REVIEW

Imatinib, sunitinib and pazopanib: From flat-fixed dosing towards a pharmacokinetically guided personalized dose

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Tyrosine kinase inhibitors (TKIs) are anti-cancer drugs that target tyrosine kinases, enzymes that are involved in multiple cellular processes. Currently, multiple oral TKIs have been introduced in the treatment of solid tumours, all administered in a fixed dose, although large interpatient pharmacokinetic (PK) variability is described. For imatinib, sunitinib and pazopanib exposure-treatment outcome (efficacy and toxicity) relationships have been established and therapeutic windows have been defined, therefore dose optimization based on the measured blood concentration, called therapeutic drug monitoring (TDM), can be valuable in increasing efficacy and reducing the toxicity of these drugs.

In this review, an overview of the current knowledge on TDM guided individualized dosing of imatinib, sunitinib and pazopanib for the treatment of solid tumours is presented. We summarize preclinical and clinical data that have defined thresholds for efficacy and toxicity. Furthermore, PK models and factors that influence the PK of these drugs which partly explain the interpatient PK variability are summarized. Finally, pharmacological interventions that have been performed to optimize plasma concentrations are described. Based on current literature, we advise which methods should be used to optimize exposure to imatinib, sunitinib and pazopanib.

KEYWORDS

anticancer drugs, pharmacodynamics, pharmacokinetics, therapeutic drug monitoring

1 | INTRODUCTION

Tyrosine kinases are the targets for anti-cancer drugs called tyrosine kinase inhibitors (TKIs).[1-3] Currently, multiple TKIs have been introduced in the treatment of solid tumours.[4] All TKIs are administered orally at a flat-fixed dose, although large interpatient pharmacokinetic (PK) variability is described.[5-8] Retrospective analyses demonstrated an exposure-treatment outcome (efficacy and toxicity) relationship for imatinib, pazopanib and sunitinib across tumour types.[9-13] More and more data show that a minimum target level of drug exposure should be achieved to gain optimal treatment benefit. Dose reductions during treatment are mainly driven by toxicity and relationships between exposure and toxicity have also been described. Upper limits have been defined above which toxicity is more frequently seen.[6,9,12] These thresholds for efficacy and toxicity have been defined either by constructing

The participating centres and members of the DPOG are listed in the appendix.

receiver operating characteristics curves or by evaluating the relation between quartile or decile drug trough levels and treatment outcome. It has been suggested that a more personalized dose should be used to address the issue of the large interpatient PK variability leading to more treatment benefit and preventing unnecessary toxicity.[14,15]

Dose optimization based on measured blood concentration is called therapeutic drug monitoring (TDM) and can be valuable for drugs with a small therapeutic window, an established exposure–response relationship and large interpatient PK variability, all applicable for TKIs.[16] TDM guided dosing is routinely used for anti-epileptics, antibiotics, immunosuppressive agents and within oncology for methotrexate (MTX), mitotane and busulfan,[17-21] but is less common for TKIs despite a similar level of available evidence that optimizing the dose will result in less toxicity or better efficacy.[22] For an increasing number of TKIs a target threshold has been defined and TDM based dosing seems promising.[23,24] For imatinib, sunitinib and pazopanib, TDM is even considered viable since studies have shown the feasibility of TDM to reach drug levels within the therapeutic window.[12,15,25-27] Despite increasing evidence, the routine use of TDM in patients treated with imatinib, pazopanib and sunitinib is still not embedded in patient care.

In this review we present an overview of the current knowledge on TDM guided individualized dosing of imatinib, sunitinib and pazopanib for the treatment of solid tumours. For this purpose, we summarize preclinical and clinical data that have defined thresholds for efficacy and toxicity. Furthermore, we describe factors that influence the PK of these drugs and factors identified by population PK model studies that possibly explain the interpatient PK variability. Finally, we present pharmacological interventions that have been performed to optimize concentrations of these three agents.

2 | METHODS

2.1 | Search strategy

We performed an electronic systematic search of the PubMed database to 18 July 2019 using predefined terms (including Medical Subject Headings (MeSH) terms). Papers were included if they were available in full text and English language. We only included papers that focused on imatinib, sunitinib or pazopanib in solid tumours and excluded papers that focused on imatinib in chronic myeloid leukaemia (CML). Our main focus was on clinical studies performed in humans. All titles and abstracts were screened. The references of key articles were additionally screened and relevant papers were included in this review. The search strategy and results are presented in the Supporting Information.

2.2 | Results

Performing the electronic search on PubMed resulted in a total of 454 papers, of which 82 papers were eligible for inclusion in this review.

Another 41 papers were selected by screening the references of the key articles.

