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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.

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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 (PDGFR α - 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 (IC₅₀) 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	$C_{\text{trough}} \geq 1100$ ng/mL	TTP	Response \rightarrow higher C_{trough} (1446 ng/mL vs 1155 ng/mL) Higher $C_{\text{trough}} \rightarrow$ longer TTP $C_{\text{trough}} \geq 1100$ ng/mL \rightarrow better OOB Higher C_{trough} in <i>c-KIT</i> exon 11 vs 9	0.25 0.0029 0.0001 0.15	12
	GIST and CML	-	Response Toxicity	Higher free imatinib \rightarrow more response Higher total + free imatinib \rightarrow higher incidence AEs	0.026	37
	GIST	-	Response	Response \rightarrow higher C_{trough} (1271 ng/mL vs 920 ng/mL)	NS	38
	GIST	$C_{\text{trough}} \geq 760$ ng/mL	PFS	$C_{\text{trough}} \geq 760$ ng/mL \rightarrow longer PFS (PFS not reached vs 56 months)	0.0256	39
	GIST	-	Toxicity	Higher free imatinib \rightarrow higher incidence neutropenia	$P < 0.001$	5
Sunitinib	Various	$C_{\text{trough}} > 50$ ng/mL	Efficacy Toxicity	Patients with OR \rightarrow received doses ≥ 50 mg OD Dose of 50 mg OD $\rightarrow C_{\text{trough}}$ 50–100 ng/mL Patients with DLT $\rightarrow C_{\text{trough}} > 100$ ng/mL	...	6
	RCC + GIST	-	Efficacy Toxicity	RCC: Higher sunitinib level \rightarrow longer TTP GIST: Higher sunitinib level \rightarrow longer TTP RCC + GIST: higher sunitinib level \rightarrow higher incidence AEs	0.001 0.001	11
	RCC	$C_{\text{trough}} < 100$ ng/mL	Toxicity	$C_{\text{trough}} \geq 100$ ng/mL \rightarrow higher incidence toxicity (75% vs 23.1%)	...	40
	RCC	-	Toxicity	Patients who discontinue treatment \rightarrow higher C_{trough}	...	41
	RCC	-	Toxicity	Higher sunitinib level \rightarrow higher incidence AEs	...	42
Pazopanib	RCC	$C_{\text{trough}} > 20.5$ mg/L	PFS	$C_{\text{trough}} > 20.5$ mg/L \rightarrow longer PFS (52.0 vs 19.6 weeks)	0.00378	9
	RCC and STS	$C_{\text{trough}} > 46$ mg/L	Toxicity	$C_{\text{trough}} > 46$ mg/L \rightarrow higher incidence AEs	...	9,43
		$C_{\text{trough}} > 20$ mg/L	PFS	RCC: $C_{\text{trough}} > 20$ mg/L \rightarrow longer PFS (34.1 vs 12.5 weeks) STS: $C_{\text{trough}} > 20$ mg/L \rightarrow longer PFS (18.7 vs 8.8 weeks)	0.027 0.142	13
		-	Toxicity	Higher $C_{\text{trough}} \rightarrow$ more patients discontinue treatment	...	
