between PK and treatment outcome and/or toxicity and treatment outcome, PK parameters were not always related to toxicity. In our opinion, it is unlikely that rash can be used to individualize erlotinib therapy because dosing to rash did not demonstrate improved treatment outcomes.

Gefitinib

Correlation between exposure and efficacy

Similar to erlotinib, a study in 44 patients with NSCLC measured C_{trough} levels [74]. A high C_{trough} day 8:C_{trough} day 3 ratio was associated with better PFS ($P = 0.0158$), although individual C_{trough} levels were not related to longer PFS. Furthermore, no correlation with OS was found. A prospective study in 30 patients with NSCLC showed that patients with high gefitinib exposure ($C_{trough} \geq 200$ ng/mL) had longer OS ($P = 0.007$) compared with patients with low exposure ($C_{trough} < 200$ ng/mL) [75]. Additionally, the patients with wild type epidermal growth factor receptor (EGFR) appeared to be more sensitive to higher exposure levels with longer survival (~2 months longer median OS) compared with the other patients. Finally, in a dose escalation to skin toxicity study with 20 patients with HNSCC, C_{trough} levels for patients with disease control (PR + SD) were higher compared with patients with PD (1117 versus 520 ng/mL, $P = 0.0103$) [76].

Correlation between exposure and toxicity

Different phase I studies explored a possible relation between gefitinib plasma concentrations and skin- and gastrointestinal toxicity [77-79]. Zhao et al. showed that patients with high gefitinib exposure ($C_{trough} \geq 200$ ng/mL) experienced more rash ($P = 0.043$) compared with patients with low exposure ($C_{trough} < 200$ ng/mL [75]. The incidence of gastrointestinal toxicity was not found to differ between the two groups [75]. However, in the population PK analysis of Li et al., gefitinib C_{trough} level was a significant predictor for the incidence of ≥ grade 1 diarrhea ($P < 0.05$) [80].

Inter- and intra-patient variability in exposure

Gefitinib shows large inter-patient variability in AUC (31-112%), Cl/F (79-90%) and C_{trough} (14-166%) [75,77,78,81-98]. The intra-patient variability for C_{trough} is 2-49% [77,91]. A phase I study designed to determine the intra-patient variability, showed a two-fold variability in AUC within subjects, whereas the variability between patients was 15-fold [85]. Population PK studies indicated that gender, age, bodyweight, ethnicity, or creatinine clearance cannot explain the large inter-patient variability [99].

Dose individualization

There are three dose individualization studies published for gefitinib; two phenotyping studies and one toxicity-driven dosing study [76,80,100].

Given that cytochrome P450, family 3, sub-family A (CYP3A) is the principal enzyme that metabolizes gefitinib, variability in its activity might be an explanation of PK variability. The first phenotyping study showed that midazolam oral clearance as a measure of CYP3A activity accounted for 37% of the inter-patient variability in gefitinib oral clearance [80]. Furthermore, midazolam clearance was strongly associated with both gefitinib clearance ($r^2 = 0.68$) and gefitinib C_{trough} ($r^2 = 0.58$). Therefore, midazolam could be used to identify those patients at risk for under- or overdosing, respectively. The second phenotyping study showed a borderline significant correlation between midazolam and gefitinib AUC [100]. In a dose escalation study in patients with HNSCC, the gefitinib dose was escalated from 500 to 750 mg in those patients without grade 2 skin toxicity [76]. In the preplanned analysis of patients with and without ≥ grade 2 skin toxicity, there was no difference observed in treatment benefit.

Conclusion

The intra-patient variability in gefitinib PK appears small compared with the large inter-patient variability. Further investigation to determine the exact correlation between gefitinib exposure and treatment benefit is required, because the two studies that showed a correlation were performed in small cohorts. Once this has been established and after prospective validation, dose individualization seems a reasonable option to improve treatment efficacy and prevent underdosing.