2.3 | Defining the optimal clinical threshold

2.3.1 | Imatinib

Imatinib inhibits BCR-ABL, platelet-derived growth factor receptor (PDGFRα-β) and cytokine receptor (c-KIT).[28,29] It is approved for the treatment of CML and gastrointestinal stromal tumour (GIST).[30-32] As our review focuses on solid tumours we only discuss imatinib in GIST. The development of GIST is associated with several gain-of-function mutations in c-KIT and PDGFR.[33]

Preclinical thresholds for response
In vitro studies showed that the inhibition of PDGFR and c-KIT is concentration-dependent, requiring an imatinib concentration of 49.4-493.6 ng/mL.[34,35] The concentration of imatinib that produces 50% inhibition (IC_{50}) of both PDGFR and c-KIT is 49.4 ng/mL.[34,35] Complete inhibition of c-KIT was observed at a concentration of 493.6 ng/mL.[35] Since 36-70% of small cell lung cancer (SCLC) tumours express c-KIT, the effect of imatinib was investigated in human SCLC xenografts. Growth inhibition of 40-80% was observed.[36]

Clinical thresholds for response
Exposure–response relationship. Details of studies evaluating the exposure–response relationship in patients treated with imatinib are presented in Table 1. In patients with advanced or metastatic GIST, who were treated with imatinib 400 mg once-daily (OD), mean plasma trough level (C_{trough}) was higher in patients who responded to treatment. Response was defined either as longer time to progression (TTP) or as radiological response according to Response Evaluation Criteria In Solid Tumours (RECIST).[12,37] A target threshold of >1,100 ng/mL has been defined.[12,37,38] These results are similar to results previously found in patients with CML.[10,46,47] One study in 96 patients with GIST reported a lower threshold of 760 ng/mL.[39] However, they measured C_{trough} after ≥3 months of treatment and a 29.3% decrease in imatinib exposure in the first 3 months of treatment, which corresponds to the lower threshold defined in this study, was previously observed.[48]

Since patients receiving adjuvant imatinib after resection are treated with 400 mg OD as well and it targets the same tumour cells, it seems reasonable to maintain the same threshold of >1100 ng/mL in the adjuvant setting.

Some studies have demonstrated that a dose of 400 mg twice-daily (BID) was correlated with a longer progression-free survival (PFS) compared to 400 mg OD.[49-52] This applied in particular to patients with a *c-KIT exon 9* mutation, in whom reported outcome was worse compared to patients with a mutation in *exon 11*.[53-55] Although the evidence is limited, it is currently advised by the ESMO guidelines to treat patients with a *c-KIT exon 9* mutation at a dose of

TABLE 1 Exposure–response and exposure–toxicity relationships for imatinib, pazopanib and sunitinib

Drug	Tumour type	Threshold	Outcome measure	Relationship	P value	References
Imatinib	GIST	$C_{trough} \geq 1100$ ng/mL	TTP	Response → higher C_{trough} (1446 ng/mL vs 1155 ng/mL) Higher C_{trough} → longer TTP $C_{trough} \geq 1100$ ng/mL → better OOBR Higher C_{trough} in c-KIT exon 11 vs 9	0.25 0.0029 0.0001 0.15	[12]
	GIST and CML	-	Response Toxicity	Higher free imatinib → more response Higher total + free imatinib → higher incidence AEs	0.026	[37]
	GIST	-	Response	Response → higher C_{trough} (1271 ng/mL vs 920 ng/mL)	NS	[38]
	GIST	$C_{trough} \geq 760$ ng/mL	PFS	$C_{trough} \geq 760$ ng/mL → longer PFS (PFS not reached vs 56 months)	0.0256	[39]
	GIST	-	Toxicity	Higher free imatinib → higher incidence neutropenia	$P < 0.001$	[5]
Sunitinib	Various	$C_{trough} > 50$ ng/mL	Efficacy Toxicity	Patients with OR → received doses ≥50 mg OD Dose of 50 mg OD → C_{trough} 50-100 ng/mL Patients with DLT → $C_{trough} > 100$ ng/mL	...	[6]
	RCC + GIST	-	Efficacy Toxicity	RCC: Higher sunitinib level → longer TTP GIST: Higher sunitinib level → longer TTP RCC + GIST: higher sunitinib level → higher incidence AEs	0.001 0.001	[11]
	RCC	$C_{trough} < 100$ ng/mL	Toxicity	$C_{trough} \geq 100$ ng/mL → higher incidence toxicity (75% vs 23.1%)	...	[40]
	RCC		Toxicity	Patients who discontinue treatment → higher C_{trough}	...	[41]
	RCC		Toxicity	Higher sunitinib level → higher incidence AEs		[42]
Pazopanib	RCC	$C_{trough} > 20.5$ mg/L	PFS	$C_{trough} > 20.5$ mg/L → longer PFS (52.0 vs 19.6 weeks)	0.00378	[9]
		$C_{trough} > 46$ mg/L	Toxicity	$C_{trough} > 46$ mg/L → higher incidence AEs	...	[9,43]
	RCC and STS	$C_{trough} > 20$ mg/L	PFS	RCC: $C_{trough} > 20$ mg/L → longer PFS (34.1 vs 12.5 weeks) STS: $C_{trough} > 20$ mg/L → longer PFS (18.7 vs 8.8 weeks)	0.027 0.142	[13]
		-	Toxicity	Higher C_{trough} → more patients discontinue treatment	...	
	RCC	$C_{trough} > 20.5$ mg/L	Response	$C_{trough} < 20.5$ mg/L → no OR	...	[44]
		$C_{trough} < 50.3$ mg/L	Toxicity	Grade ≥ 3 toxicities → higher C_{trough} (69.3 mg/L vs 41.2 mg/L) $C_{trough} \geq 50.3$ mg/L → higher incidence toxicity (61.5% vs 7.1%)	$P < 0.05$	
	RCC	$C_{trough} > 20.5$ mg/L	DFS	$C_{trough} > 20.5$ mg/L → longer DFS	0.0078	[45]

AE, adverse event; CML, chronic myeloid leukaemia; C_{trough}, plasma trough level; DFS, disease-free survival; DLT, dose-limiting toxicity; GIST, gastrointestinal stromal tumour; NS, non significant; OD, once a day; OOBR, overall objective benefit rate (complete response + partial response + stable disease); OR, objective response; PFS, progression free survival; RCC, renal cell carcinoma; STS, soft tissue sarcoma; TTP, time to progression.