	RCC	$C_{\text{trough}} > 20.5$ mg/L $C_{\text{trough}} < 50.3$ mg/L	Response Toxicity	$C_{\text{trough}} < 20.5$ mg/L \rightarrow no OR Grade ≥ 3 toxicities \rightarrow higher C_{trough} (69.3 mg/L vs 41.2 mg/L) $C_{\text{trough}} \geq 50.3$ mg/L \rightarrow higher incidence toxicity (61.5% vs 7.1%)	... $P < 0.05$	44
RCC	$C_{\text{trough}} > 20.5$ mg/L	DFS	$C_{\text{trough}} > 20.5$ mg/L \rightarrow 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; OOB, 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 $C_{\text{trough}} > 3180$ 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 PDGFR α - 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 $C_{\text{trough}} > 50$ ng/mL. Dose limiting toxicity (DLT) was experienced at a dose ≥ 75 mg OD with $C_{\text{trough}} \geq 100$ 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 $C_{\text{trough}} > 50$ 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 $C_{\text{trough}} \geq 100$ 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 $C_{\text{trough}} > 75$ 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 $C_{\text{trough}} > 50$ 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, PDGFR α - 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 $\mu\text{mol/l}$ ($= 17.5$ 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 $C_{\text{trough}} > 20.5$ 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 $C_{\text{trough}} < 20.5$ 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 $C_{\text{trough}} > 46$ 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 $C_{\text{trough}} > 20.5$ 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 inpatient 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	Imatinib	concentration in CSF is 40- to 100-fold lower than in plasma	86,87	Unknown	
Low penetration is assumed due to high protein binding	77					
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
Inpatient 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 inpatient 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 contradictory, 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 inpatient PK variability is observed. This, however, is more challenging for pazopanib considering its large inpatient 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

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. 600 mg pazopanib with continental breakfast bioequivalent to 800 mg fasted	131 138
	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%.	8,77
	Splitting the dose	Relative bioavailability of 400 mg 40-59% higher compared to 800 mg. 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.

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

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 inpatient 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 doses.^{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 inpatient 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 inpatient PK variability. A variety of alternative methods is available to influence pazopanib plasma trough levels and potentially reduce the significant inpatient 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 PHARMACOLOGY¹⁵¹, and are permanently archived in the Concise Guide to PHARMACOLOGY 2016/2017: overview¹⁵².

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 inpatient 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 inpatient 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 throughout treatment to carefully monitor the effect of any intervention.

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CONTRIBUTORS

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REFERENCES

- Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med*. 2005;353(2):172-187. <https://doi.org/10.1056/NEJMra044389>
- Di Gion P, Kanefendt F, Lindauer A, et al. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. *Clin Pharmacokinet*. 2011;50(9):551-603. <https://doi.org/10.2165/11593320-000000000-00000>
- van Erp NP, Gelderblom H, Guchelaar HJ. Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treat Rev*. 2009;35(8):692-706. <https://doi.org/10.1016/j.ctrv.2009.08.004> Epub Sep 5
- Hussaarts K, Veerman GDM, Jansman FGA, van Gelder T, Mathijssen RHJ, van Leeuwen RWF. Clinically relevant drug interactions with multikinase inhibitors: a review. *Ther Adv Med Oncol*. 2019;11:1-34. <https://doi.org/10.1177/1758835918818347> eCollection 2019.
- Delbaldo C, Chatelut E, Re M, et al. Pharmacokinetic-pharmacodynamic relationships of imatinib and its main metabolite in patients with advanced gastrointestinal stromal tumors. *Clin Cancer Res*. 2006;12(20):6073-6078. <https://doi.org/10.1158/1078-0432.CCR-05-2596>
- Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and anti-tumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol*. 2006;24(1):25-35. <https://doi.org/10.1200/JCO.2005.02.194> Epub Nov 28.
- Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res*. 2009;15(12):4220-4227. <https://doi.org/10.1158/1078-0432.CCR-08-2740> Epub 009 Jun 9
- Yu H, van Erp N, Bins S, et al. Development of a pharmacokinetic model to describe the complex pharmacokinetics of Pazopanib in cancer patients. *Clin Pharmacokinet*. 2017;56(3):293-303. <https://doi.org/10.1007/s40262-016-0443-y>
- Suttle AB, Ball HA, Molimard M, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. *Br J Cancer*. 2014;111(10):1909-1916. <https://doi.org/10.1038/bjc.2014.503> Epub Oct 28
- Guilhot F, Hughes TP, Cortes J, et al. Plasma exposure of imatinib and its correlation with clinical response in the tyrosine kinase inhibitor optimization and selectivity trial. *Haematologica*. 2012;97(5):731-738. <https://doi.org/10.3324/haematol.2011.045666> Epub 2012 Feb 7
- Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol*. 2010;66(2):357-371. <https://doi.org/10.1007/s00280-009-1170-y> Epub 2009 Dec 5.
- Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol*. 2009;27(19):3141-3147. <https://doi.org/10.1200/JCO.2008.20.4818> Epub 2009 May 18.
- Verheijen RB, Swart LE, Beijnen JH, Schellens JHM, Huitema AD, Steeghs N. Exposure-survival analyses of pazopanib in renal cell carcinoma and soft tissue sarcoma patients: opportunities for dose optimization. *Cancer Chemother Pharmacol*. 2017;80(6):1171-1178. <https://doi.org/10.1007/s00280-017-3463-x> Epub 2017 Oct 19.
- Lankheet NA, Knapen LM, Schellens JH, Beijnen JH, Steeghs N, Huitema AD. Plasma concentrations of tyrosine kinase inhibitors imatinib, erlotinib, and sunitinib in routine clinical outpatient cancer care. *The Drug Monit*. 2014;36(3):326-334. <https://doi.org/10.1097/FTD.0000000000000004>
- Lankheet NAG, Desar IME, Mulder SF, et al. Optimizing the dose in cancer patients treated with imatinib, sunitinib and pazopanib. *Br J Clin Pharmacol*. 2017;83(10):2195-2204. <https://doi.org/10.1111/bcp.13327> Epub 2017 Jul 4.
- de Jonge ME, Huitema AD, Schellens JH, Rodenhuis S, Beijnen JH. Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet*. 2005;44(2):147-173. <https://doi.org/10.2165/00003088-200544020-00002>
- Stoller RG, Hande KR, Jacobs SA, Rosenberg SA, Chabner BA. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. *N Engl J Med*. 1977;297(12):630-634. <https://doi.org/10.1056/NEJM197709222971203>

18. Bartelink IH, Bredius RG, Ververs TT, et al. Once-daily intravenous busulfan with therapeutic drug monitoring compared to conventional oral busulfan improves survival and engraftment in children undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14(1):88-98. <https://doi.org/10.1016/j.bbmt.2007.09.015>
19. Baudin E, Pellegriti G, Bonnay M, et al. Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer.* 2001;92(6):1385-1392.
20. Landmark CJ, Johannessen SI, Tomson T. Dosing strategies for anti-epileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. *Epileptic Disord.* 2016;18(4):367-383. <https://doi.org/10.1684/epd.2016.0880>
21. Ye ZK, Tang HL, Zhai SD. Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. *PLoS One.* 2013;8(10):1-10. <https://doi.org/10.1371/journal.pone.0077169> eCollection 2013.
22. Gao B, Yeap S, Clements A, Balakrishnar B, Wong M, Gurney H. Evidence for therapeutic drug monitoring of targeted anticancer therapies. *J Clin Oncol.* 2012;30(32):4017-4025. <https://doi.org/10.1200/JCO.2012.43.5362> Epub 2012 Aug 27
23. US Food and Drug Administration, Center for Drug Evaluation and Research. Crizotinib clinical pharmacology and biopharmaceutics review(s). 2011, March 30 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000ClinPharmR.pdf].
24. Kramkimel N, Thomas-Schoemann A, Sakji L, et al. Vemurafenib pharmacokinetics and its correlation with efficacy and safety in outpatients with advanced BRAF-mutated melanoma. *Target Oncol.* 2016;11(1):59-69. <https://doi.org/10.1007/s11523-015-0375-8>
25. Verheijen RB, Bins S, Mathijssen RH, et al. Individualized Pazopanib dosing: a prospective feasibility study in cancer patients. *Clin Cancer Res.* 2016;22(23):5738-5746. <https://doi.org/10.1158/1078-0432.CCR-16-1255> Epub 2016 Jul 28.
26. de Wit D, Guchelaar HJ, den Hartigh J, Gelderblom H, van Erp NP. Individualized dosing of tyrosine kinase inhibitors: are we there yet? *Drug Discov Today.* 2015;20(1):18-36. <https://doi.org/10.1016/j.drudis.2014.09.007> Epub Sep 22.