Imatinib

Correlation between exposure and efficacy

The most convincing evidence for a correlation in solid tumors comes from a retrospective analysis of a phase II trial including 73 patients with gastrointestinal stromal tumors (GIST). This analysis showed that patients with C_{trough} levels < 1100 ng/mL after 29 days of therapy, had shorter TTP (11.3 months) compared with patients with C_{trough} levels above this concentration (> 30 months, $P = 0.0029$) [4]. Patients with low exposure also showed a trend towards a lower overall objective benefit rate (OOBR; CR + PR + SD). These findings suggest that a minimal concentration of imatinib is necessary to achieve and maintain clinical response in patients with GIST. A prospective population PK study on imatinib C_{trough} levels observed a decrease in imatinib exposure of approximately 30% after 3 months of therapy [101]. Therefore, measuring levels should be time-point specific and repeated after 3 months of therapy. Widmer et al. similarly demonstrated the importance of sufficient drug exposure to achieve and maintain therapeutic responses with the use of PK-PD data from 38 patients with GIST [102]. However, this analysis suggested that it is unbound imatinib exposure, rather than total imatinib exposure, which is associated with response.

Correlation between exposure and toxicity

Widmer et al. also showed that the occurrence and number of adverse effects were associated with both imatinib total and free plasma concentrations ($P < 0.001$) in patients with GIST [102]. A phase III trial in patients with GIST showed that hematologic toxicity (% decrease in ANC and platelets) was also correlated with unbound imatinib $AUC_{0\text{-}24}$ at steady-state ($P < 0.001$) [103]. Larson et al. showed that the discontinuation rate of imatinib resulting from toxicity was higher in patients with high C_{trough} levels (> 1170 ng/mL) compared with patients with low C_{trough} levels (≤ 1170 ng/mL) [3]. Another study showed that high C_{trough} levels (Q4, C_{trough} > 3180 ng/mL) were associated with the frequency of all-grade and grade 3/4 neutropenia, anemia, and leukopenia observed within the first 3 months of therapy and, to a lesser extent, all-grade thrombocytopenia. For non-hematologic toxicities, C_{trough} levels were associated with the frequency of all-grade rash, edema, nausea, diarrhea, vomiting, arthralgia, myalgia, and extremity pain within the first 3 months of therapy [104].

Inter- and intra-patient variability in exposure

Imatinib shows large inter-patient variability in AUC (21-66%) and C_{trough} (25-64%) [4,105-121]. There are four studies that report both the intra- and inter-patient variability in C_{trough}; these ranged from 19% to 27% versus from 37% to 47%, respectively [117,119,121,122]. A fifth study showed an intra-patient variability in AUC of 12.4% versus 11.6% for the inter-patient variability [123]. In different population PK analysis, body weight, age, sex, disease diagnosis, plasma α1-acid glycoprotein, albumin, granulocyte count, white blood cells (WBC), hemoglobin (Hb), and major gastrectomy were found to explain a certain part of the inter-patient variability, but dose adjustment based on these covariates was not considered necessary [103,119,124-132].

Dose individualization

Although several retrospective studies are in support of dose individualization, the results of the first prospective trials assessing the influence on treatment outcome are awaited. There are ongoing trials aiming to establish the optimal use of therapeutic drug monitoring (TDM) for imatinib in chronic myeloid leukemia (CML; ISRCTN 31181395) and two studies to determine whether dose adjustments to reach a target exposure will improve treatment outcome in GIST patients (NCT01031628) and CML (NCT01827930). Meanwhile, several case reports underscore the value of dose individualization of imatinib [133-135].

Conclusion

We consider imatinib the TKI with currently the most evidence available to justify the measurement of C_{trough} levels. There is a clear correlation

between exposure and efficacy with C_{trough} levels > 1000-1100 ng/mL associated with better treatment outcome. Moreover, the intra-patient variability is small compared with the inter-patient variability. However, prospective trials investigating the influence of dose individualization on treatment outcome are awaited. Currently, TDM is already applied by some clinicians, although it is not part of routine clinical practice yet [136-143]. If measurement takes place, this should be time-point specific and repeated every 3 months because patients with GIST show a decrease in exposure over time [101].