400 mg BID.[51,56] No data on plasma concentrations are available in c-KIT exon 9 mutated GIST treated with imatinib 400 mg BID. Taking into account the dose proportional relationship, a threshold of >2200 ng/mL for imatinib 400 mg BID could be considered.[57] Currently, there are no threshold recommendations for patients with a mutation in PDGFR or wild-type tumour genotype.

In the metabolism of imatinib, an active metabolite (N-desmethyl-imatinib, CGP74588) is formed with similar pharmacological activity that accounts for 16% of the area under the curve (AUC) of imatinib.[31,58] However, since the active metabolite represents a modest amount of the total exposure, studies that examined the exposure–response relationships have focused on imatinib alone.

Exposure–toxicity relationship. Higher exposure is associated with increased toxicity (Table 1).[5,10,37] However, since imatinib is a relatively well-tolerated TKI, limited data is available on the upper limit of

dosing in the view of toxicity. One study in patients with CML described an association between haematologic adverse events (AEs) and an imatinib C_{trough} > 3180 ng/mL.[10] This has not been confirmed by other studies yet.

Conclusion

Based on previous studies in which response to imatinib treatment was correlated with imatinib exposure of >1100 ng/mL, we recommend a target imatinib exposure threshold of >1100 ng/mL in patients with *c-KIT exon 11* mutated GIST who are treated with 400 mg OD. For *c-KIT exon 9* mutated GIST, treated with a dose of 400 mg BID and considering the linear dose-exposure relationship, a threshold of >2200 ng/mL might be considered.

2.3.2 | Sunitinib

Sunitinib is an inhibitor of PDGFRα-β, **vascular endothelial growth factor receptor (VEGFR1-2)**, **fetal liver tyrosine kinase receptor 3 (FLT3)** and c-KIT, and is registered for the treatment of renal cell carcinoma (RCC), GIST and neuroendocrine tumours.[59,60]

Preclinical and early phase clinical thresholds for response

Preclinical studies in mouse xenograft models and in small cell lung cancer cell lines have shown that the inhibition of VEGFR, PDGFR and c-KIT by sunitinib requires a plasma concentration of 50-100 ng/mL.[61,62] In a phase I study, including patients with RCC or GIST, all patients with an objective response (OR) received doses of sunitinib of ≥50 mg OD 4 weeks on, 2 weeks off (4/2).[6] An increase in dose led to a linear increase in C_{trough} and doses of 50 mg OD resulted in C_{trough} ranging from 50 to 100 ng/mL. All responders had sunitinib C_{trough} > 50 ng/mL. Dose limiting toxicity (DLT) was experienced at a dose ≥75 mg OD with C_{trough} ≥ 100 ng/mL.[6]

Patients with GIST are generally treated at a lower but continuous dose of sunitinib of 37.5 mg OD. Several studies have shown, albeit not in a head-to-head comparison, that this results in similar PFS but less toxicity when compared to a dose of 50 mg OD 4/2.[63,64]

In the metabolism of sunitinib, an active metabolite (desethylsunitinib, SU012662) is produced with similar potency as sunitinib. Since SU012662 accounts for 23-37% of the total exposure at steady state, this metabolite contributes to the anti-tumour effect of sunitinib,[6,59,65] therefore sunitinib exposure–response relationships are studies based on the sum C_{trough} (sunitinib + SU012662).

Clinical thresholds for response

Exposure–response relationship. The details and findings of studies evaluating the relationship between exposure and treatment outcome for sunitinib are shown in Table 1.

Houk et al demonstrated in 443 patients that sunitinib exposure above the median AUC was correlated with improved clinical outcome in patients with RCC or GIST.[11] Previously it was shown that sum C_{trough} and AUC are highly correlated.[66] The reported median sum

C_{trough} in patients treated with sunitinib 50 mg OD is between 50 and 84 ng/mL,[6,59,67] therefore the findings of Houk et al support a target threshold for sum C_{trough} of >50 ng/mL for a dose of 50 mg OD 4/2. In order to manage toxicity, an alternate schedule with sunitinib 50 mg OD 2 weeks on, 1 week off (2/1) has been investigated as well, resulting in comparable complete or partial response, but superior tolerability.[68] Since the sunitinib dose is similar in this treatment schedule, a steady-state threshold of sunitinib sum C_{trough} > 50 ng/mL can be advised here as well. Considering the linearity of dose with C_{trough}, a threshold for sum C_{trough} of >37.5 ng/mL has been advised for treatment with 37.5 mg OD continuous dosing.[69]