27. Verheijen RB, Yu H, Schellens JHM, Beijnen JH, Steeghs N, Huitema ADR. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther.* 2017;102(5):765-776. <https://doi.org/10.1002/cpt.787> Epub 2017 Sep 7.
28. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet.* 2005;44(9):879-894. <https://doi.org/10.2165/00003088-200544090-00001>
29. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med.* 2001;344(14):1038-1042. <https://doi.org/10.1056/NEJM200104053441402>
30. US Food and Drug Administration, Center for Drug Evaluation and Research. Imatinib clinical pharmacology and biopharmaceutics review. 2000 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-3355001_Gleevec_BioPharmr_P1.pdf].
31. European Medicines Agency CfMPfHUC. Imatinib summary of product characteristics. 2013 [Available from: https://www.ema.europa.eu/en/documents/product-information/imatinib-accord-epar-product-information_en.pdf].
32. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet.* 2001;358(9291):1421-1423.
33. Li K, Cheng H, Li Z, et al. Genetic progression in gastrointestinal stromal tumors: mechanisms and molecular interventions. *Oncotarget.* 2017;8(36):60589-60604. <https://doi.org/10.18632/oncotarget.6014> eCollection 2017 Sep 1.
34. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther.* 2000;295(1):139-145.
35. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Ziegler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood.* 2000;96(3):925-932.
36. Decaudin D, de Cremoux P, Sastre X, et al. In vivo efficacy of STI571 in xenografted human small cell lung cancer alone or combined with chemotherapy. *Int J Cancer.* 2005;113(5):849-856. <https://doi.org/10.1002/ijc.20652>
37. Widmer N, Decosterd LA, Leyvraz S, et al. Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability. *Br J Cancer.* 2008;98(10):1633-1640. <https://doi.org/10.1038/sj.bjc.6604355> Epub 2008 May 6.
38. Farag S, Verheijen RB, Martijn Kerst J, Cats A, Huitema AD, Steeghs N. Imatinib pharmacokinetics in a large observational cohort of gastrointestinal stromal tumour patients. *Clin Pharmacokinet.* 2017;56(3):287-292. <https://doi.org/10.1007/s40262-016-0439-7>
39. Bouchet S, Poulette S, Titier K, et al. Relationship between imatinib trough concentration and outcomes in the treatment of advanced gastrointestinal stromal tumours in a real-life setting. *Eur J Cancer.* 2016;57:31-38. <https://doi.org/10.1016/j.ejca.2015.12.029> Epub 6 Feb 4.
40. Noda S, Otsuji T, Baba M, et al. Assessment of Sunitinib-induced toxicities and clinical outcomes based on therapeutic drug monitoring of Sunitinib for patients with renal cell carcinoma. *Clin Genitourin Cancer.* 2015;13(4):350-358. <https://doi.org/10.1016/j.jglc.2015.01.007> Epub Jan 21.
41. Takasaki S, Kawasaki Y, Kikuchi M, et al. Relationships between sunitinib plasma concentration and clinical outcomes in Japanese patients with metastatic renal cell carcinoma. *Int J Clin Oncol.* 2018;23(5):936-943. <https://doi.org/10.1007/s10147-018-1302-7> Epub 2018 Jun 2.
42. Teo YL, Chue XP, Chau NM, et al. Association of drug exposure with toxicity and clinical response in metastatic renal cell carcinoma patients receiving an attenuated dosing regimen of sunitinib. *Target Oncol.* 2015;10(3):429-437. <https://doi.org/10.1007/s11523-014-0349-2> Epub 2014 Dec 13.
43. Lin Y, Ball HA, Suttle B, et al. Relationship between plasma pazopanib concentration and incidence of adverse events in renal cell carcinoma. *J Clin Oncol.* 2011;29(7_suppl):345-345.
44. Noda S, Yoshida T, Hira D, et al. Exploratory investigation of target Pazopanib concentration range for patients with renal cell carcinoma. *Clin Genitourin Cancer.* 2018;7(18):30734-30731.