Lapatinib

Correlation between exposure and efficacy

The only suggestion for a correlation comes from the first phase I trial in which most responders had a C_{trough} level within the 0.3-0.6 µg/mL range [144].

Correlation between exposure and toxicity

Another phase I study reported that the frequency and severity of rash seemed to be related to AUC_{0-24}, C_{max}, and C_{trough} rather than the dose [145]. The FDA approval report states that a relation between lapatinib concentrations and prolonged QTc-interval is possible, although convincing evidence is lacking [146].

Inter- and intra-patient variability in exposure

The CV% in AUC and C_{trough} ranged from 42% to 117% and 55% to 97%, respectively [147-159,145,160-162]. The only data considering intra-patient variability are reported in the EPAR and is estimated to be 30-36% for AUC_{0-24} [161]. Sex, weight, ethnicity, or age could not explain the inter-patient variability in PK [161].

Dose individualization

There are currently no studies considering individualization strategies for lapatinib.

Conclusion

In theory, lapatinib meets many of the criteria for dose individualization. Moreover, the inter-patient variability is relatively large compared with the intra-patient variability. However, evidence for a correlation between lapatinib exposure and treatment benefit or toxicity is lacking. Currently, there is insufficient evidence to support dose individualization of lapatinib.

Pazopanib

Correlation between exposure and efficacy

Several smaller studies with pazopanib have shown a threshold for efficacy of approximately 20 µg/mL [163-165]. The most convincing evidence for this threshold comes from a retrospective PK analysis of a phase II trial in 205 patients with mRCC [7,166]. Patients with a C_{trough} > 20.6 µg/mL after 4 weeks of pazopanib 800 mg QD, showed significantly longer PFS ($P = 0.0041$) [7]. In addition, the RR as well as the mean percentage tumor shrinkage was improved in patients with C_{trough} levels > 20.6 µg/mL ($P < 0.0001$) [7].

Correlation between exposure and toxicity

The first suggestion for a correlation between pazopanib exposure and toxicity comes from the same first phase I study [163]. Twenty out of 26 patients (77%) with C_{trough} levels ≥ 15 µg/mL on day 22 developed hypertension, whereas only 11 out of 28 patients (39%) with C_{trough} levels < 15 µg/mL did so [163]. In a phase I trial in children, patients with DLT had a significantly larger AUC_{0-24} and C_{trough} compared with those without (896 versus 367 µg·hr/mL, $P < 0.039$ and 38.8 versus 29.6 µg/mL, $P < 0.040$, respectively) [167]. Moreover, a significant relation between BP and C_{trough} was identified. In patients with drug-related grade 2 or 3 hypertension after a median of two cycles, mean C_{trough} was 43.7 µg/mL versus 29.4 µg/mL in normotensive patients ($P < 0.004$) [167].

In a food interaction study with pazopanib, the incidence of elevated systolic blood pressure (≥ 140 mmHg) was found to be similar in both fed and fasted conditions. However, the magnitude and duration of elevated BP were greater when the drug was administered with a meal, correlating with an increased AUC_{0-24} [168].

The most convincing evidence comes from analysis of the before mentioned 205 patients with mRCC included in a phase II trial [6,166]. This analysis showed that the incidence of different pazopanib-induced toxicities seemed to be concentration dependent; there was a more than twofold increase in the incidence of diarrhea, hair color change, ALT increase, hand-foot syndrome (HFS), and stomatitis when C_{trough} after 4 weeks of treatment increased from 12.6 to 46 µg/mL. Additionally, the occurrence and severity of HFS was also correlated with higher week 4 C_{trough} levels ($P < 0.001$) [169].

Inter- and intra-patient variability in exposure

Pazopanib shows large inter-patient variability in PK with values ranging from 11% to 67% for C_{trough} and from 19% to 76% for AUC [158,163,165,167, 168,170,171]. Data considering the intra-patient variability are lacking thus far. Our own unpublished results indicate that the intra-patient variability

is relatively large, possibly because of the large effect of food on the low and variable bio-availability of pazopanib.