Exposure–toxicity relationship. Following Faivre et al, who described DLT at sum C_{trough} ≥ 100 ng/mL, four other studies described a correlation between a high C_{trough} and the occurrence of AEs.[6,11,40-42] Two studies described treatment discontinuation for AEs at sum C_{trough} > 75 ng/mL and > 100 ng/mL, respectively.[40,41]

Interestingly, toxicity also seems to be related to the country where patients are treated Lee et al. described substantial differences in the incidences of various AEs between Asian patients who were treated in Asia or in countries outside of Asia.[70]

Conclusion

In conclusion, since sunitinib sum C_{trough} > 50 ng/mL is associated with clinical response, we recommend a target exposure threshold for sunitinib sum C_{trough} of >50 ng/mL for intermittent dosing (50 mg OD 4/2 or 2/1). Taking into account the dose proportional relation for sunitinib, we recommend a threshold of >37.5 ng/mL for continuous dosing (37.5 mg OD). Toxicity increases above sunitinib sum C_{trough} levels of >87.5 ng/mL and > 75 ng/mL for intermittent and continuous dosing, respectively.

2.3.3 | Pazopanib

Pazopanib is an inhibitor of VEGFR1-2-3, PDGFRα-β and c-KIT.[71] Pazopanib is used for the treatment of RCC and soft tissue sarcoma (STS).[72-74]

Preclinical and early-phase clinical thresholds for response

In preclinical studies with multiple myeloma cells and mouse xenograft models, the antitumor and antiangiogenic activity of pazopanib is concentration-dependent, requiring a steady-state plasma concentration of >40 μmol/l (= 17.5 mg/L).[75,76] In a phase I dose-escalating trial in which patients received doses ranging from 50 mg three times weekly to 2000 mg OD and 300-400 mg BID, effectiveness of pazopanib in patients with metastatic RCC was correlated with a pazopanib C_{trough} of ≥15 mg/L.[7] The patients with clinical response received doses of ≥800 mg OD or 300 mg BID. The maximum tolerated dose (MTD) was not reached, but the exposure to pazopanib did not increase at a dose of ≥800 mg OD, therefore the recommended dose was defined as 800 mg OD with predefined dose reductions in case of unacceptable toxicity.[7]

Pazopanib also has active metabolites that together represent approximately 6% of the total drug exposure.[77] In accordance with imatinib, these metabolites were not measured in studies examining the relationship between exposure and outcome.

Clinical thresholds for response

Exposure–response relationship. Clinical studies on the exposure–effectiveness relationship for pazopanib are presented in Table 1. Suttle et al defined a pazopanib threshold C_{trough} > 20.5 mg/L to be correlated with a significant increase in median PFS in patients with RCC.[9] Patients below this threshold showed comparable efficacy to placebo. This threshold approximates the findings in the preclinical/early-phase trials and was confirmed independently by Verheijen et al.[13] Although differences in response at the same threshold were seen for patients with STS, the difference did not reach statistical significance, potentially due to the limited number of patients and the more modest effect size in patients with STS compared to mRCC,[13] therefore, although less robust, the same threshold might be applicable for patients with STS.[13]

Not only survival but also response rates (assessed using the RECIST criteria) have been correlated with pazopanib trough levels; out of 27 RCC patients, none of the three patients with a pazopanib C_{trough} < 20.5 mg/L experienced an OR, while 11 out of the remaining 24 patients showed OR.[44]

Exposure–toxicity relationship. The relationship between exposure and toxicity has also been established[9,13,43,44] (overview Table 1), showing that increasing pazopanib C_{trough} is associated with increased incidence of AEs.[9,13] Two studies (n = 205) calculated that the highest incidence of AEs occurred in patients with a pazopanib C_{trough} > 46 mg/L, especially for hand-foot syndrome and hypertension (all grades).[9,43] Noda et al (n = 27) recently calculated a nearly similar upper threshold of ≥50.3 mg/L for grade ≥ 3 toxicity.[44] Results were most convincing for fatigue, anorexia and hypertension.

Conclusion

In several clinical studies, a pazopanib C_{trough} > 20.5 mg/L is correlated with a significant increase in median PFS, therefore we recommend a target exposure threshold for pazopanib C_{trough} of >20.5 mg/L. More toxicity is reported in patients with pazopanib C_{trough} levels >46 mg/L.

2.4 | Explaining interpatient variability in pharmacokinetics

2.4.1 | Imatinib

Imatinib shows dose proportional PK and high interpatient variability (38-78%), though modest intrapatient variability (21-35%).[10,38,39] A summary of the PK parameters of imatinib is shown in Table 2.

Factors identified in pharmacokinetic models that explain interpatient variability

Many population PK model studies for imatinib have been published, describing imatinib PK as a one-compartment model with zero- or first-order absorption and first-order elimination.[5,12,83,98-104] Many covariates were explored, some of which showed significant correlations with imatinib exposure.