45. Sternberg CN, Donskov F, Haas NB, et al. Pazopanib exposure relationship with clinical efficacy and safety in the adjuvant treatment of advanced renal cell carcinoma. *Clin Cancer Res.* 2018;24(13):3005-3013. <https://doi.org/10.1158/1078-0432.CCR-17-2652> Epub 018 Jan 12.
46. Bouchet S, Titier K, Moore N, et al. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: experience from 1216 patients at a centralized laboratory. *Fundam Clin Pharmacol.* 2013;27(6):690-697. <https://doi.org/10.1111/fcp.12007> Epub 2012 Oct 31.
47. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood.* 2007;109(8):3496-3499. <https://doi.org/10.1182/blood-2006-07-036012> Epub 2006 Dec 27.
48. Eechoute K, Fransson MN, Reyners AK, et al. A long-term prospective population pharmacokinetic study on imatinib plasma

- concentrations in GIST patients. *Clin Cancer Res.* 2012;18(20):5780-5787. <https://doi.org/10.1158/1078-0432.CCR-12-90> Epub 2012 Jul 31.
49. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002;347(7):472-480. <https://doi.org/10.1056/NEJMoa020461>
 50. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004;364(9440):1127-1134. [https://doi.org/10.1016/S0140-6736\(04\)17098-0](https://doi.org/10.1016/S0140-6736(04)17098-0)
 51. MetaGIST. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol.* 2010;28(7):1247-1253. <https://doi.org/10.1200/JCO.2009.24.2099> Epub 10 Feb 1.
 52. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol.* 2008;26(4):626-632. <https://doi.org/10.1200/JCO.2007.13.4452>
 53. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer.* 2006;42(8):1093-1103. <https://doi.org/10.1016/j.ejca.2006.01.030> Epub Apr 18
 54. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the north American intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 study by cancer and Leukemia group B and southwest oncology group. *J Clin Oncol.* 2008;26(33):5360-5367. <https://doi.org/10.1200/JCO.2008.17.4284> Epub 2008 Oct 27.
 55. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol.* 2003;21(23):4342-4349. <https://doi.org/10.1200/JCO.2003.04.190>
 56. Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal stromal tumours: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* 2018;29(Supplement_4):iv68-iv78.
 57. Peng B, Hayes M, Resta D, et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. *J Clin Oncol.* 2004;22(5):935-942. <https://doi.org/10.1200/JCO.2004.03.050>
 58. Committee for Medicinal Products for Human Use (CHMP) EMA. Imatinib assessment report 2013 [Available from: https://www.ema.europa.eu/en/documents/variation-report/glivec-h-c-406-ii-0080-epar-assessment-report-variation_en.pdf].
 59. Committee for Medicinal Products for Human Use (CHMP) EMA. Sunitinib assessment report 2019 [Available from: https://www.ema.europa.eu/en/documents/variation-report/sutent-h-c-687-ii-0070-epar-assessment-report-variation_en.pdf].
 60. US Food and Drug Administration, Center for Drug Evaluation and Research. Sunitinib clinical pharmacology and biopharmaceutics review. 2006 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938_S000_Sutent_BioPharmR.pdf].
 61. Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in pre-clinical models of human small cell lung cancer. *Mol Cancer Ther.* 2003;2(5):471-478.
 62. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res.* 2003;9(1):327-337.
 63. Li J, Gao J, Hong J, Shen L. Efficacy and safety of sunitinib in Chinese patients with imatinib-resistant or -intolerant gastrointestinal stromal tumors. *Future Oncol.* 2012;8(5):617-624. <https://doi.org/10.2217/fon.12.29>
 64. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer.* 2009;45(11):1959-1968. <https://doi.org/10.1016/j.ejca.2009.02.011> Epub Mar 11.
 65. Committee for Medicinal Products for Human Use (CHMP) EMA. Sunitinib summary of product characteristics 2019 [Available from: https://www.ema.europa.eu/en/documents/product-information/sutent-epar-product-information_en.pdf].