Dose individualization
Different studies are currently investigating the feasibility of TDM for pazopanib. We investigated the feasibility of TDM to reach a target exposure within a predefined window. There is also a study designed to reach a target pazopanib C_{trough} 20 > µg/mL by TDM. Outcomes of these studies are awaited.

Conclusion
In our opinion, a C_{trough} level above 20 µg/mL should be targeted in clinical practice to prevent underdosing and unjustified discontinuation of pazopanib treatment. Given that our results show a relatively large intra-patient compared with inter-patient variability, measuring C_{trough} levels should be performed under standardized conditions to make interpretation possible. The described saturated absorption of pazopanib might be challenging for dose adjustment, although we hypothesize that dividing the daily dose or the administration with food might overcome this problem [163]. Given that pazopanib exposure has been correlated with hypertension, BP could be a potential valuable biomarker.

Regorafenib
Correlation between exposure and efficacy and toxicity
There are no data available that report on PK-PD relations. Both FDA and EMA approval reports state that this will be investigated post-marketing [172,173].

Inter- and intra-patient variability in exposure
The inter-patient variability in PK is relatively large, with CV% for AUC and C_{trough} of 43-88% and 57%, respectively [172,174-176]. The reported intra-patient variability in AUC is 34% [175]. No significant or clinically relevant influence of weight, age or gender, race, or bilirubin on PK parameters could be shown [173].

Dose individualization
There are no studies that investigate dose individualization strategies.

Conclusion
In theory, regorafenib meets many of the criteria for dose individualization. Moreover, the inter-patient variability is relatively large compared with the intra-patient variability, although its dose-limited absorption might be challenging [172-174]. However, most importantly, there are currently no data that show a correlation between regorafenib exposure and treatment benefit or toxicity. Therefore, there is currently insufficient evidence to support dose individualization of regorafenib therapy.

Sorafenib
Correlation between exposure and efficacy
Although sorafenib is not registered for this indication, the first PK-PD analysis was performed in 27 melanoma patients. Patients with high sorafenib exposure ($AUC_{ss} \geq 100$ µg·hr/mL) showed higher tumor control ($P = 0.04$), tumor response (PR and SD) ($P = 0.02$) and longer PFS ($P = 0.005$) [177]. Another analysis showed that patients with hepatocellular carcinoma (HCC) with high exposure ($C_{max} \geq 4.78$ µg/mL) had a trend ($P = 0.0824$) towards longer OS compared with patients below this threshold [178].

Correlation between exposure and toxicity
The first suggestion for a relation between sorafenib exposure and toxicity comes from a phase I trial and different later studies have also reported this observation [177-184]. In a retrospective analysis of 83 patients treated with sorafenib at a dose of 200-400 mg BID, patients with severe toxicity (grade 3-4 adverse events) had significantly higher sorafenib exposure than that observed in the remaining patients (61.9 versus 53 µg·hr/mL, $P = 0.017$) [179]. Additionally, a high AUC_{0-12} on day 30 of treatment was significantly ($P = 0.03$) associated with the occurrence of hand food skin reaction (HFSR).

In the aforementioned study, sorafenib median AUC_{0-12} after 1 month was greater in patients with grade ≥ 2 hypertension compared with those with normal BP (82 versus 54 µg·hr/mL, $P = 0.02$) and patients with grade ≥ 2 HFSR compared with those without HFSR (76 versus 61 µg·hr/mL, $P = 0.0008$). However, no correlations were observed for other toxicities, such as diarrhea, anorexia, allergic, and nonallergic skin rash [177]. Another analysis showed that increased AUC_{cum} was associated with any grade ≥ 3 toxicity ($P = 0.037$) [180]. The opposed AUC_{cum} threshold acquired by simulation that predicted a toxicity of grade ≥ 3 was 3161 µg·hr/mL.