A higher level of alpha-acid glycoprotein (AAG) is correlated with a lower clearance of imatinib in multiple studies.[5,100,105] Some PK models describe a positive correlation between imatinib clearance and body weight.[83,98-100] Single nucleotide polymorphisms (SNPs) in *ABCB1* (*1236 T > C, 2766G > T/A* and *3435C > T*), *SLCOB3* (*SLOCB3 334GG* genotype) or *CYP3A5* (eg *CYP3A5*3*) are potentially also associated with imatinib clearance and can increase imatinib clearance by 36-61%.[102-104] Furthermore, one study described a 45% reduction in dose-adjusted imatinib C_{trough} in patients with a SNP in *CYP3A4* (*20239G > A allele* or *20239G > A homozygote*).[106] One study reported a significant association between SNPs in *ABCG2* and *CYP1A2* and the need for dose reductions, although no imatinib exposure was measured.[107]

An observation in one study is that imatinib exposure decreased by 29.3% in the first 3 months after the start of therapy (n = 50).[48] Several hypotheses have been proposed to explain this finding, for example reduced bioavailability of imatinib.[48] Another hypothesis could be that reduced imatinib exposure is caused by a decrease in AAG level, since imatinib is mainly bound to AAG, as a consequence of the reduction of inflammation after the start of imatinib.[108] However, this hypothesis could not be confirmed by Bins et al, who observed no decrease in AAG level during imatinib treatment.[109] The observation of a decrease in imatinib exposure was not supported by two other studies (n = 108 and n = 65).[38,97] However, one of those studies measured the initial imatinib C_{trough} after patients had been treated with imatinib for a median time of 5.5 months.[97]

Other factors that influence pharmacokinetics

Major gastrectomy has been shown to significantly lower imatinib exposure.[110,111] However, no significant correlation between the use of proton pump inhibitors and imatinib exposure was found.[14]

Conflicting results are reported for the influence of renal function on imatinib pharmacokinetics, with some studies describing higher imatinib AUCs in patients with renal dysfunction, while other studies describe no correlation.[5,12,105,110] Since imatinib is predominantly eliminated by the liver, it was hypothesized that renal failure causes decreased **cytochrome P450** activity, thereby increasing systemic exposure to imatinib.[105] Another explanation might be that patients with end-stage renal disease have increased levels of uremic toxins, which can inhibit the uptake of imatinib in hepatocytes.[112] Co-medication inducing **CYP3A4** can cause a significant decrease in imatinib exposure.[14] However, van Erp et al demonstrated that at steady state, imatinib is insensitive to CYP3A4 inhibition.[88] This might be explained by other metabolic pathways that are predominantly used at steady-state pharmacokinetics due to auto-inhibition of

TABLE 2 PK parameters of imatinib, pazopanib and sunitinib

PK parameters	Imatinib	References	Sunitinib	References	Pazopanib	References
Bioavailability (%)	98.8	78 79,80	41-58	81	14-39 Solubility and absorption pH-dependent (easily soluble at pH < 4)	8,82
T_{max} (h)	2-4	57,78	6-12	60,65	2-4	82
Protein binding (%)	95	83,84	95% for sunitinib 90% for SU012662	60	>99	85
Distribution volume (L)	435	78	2200	65	9-13	82,85
Penetration of blood–brain-barrier Low penetration is assumed due to high protein binding	Imatinib 77		concentration in CSF is 40- to 100-fold lower than in plasma	86,87	Unknown	
Metabolism	Mainly by CYP3A4 and CYP3A5, to a lesser extent by CYP2D6	31,88	CYP3A4	60	Mainly CYP3A4, also by CYP1A2 and CYP2C8	2,89,90
Metabolites produced	Equipotent metabolite CGP74588 ± 10% of AUC of imatinib	91	Equipotent metabolite SU012662 ± 21% of AUC of sunitinib	81	Metabolites do not contribute to therapeutic effect	2,89,90
Clearance (L/h)	8.48-9.06	30,58	37.2	59	0.21-0.35	2,92
$T_{1/2}$ (h)	Imatinib: 18 CGP74588: 40	91	Sunitinib: 40-60 SU012662: 80-100	60,93	31.1	2,7
Excretion	Mainly through faeces	31,91	Faeces: 50-72% Urine: 13-20%	93,94	Mainly through faeces	2,7
Interpatient variability (%)	38-75	10,30,38,39,46,95	31-38% for sunitinib 41-60% for SU012662	59,60,96	36-67	7,77,92
Intrapatient variability (%)	21-35	10,38,39,46,97	29-38% for sunitinib 38-52% for SU012662	60	75	8

AUC, area under the curve; CSF, cerebrospinal fluid; PK, pharmacokinetic; T_{max}, time to reach maximum plasma concentration.

CYP3A4 metabolism by imatinib, for example CYP2D6, which is known to play a role in imatinib metabolism.[31,88]

Conclusion
Imatinib clearance can be affected by body weight and AAG level. Imatinib exposure is significantly lower in patients who underwent major gastrectomy. Furthermore, renal function and SNPs in *ABCB1*, *SLCOB3*, *CYP3A4* or *CYP3A5* can significantly alter imatinib exposure. Although the mechanism remains unknown, some studies describe a decrease in imatinib exposure in the first months after start of treatment, therefore imatinib exposure should be measured after the start of therapy and repeated at least after three months.