 66. de Wit D, Gelderblom H, Sparreboom A, et al. Midazolam as a phenotyping probe to predict sunitinib exposure in patients with cancer. *Cancer Chemother Pharmacol.* 2014;73(1):87-96. <https://doi.org/10.1007/s00280-013-2322-7> Epub 2013 Oct 23.
 67. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006;24(1):16-24. <https://doi.org/10.1200/JCO.2005.02.2574> Epub Dec 5.
 68. Sun Y, Li J, Yang X, Zhang G, Fan X. The alternative 2/1 schedule of Sunitinib is superior to the traditional 4/2 schedule in patients with metastatic renal cell carcinoma: a meta-analysis. *Clin Genitourin Cancer.* 2019;21(18):30603-30607.
 69. Yu H, Steeghs N, Nijenhuis CM, Schellens JH, Beijnen JH, Huitema AD. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet.* 2014;53(4):305-325. <https://doi.org/10.1007/s40262-014-0137-2>
 70. Lee SH, Bang YJ, Mainwaring P, et al. Sunitinib in metastatic renal cell carcinoma: an ethnic Asian subpopulation analysis for safety and efficacy. *Asia Pac J Clin Oncol.* 2014;10(3):237-245. <https://doi.org/10.1111/ajco.12163> Epub 2014 Feb 27.
 71. Sonpavde G, Hutson TE. Pazopanib: a novel multitargeted tyrosine kinase inhibitor. *Curr Oncol Rep.* 2007;9(2):115-119.
 72. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2010;28(3):475-480. <https://doi.org/10.1200/JCO.2008.21.6994> Epub 2009 Dec 14.
 73. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379(9829):1879-1886. [https://doi.org/10.1016/S0140-6736\(12\)60651-5](https://doi.org/10.1016/S0140-6736(12)60651-5) Epub 2012 May 16.
 74. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28(6):1061-1068. <https://doi.org/10.1200/JCO.2009.23.9764> Epub 2010 Jan 25.
 75. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther.* 2007;6(7):2012-2021. <https://doi.org/10.1158/1535-7163.MCT-07-0193>
 76. Podar K, Tonon G, Sattler M, et al. The small-molecule VEGF receptor inhibitor pazopanib (GW786034B) targets both tumor and endothelial cells in multiple myeloma. *Proc Natl Acad Sci U S A.* 2006;103(51):19478-19483. <https://doi.org/10.1073/pnas.0609329103> Epub 2006 Dec 12.
 77. US Food and Drug Administration, Center for Drug Evaluation and Research. Pazopanib clinical pharmacology and biopharmaceutics review(s). 2008, December 19 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_ClinPharmR.pdf].

78. Peng B, Dutreix C, Mehring G, et al. Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol*. 2004;44(2):158-162. <https://doi.org/10.1177/0091270003262101>
79. Hamada A, Miyano H, Watanabe H, Saito H. Interaction of imatinib mesilate with human P-glycoprotein. *J Pharmacol Exp Ther*. 2003;307(2):824-828. <https://doi.org/10.1124/jpet.103.055574> Epub 2003 Sep 15.
80. Burger H, van Tol H, Boersma AW, et al. Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. *Blood*. 2004;104(9):2940-2942. <https://doi.org/10.1182/blood-2004-04-1398> Epub 2004 Jul 13.