A PK-PD analysis by Fukudo et al. showed that steady-state C_{trough} in patients with grade ≥ 2 HFSR ($P = 0.0045$) and hypertension ($P = 0.0453$) were larger than in patients with < grade 2 adverse events. The proposed C_{trough} threshold for grade ≥ 2 HFSR and grade ≥ 2 hypertension were estimated to be 5.78 µg/mL and 4.78 µg/mL, respectively [178]. Another study showed that the severity of rash increased ($P = 0.02$) with increasing AUC_{0-12} [181]. Additionally, Mir et al. showed that patients who experienced a DLT during the first 4 weeks of treatment had higher AUC_{0-12} (106.4 versus 56.7 µg·hr/mL, $P = 0.09$) [182].

Inter- and intra-patient variability in exposure
Sorafenib exhibits high variability in C_{trough} (25-104%), AUC (12-117%) and CI/F (13-80%) compared with modest intra-patient variability in AUC (31-47%) [92,177-180,184-210]. Gender is suggested to be a covariate of significant influence on sorafenib PK, whereas bodyweight could only explain a clinically non-relevant part of the inter-patient variability [180,211].

Dose individualization
There are no studies that investigated sorafenib dose individualization strategies.

Conclusion
It can be concluded that the inter-patient variability of sorafenib is relatively large compared with the intra-patient variability. The dose-limited absorption of this drug might be challenging for dose individualization [212]. Further research to determine the exact correlation between sorafenib exposure and treatment benefit is required. Similar to imatinib, it seems that sorafenib exposure decreases after 3-4 months of treatment [177-179,213]. This might have relevant clinical implications in patients with initial clinical benefit who develop subsequent progression. Dose escalation in these patients could be supported by measuring plasma concentration levels, although routine application of TDM for sorafenib is currently not justified.

Sunitinib
Correlation between exposure and efficacy
The most convincing evidence for a correlation between exposure and treatment response in humans comes from a PK-PD analysis by Houk et al. This analysis showed that patients with mRCC (n = 169), GIST (n = 401), or solid tumors (n = 69) and a sunitinib $AUC_{ss} \geq 800$, 600, and 700 ng·hr/mL, respectively, had longer TTP and better OS [5]. Extrapolation of these sunitinib AUCs would correspond with sunitinib + SU12661 C_{trough} levels of 36.4, 24.6, and 30.5 ng/mL respectively, which are close to the concentrations (50-100 ng/mL) found in preclinical in vivo research [214,215]. Additionally, there was a significant relation ($P < 0.001$) between exposure and the probability of a PR or CR in patients with mRCC. Finally, a relation between the probability of SD and sunitinib exposure was demonstrated for patients with mRCC ($P = 0.002$) and GIST ($P < 0.001$) [5]. Sunitinib is also continuously dosed as 37.5 mg QD in patients with pancreatic neuroendocrine tumors (pNET) and sometimes those with GIST. For this indication, it is reasonable to use a lower target for C_{trough} that corresponds with this lower dose. Given that sunitinib shows dose proportional PK, a realistic recommendation is a target sunitinib + SU12661 C_{trough} of > 37.5 ng/mL.

Correlation between exposure and toxicity
The first phase I trial in 28 patients treated with sunitinib showed that the occurrence of DLTs was associated with total sunitinib trough levels > 100 ng/mL [216]. In an explorative study in 19 patients with mRCC, those with high sunitinib exposure ($AUC_{0\text{-}24}$ > 2600 ng·hr/mL and C_{trough} > 90 ng/mL) experienced more grade ≥ 2 thrombocytopenia ($P = 0.033$) and hypertension ($P = 0.0055$) compared with patients with low sunitinib exposure [217]. The meta analysis by Houk et al. showed a positive relation between total AUC and the incidence of fatigue; a negative relation between absolute neutrophil count (ANC) and AUC_{cum} after 28 days; and a positive relation between total C_{trough} level and dBP changes [5]. A PK-PD analysis in 24 patients showed that changes in QTc interval correlated with sunitinib exposure AUC, and C_{trough} [218]. In a recently published phenotyping study, patients with any type of grade 3 toxicity had a significantly lower clearance of sunitinib than patients without grade 3 toxicities (34.4 versus 41.4 L/hr, $P = 0.025$) [219]. Additionally, total C_{trough} levels were positively correlated with the occurrence of fatigue ($P = 0.007$) [219].