2.4.2 | Sunitinib

Similar to imatinib, sunitinib shows dose proportional PK, large interpatient PK variability (34-60%) and modest intrapatient PK variability (29-52%).[59,60,96] PK parameters of sunitinib are shown in Table 2.

Factors identified in pharmacokinetic models that explain interpatient variability
For sunitinib, several population PK models have been developed.[96,113-120] The PK of sunitinib and SU012662 is described as a one- or two-compartment model with first-order absorption and elimination. Some covariates might explain part of the interpatient PK variability.

SNPs in *ABCG2* (eg *ABCG2 421 C > A*) and *ABCB1* were found to be significantly correlated with sunitinib clearance.[115,118,119] Sunitinib clearance is decreased by 12-15% in Asian patients compared to non-Asian patients.[113,116] This might partly be explained by a higher prevalence of the *ABCG2 421 C > A* genotype in Asian patients.[121] The effect of *CYP3A4*22* was also studied and resulted in a 22.5% lower clearance of sunitinib.[120] *CYP3A5*1* has been associated with an increased risk of dose reductions of sunitinib in several studies.[122,123] No sunitinib levels were measured, but considering the exposure–toxicity relationship, it is reasonable to assume that *CYP3A5*1* results in lower sunitinib clearance.

Several studies have shown that sunitinib clearance decreases with decreasing body weight, body surface area and lean body mass.[113,117,119] Also, increasing age causes a slight decrease in sunitinib clearance of 0.7% per year.[116] Finally, sunitinib clearance is decreased in women compared to men.[113,116] However, considering the minor effects of these clinical characteristics on sunitinib PK, no adjusted dose is advised.[65]

Other factors that influence pharmacokinetics

Co-medication inducing or inhibiting CYP3A4 can cause a significant decrease or increase in sunitinib exposure of 46% and 51%, respectively.[65] Furthermore, consumption of grapefruit juice results in an 11% increase in sunitinib exposure, which is not considered clinically relevant.[124]

There is no necessity for dose adjustments in patients with renal or mild to moderate hepatic impairment.[65,125,126]

Conclusion

Sunitinib clearance is affected by weight, gender and race, although effects are limited and adjustments of the starting dose are not recommended based on these patient characteristics. Both *CYP3A4*22* and *CYP3A5*1* can significantly lower sunitinib clearance, although the occurrence of these alleles is rare. Co-medication inducing or inhibiting CYP3A4 can significantly decrease or increase sunitinib exposure by 50%. This can potentially lead to under- or overdosing of sunitinib, which might result in decreased treatment efficacy or increased toxicity. However, considering the comorbidities of patients, it is not always possible to discontinue treatment with co-medication interacting with CYP3A4, therefore TDM should be considered as an elegant tool to monitor the exposure to sunitinib in order to be able to continue treatment with sunitinib and CYP3A4 inducers or inhibitors simultaneously.

2.4.3 | Pazopanib

Pazopanib has challenging PK characteristics with, for example, saturated absorption and low bioavailability. Multiple studies have shown that there is large intra- and interpatient variability (75% and 36-67%, respectively) in the PK of pazopanib.[7,13,25,127] A summary of the PK parameters of pazopanib is shown in Table 2.

Factors identified in pharmacokinetic models that explain interpatient variability

In order to be able to understand the PK characteristics of pazopanib and to investigate the influence of different factors (covariates), population PK models for pazopanib have been developed.[8,128-130] Some covariates were identified that explain part of the interpatient variability observed.

The registration file of the Food and Drug Administration (FDA) for pazopanib mentioned that in patients with an Eastern Cooperative Oncology Group (ECOG) score of 1, pazopanib clearance increased by 14% compared to patients with an ECOG score of 0.[77] Although contradictive, this observation was recently confirmed in PK data analysis of the PROTECT study where more patients had an ECOG score of 0 and pazopanib C_{trough} levels were higher, compared to historical data.[45]

Bins et al reported that the SNP in *CYP3A4* which was also related to sunitinib clearance, namely *CYP3A4*22*, resulted in a decreased clearance of pazopanib of 35%.[130]

Finally, two PK models described saturated absorption of pazopanib and a 40-59% higher relative bioavailability for a dose of 400 mg compared to 800 mg.[8,129] Furthermore, these models observed that the exposure of pazopanib decreases in the first 4 weeks after start of treatment with ~25%.[8,129] This observation is in line with findings in an earlier study.[127] The mechanism behind the decrease in exposure over the first few weeks has not been clarified yet.

Other factors that influence pharmacokinetics

Based on PK drug interaction studies, other factors have been identified that also influence pazopanib PK. Food has a major effect on the absorption of pazopanib. Heath et al demonstrated that pazopanib exposure increased two-fold with the intake of a high-fat or low-fat meal.[131] Pazopanib is primarily metabolized by the liver. In patients with moderate or severe hepatic dysfunction, the maximum tolerated dose was only 200 mg OD. Since this dose resulted in subtherapeutic exposure, pazopanib is not recommended in patients with moderate or severe hepatic dysfunction.[132,133] Finally, Tan et al reported a significant increase in pazopanib exposure in patients using co-medication inhibiting CYP3A4 and a significant decrease in pazopanib exposure in patients using concomitant pH-elevating medication.[134] Yu et al incorporated this latter observation in their PK model, suggesting the absorption of pazopanib could best be described by a fast absorption process in the stomach and duodenum, where pH is low, followed by a slower process in the latter part of the intestine, where pH rises.[8]

Conclusion

PK model studies have shown that ECOG score and *CYP3A4*22* genotype explain part of the interpatient variability in pazopanib PK. Furthermore, a saturated absorption of pazopanib and a decrease in pazopanib exposure at the beginning of treatment were observed. Finally, the concomitant intake of food, gastric acid reducing agents and the use of co-medication affecting CYP3A4 activity can lead to clinically relevant changes in pazopanib exposure.

2.5 | Dose optimization strategies to reach threshold

For imatinib, sunitinib and pazopanib, thresholds have been established above which more treatment benefit and toxicity, respectively, are observed.[6,9,11,12] For an overview of the recommended thresholds for imatinib, sunitinib and pazopanib, see Table 3. Therefore, TDM guided dose interventions might be a valuable tool to optimize individual drug exposure in order to maximize the number of patients treated effectively and to decrease the number of patients suffering from toxicity.[135] This applies particularly for imatinib and sunitinib, where low intrapatient PK variability is observed. This, however, is more challenging for pazopanib considering its large intrapatient PK variability. In the next part of the review the pharmacological tools available to optimize the plasma levels of imatinib, sunitinib and pazopanib are described. For detailed information, see Table 4.

TABLE 3 Exposure thresholds for efficacy and toxicity for imatinib, sunitinib and pazopanib

Drug	Threshold efficacy	Threshold toxicity
Imatinib	>1100 ng/mL	Not defined
Sunitinib	Intermittent dosing: >50 ng/mL Continuous dosing: >37.5 ng/mL	Intermittent dosing: <87.5 ng/mL Continuous dosing: <75 ng/mL
Pazopanib	>20.5 mg/L	<46 mg/L

2.5.1 | Imatinib

Dose interventions

For imatinib, one study has evaluated the feasibility of TDM in achieving the target exposure threshold of >1100 ng/mL in patients with GIST.[15] This study in 68 patients demonstrated the feasibility of TDM in achieving the target exposure threshold, although physician adherence to dose recommendations was low (~54%).[15] However, 95% of patients in whom dose intervention was implemented achieved adequate imatinib C_{trough}.

Other interventions

It has previously been demonstrated that imatinib exposure significantly decreases after gastrectomy.[110] It was therefore investigated whether co-administration of imatinib with an acidic beverage could increase the exposure to imatinib. This was previously described for erlotinib,[140] but could not be substantiated for imatinib.[141]

2.5.2 | Sunitinib

Dose interventions

Two studies were published evaluating the feasibility of TDM guided dosing to reach adequate drug levels for patients treated with sunitinib.[15,136]

Lankheet et al reported that in 5/5 patients with an initial C_{trough} below the threshold of 50 ng/mL and the absence of severe toxicity, dose was successfully increased without increasing toxicity, resulting

TABLE 4 Interventions to reach threshold for imatinib, sunitinib and pazopanib

Drug	Intervention	Findings	References
Imatinib	Dose interventions	Patients with TDM guided increase in dose 95% adequate C_{trough}	15
Sunitinib	Dose interventions	Patients with TDM guided increase in dose 76-100% adequate C_{trough}	15,136
Pazopanib	Dose intervention	Patients with TDM guided increase in dose 70% adequate C_{trough} Patients with TDM guided decrease in dose 78% reduction in toxicity Interpatient variability 71.9% 33.9%	15,25,137
	Food interventions	AUC doubled with both high-fat FDA meal and low-fat FDA meal.	131
		600 mg pazopanib with continental breakfast bioequivalent to 800 mg fasted	138
	Crushed tablet or oral suspension	Crushed tablet increase in AUC of 46% Interpatient variability 72.5% 26.8% Oral suspension increase in AUC of 33%.	
	Splitting the dose	Relative bioavailability of 400 mg 40-59% higher compared to 800 mg.	8,77
		400 mg BID instead of 800 mg OD increase in C_{trough} of 52%	139

AUC, area under the curve; BID, twice a day; C_{trough}, plasma trough level; FDA, Food and Drug Administration; OD, once a day; TDM, therapeutic drug monitoring.

in an adequate sunitinib C_{trough}.[136] Another study demonstrated that of 17 patients in whom the recommended dose adjustment was implemented, 13 patients (~77%) reached adequate C_{trough} of >50 ng/mL after dose adjustment.[15] Furthermore, the percentage of patients with a sunitinib C_{trough} above threshold increased from ~48% to ~74% with TDM guided dosing.[15]

Several case reports have reported on the added value of TDM guided dosing to reduce toxicity, for instance in vulnerable patients with extensive comorbidity (eg haemodialysis, previous bariatric surgery or cardiac transplantation).[142-145]

CYP3A4 boosting

A significant increase in sunitinib exposure was observed when co-administering sunitinib with CYP3A4 inhibitors.[65] This might therefore be a tool to increase exposure to sunitinib without increasing the dose, as for protease inhibitors in patients with HIV, though no studies have been published investigating this approach for TKIs.[146]