Inter- and intra-patient variability in exposure
The reported inter-patient variability is large for C_{trough} (34-59%), AUC (13-49%) and CI/F (26-46%) [209,216,220-236]. Data on intra-patient variability are lacking. A population PK analysis showed that tumor type, race, gender, body weight, and Eastern Cooperative Oncology Group (ECOG) score could explain some of the inter-patient PK variability, although dose adjustment based on these covariates is not advised [237].

Dose individualization
Two phenotyping studies with midazolam have been conducted [214, 219]. The first study showed that midazolam exposure was highly correlated with both sunitinib and total sunitinib $AUC_{0\text{-}24}$, as well as with C_{trough} levels and that CYP3A4-activity explained a large proportion of the inter-patient variability in sunitinib PK [214]. The second phenotyping study found a significant, although weak correlation between the 1'OH-midazolam:midazolam ratio and sunitinib clearance [219].

Data considering TDM as an approach to individualize sunitinib therapy are limited to case reports and conference abstracts [238-242]. However, all reports show the feasibility of TDM as an approach to achieve optimal C_{trough} plasma concentrations.

Conclusion
In our opinion, sunitinib is, after imatinib, the TKI with the most evidence available to support dose individualization. There is an evident correlation between sunitinib exposure and efficacy as well as toxicity and the report-

ed inter-patient variability is large. In addition, different reports have shown the feasibility of TDM to achieve an optimal target sunitinib exposure. However, prospective trials assessing treatment outcome with dose individualization are warranted. Alternative biomarkers for dose individualization could be phenotyping CYP3A(4) activity, although this also needs prospective validation. Although it is not yet part of routine clinical practice, we believe that a drug level-based dose adjustment with a target C_{trough} level of > 50 ng/mL for intermittent dosing and > 37.5 ng/mL for continuous dosing is justified.

Vandetanib

Correlation between exposure and efficacy

In the phase III study in 226 patients with medullary thyroid cancer (MTC) treated with 300 mg vandetanib QD, no evidence was found for a correlation between C_{trough} levels at day 56 and PFS [243,244].

Correlation between exposure and toxicity

Significant relations were identified between exposure and diarrhea and fatigue, but not for hypertension and rash [274]. In addition, the QTc-interval prolongation was concentration dependent [244].

Inter- and intra-patient variability in exposure

The first phase I trial with vandetanib in solid tumors showed inter-patient variability in exposure of 44-99% [245]. Inter-patient variability in AUC has also been reported by other studies in both healthy subjects as well as in patients with different types of cancer, ranging from 8% to 59% [245-253]. Intra-subject variability in vandetanib exposure was found to be small; AUC of 8-10% and C_{max} of 11% [253]. The EPAR describes weight as a clinically non-relevant covariate. Race, gender, and age showed no effect on vandetanib PK [254].

Dose individualization

There are no studies investigating dose individualization strategies.

Conclusion

The intra-patient variability in vandetanib PK is small compared with the described inter-patient variability, although some reported inter-patient variability is also not large. Most importantly, evidence for an exposure-response relation is lacking and the evidence for a correlation with toxicity is marginal. Given that vandetanib is an EGFR inhibitor, rash might be a relevant early biomarker, although no correlations have yet been observed. There is currently insufficient evidence to support dose individualization of vandetanib therapy.

Vemurafenib

Correlation between exposure and efficacy

In a phase III study in patients with B-rapidly accelerated fibrosarcoma oncoprotein (BRAF) mutant melanoma, a statistically significant ($P = 0.0014$) relation between C_{trough} and PFS was shown [255]. The population PK-PD analysis reported in the EPAR showed that patients with low exposure had more increase in tumor size compared with the medium and high exposure group, suggestive of a correlation [256].

Correlation between exposure and toxicity

Analysis of the pivotal phase III trial also showed a relation between C_{trough} and the risk of developing squamous cell carcinomas ($P < 0.0001$) [255]. Exposure-QTc response analysis showed that vemurafenib prolonged the QTc interval in a concentration dependent manner ($P < 0.0001$). However, no major changes (i.e., >20 ms) in the mean QTc interval were detected and, therefore, the clinical relevance of this observation should be considered [256].

Inter- and intra-patient variability in exposure

The reported inter-patient variability in vemurafenib AUC ranged from 28% to 52% [255-258]. There are no data available considering the intra-patient variability. Covariates including baseline total bilirubin, AST and ALT, baseline creatinine clearance, age, gender, race, bodyweight, height, or body mass index had no influence on vemurafenib PK.

Dose individualization

There are no studies investigating dose individualization of vemurafenib.

Conclusion

In theory, vemurafenib meets many of the criteria for dose individualization. However, although the inter-patient variability is large, data considering the intra-patient variability are unreported. Moreover, there is only marginal evidence for a correlation between vemurafenib exposure and treatment benefit or toxicity. Therefore, there is currently insufficient evidence to support dose individualization of vemurafenib therapy.

Concluding remarks

Compared with conventional chemotherapy, TKIs are generally less toxic and have the advantage of oral administration. Although convenient to patients, oral administration might have the potential disadvantage of introducing variability in drug exposure between and within patients. Review of the literature shows that there is increasing evidence that treatment outcome of TKIs is related to their exposure. The current available

data suggest that a target C_{trough} level of > 1100 ng/mL, > 50 ng/mL, > 37.5 ng/mL, and > 20 µg/mL could be used for imatinib, sunitinib 50 mg 4/2, sunitinib 37.5 mg continuously, and pazopanib, respectively. For axitinib, dose adjustment should be toxicity driven.

An important limitation is that most exposure-response correlations are defined by retrospective analysis. Therefore, the effect of drug levels on treatment outcome is still lacking for most TKIs. In addition, studies are generally small, except those with axitinib, imatinib, pazopanib, and sunitinib. More attention should be paid to exposure-response relations during drug development, which would facilitate dose individualization and treatment optimization right after registration of a drug. Surprisingly, neither the time a drug is used nor the potential for dose individualization seems to be a predictor for the amount of data available on exposure-response relations. Most importantly, prospective studies investigating the clinical feasibility of dose individualization with treatment benefit as the primary outcome are awaited.

Nevertheless, monitoring C_{trough} levels of at least imatinib, sunitinib, and pazopanib might be indicated in clinical practice, for example in cases of extreme or unexpected toxicity, a lack of clinical benefit, suspected PK drug-drug interactions, in patients with a major gastrectomy or in suspected therapy nonadherence, to support clinical decision making. A difficulty for drug-level monitoring is the reported high, or sometimes unknown, intra-patient variability of some TKIs, which can depend on the individual physicochemical properties of the TKI (e.g. low oral bioavailability).

Challenges for dose individualization are the facilities required (e.g. equipment and trained personnel for the determination of TKI plasma concentrations). However, PK samples are readily transferable and there are multiple laboratories available that can measure the drug concentrations of TKIs. Another challenge encountered is that some exposure-efficacy/toxicity relations are based on AUCs, which are patient unfriendly and time consuming to measure. Effort should be made to determine surrogate PK markers (C_{trough} or limited sampling) that show a good correlation with the AUC to make TDM feasible for the clinical practice.

Obviously, drug exposure is not the sole determinant of clinical outcome in patients with cancer. PD factors and patient- or tumor-specific characteristics also contribute to the efficacy of TKIs [20]. For different reasons, such as unnecessary toxicity, treatment delay, de novo inefficacy but also costs, it is crucial to identify those patients who are most likely to respond to TKI therapy. After selecting the most effective drug for a specific tumor type, dose individualization could further help to optimize the individual treatment benefit-risk ratio, with the highest possible efficacy and the lowest possible toxicity of therapy.

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