2.5.3 | Pazopanib

Dose interventions

Several studies have evaluated the feasibility of TDM in the treatment of patients with solid tumours with pazopanib.[15,25,127]

One study could not establish the feasibility of TDM for pazopanib in 13 patients due to large intrapatient variability.[127] However, two other studies (n = 30 and n = 12) demonstrated that the number of patients reaching adequate pazopanib C_{trough} can be increased by 50% by using TDM.[15,25]

Food interventions

Heath et al demonstrated a higher exposure to pazopanib when administering pazopanib concomitant with food.[131] Thereafter, it was demonstrated that a lower dose of pazopanib can be administered with food while maintaining bio-equivalent C_{trough} levels of a higher dose without food (n = 78) while gastrointestinal toxicity was comparable when a reduced dose of pazopanib was taken with food.[138] Recently, another study reported that administering pazopanib with food did not increase the risk of toxicity (n = 16), while all but two patients reached adequate C_{trough}.[147] Not having to fast around the pazopanib intake may positively affect quality of life for cancer patients, especially those experiencing difficulty in maintaining bodyweight. The preference of patients for intake with food was shown in the DIET study where 68% of patients preferred the intake of pazopanib with food compared to without food.[138]

Gastric pH

Two studies reported shorter PFS and overall survival (OS) in patients treated with pazopanib receiving concomitant pH-elevating medication, though in one of these studies the effect on treatment outcome was not statistically significant.[148,149] Unfortunately, no pazopanib plasma concentrations were measured. However, considering the essential role of gastric pH in the absorption of pazopanib and the previously established decrease in pazopanib AUC when combined with a proton pump inhibitor, it is likely that the shortened survival is caused by underexposure to pazopanib.[134]

Crushed tablet or oral suspension

Administering pazopanib as a crushed tablet or an oral suspension increases the AUC by 46% and 33%, respectively, and decreases the interpatient PK variability from ~73% to ~27%.[150] For a significant amount of patients with cancer it can be difficult to swallow whole tablets and this might be a good alternative.

Splitting the dose

Previous studies and simulations have described a saturated absorption of pazopanib and a higher relative bioavailability for lower dosages.[7,8,77] Recently, the effect on exposure levels of splitting the dose of pazopanib was investigated.[139] It was demonstrated that administering pazopanib 400 mg BID led to an increase of C_{trough} of 52% compared to 800 mg OD (n = 10). Splitting the dose might be a good tool to increase pazopanib exposure in patients underdosed with 800 mg OD.

CYP3A4 boosting

Since a significant increase in pazopanib exposure was observed in patients using co-medication inhibiting CYP3A4, this might be an alternative approach to optimize pazopanib plasma levels, though this has not been investigated yet.[134]

Conclusion

For imatinib and sunitinib, the optimal method for dose optimization is to adjust the dose according to measurements of C_{trough}. Considering the large interpatient PK variability compared to intrapatient PK variability it is advisable to monitor plasma C_{trough} levels after the start of therapy and after dose adjustments.

Reaching the exposure threshold of pazopanib by dose increments only might be challenging due to the complex absorption profile of pazopanib and the large intrapatient PK variability. A variety of alternative methods is available to influence pazopanib plasma trough levels and potentially reduce the significant intrapatient variability. Currently, peer-reviewed data has been published on administering pazopanib concomitant with food. However, regardless of the method used to optimize pazopanib exposure, it is of the utmost importance that the effect of any intervention is monitored with plasma C_{trough} levels measurement.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [151], and are permanently archived in the Concise Guide to PHARMACOLOGY 2016/2017: overview[152].

3 | CONCLUSION

For imatinib, sunitinib and pazopanib, an exposure–outcome relationship has been demonstrated and the concentration thresholds to optimize efficacy and minimize toxicity (therapeutic window) have been defined. It has been demonstrated that the percentage of patients with drug levels within the predefined target range is low for all three anti-cancer agents, ranging from 27% to 52%. It has therefore been suggested that TDM guided dosing can result in a higher efficacy and lower toxicity rate. The feasibility of TDM guided dosing and of reaching target drug exposure with TDM guided dosing has been shown for imatinib, sunitinib and pazopanib.

For imatinib and sunitinib, considering the relatively small intrapatient PK variability, TDM guided dosing can be a valuable tool to optimize individual exposure to these drugs in order to either maximize the effect by increasing the dose or reduce toxicity by decreasing the dose. For pazopanib, however, reaching the target range by dose adjustments might be more challenging due to large intrapatient PK variability. Based on the available literature, food should be considered as an intervention to reach the target threshold. Another approach to examine could be to boost pazopanib exposure by using CYP3A4 inhibitors or splitting the pazopanib dose.

Regardless of the intervention applied to optimize exposure to these drugs, it is of the utmost importance to measure drug levels after interventions and troughout treatment to carefully monitor the effect of any intervention.

COMPETING INTERESTS
All authors declare no conflict of interest.

CONTRIBUTORS
All authors were involved in the conception, design and final approval of the manuscript. K.W., I.D. and N.E. also drafted the manuscript. I.D., N.S., W.G. and N.E. revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

APPENDIX A: | Participating centres and members of the Dutch Pharmacology and Oncology Group (DPOG)

DPOG centres

The Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, the Netherlands

Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

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