81. Haznedar JO, Patyna S, Bello CL, et al. Single- and multiple-dose disposition kinetics of sunitinib malate, a multitargeted receptor tyrosine kinase inhibitor: comparative plasma kinetics in non-clinical species. *Cancer Chemother Pharmacol*. 2009;64(4):691-706. <https://doi.org/10.1007/s00280-008-0917-1> Epub 2009 Jan 25
82. Deng Y, Sychterz C, Suttle AB, et al. Bioavailability, metabolism and disposition of oral pazopanib in patients with advanced cancer. *Xenobiotica*. 2013;43(5):443-453. <https://doi.org/10.3109/00498254.2012.734642> Epub 2012 Nov 16
83. Widmer N, Decosterd LA, Csajka C, et al. Population pharmacokinetics of imatinib and the role of alpha-acid glycoprotein. *Br J Clin Pharmacol*. 2006;62(1):97-112. <https://doi.org/10.1111/j.1365-2125.2006.02719.x>
84. Kretz O, Weiss HM, Schumacher MM, Gross G. In vitro blood distribution and plasma protein binding of the tyrosine kinase inhibitor imatinib and its active metabolite, CGP74588, in rat, mouse, dog, monkey, healthy humans and patients with acute lymphatic leukaemia. *Br J Clin Pharmacol*. 2004;58(2):212-216. <https://doi.org/10.1111/j.1365-2125.2004.02117.x>
85. Imbs DC, Paludetto MN, Negrier S, et al. Determination of unbound fraction of pazopanib in vitro and in cancer patients reveals albumin as the main binding site. *Invest New Drugs*. 2016;34(1):41-48. <https://doi.org/10.1007/s10637-015-0304-9> Epub 2015 Nov 16
86. le Coutre P, Kreuzer KA, Pursche S, et al. Pharmacokinetics and cellular uptake of imatinib and its main metabolite CGP74588. *Cancer Chemother Pharmacol*. 2004;53(4):313-323. <https://doi.org/10.1007/s00280-003-0741-6> Epub 2003 Dec 5.
87. Takayama N, Sato N, O'Brien SG, Ikeda Y, Okamoto S. Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. *Br J Haematol*. 2002;119(1):106-108.
88. van Erp NP, Gelderblom H, Karlsson MO, et al. Influence of CYP3A4 inhibition on the steady-state pharmacokinetics of imatinib. *Clin Cancer Res*. 2007;13(24):7394-7400. <https://doi.org/10.1158/1078-0432.CCR-07-0346>
89. Pick AM, Nystrom KK. Pazopanib for the treatment of metastatic renal cell carcinoma. *Clin Ther*. 2012;34(3):511-520. <https://doi.org/10.1016/j.clinthera.2012.01.014> Epub Feb 16.
90. Boudou-Rouquette P, Tlemsani C, Blanchet B, et al. Clinical pharmacology, drug-drug interactions and safety of pazopanib: a review. *Expert Opin Drug Metab Toxicol*. 2016;12(12):1433-1444. <https://doi.org/10.1080/17425255.2016.1225038> Epub 2016 Aug 24.
91. Gschwind HP, Pfaar U, Waldmeier F, et al. Metabolism and disposition of imatinib mesylate in healthy volunteers. *Drug Metab Dispos*. 2005;33(10):1503-1512. <https://doi.org/10.1124/dmd.105.004283> Epub 2005 Jul 8.
92. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. Pazopanib assessment report. 2010, June 14.
93. Bello CL, Sherman L, Zhou J, et al. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects. *Anticancer Drugs*. 2006;17(3):353-358.
94. Bello C, Bu H-Z, Patyna S, et al. A phase I mass-balance study to evaluate the metabolism and excretion of sunitinib (SU11248) in healthy male subjects. *Cancer Res*. 2007;67(9 Supplement):LB-354-LB.
95. Natarajan H, Kumar L, Bakhshi S, et al. Imatinib trough levels: a potential biomarker to predict cytogenetic and molecular response in newly diagnosed patients with chronic myeloid leukemia. *Leuk Lymphoma*. 2018;20:1-8.
96. Yu H, Steeghs N, Kloth JS, et al. Integrated semi-physiological pharmacokinetic model for both sunitinib and its active metabolite SU12662. *Br J Clin Pharmacol*. 2015;79(5):809-819. <https://doi.org/10.1111/bcp.12550>
97. Yoo C, Ryu MH, Ryoo BY, et al. Changes in imatinib plasma trough level during long-term treatment of patients with advanced gastrointestinal stromal tumors: correlation between changes in covariates and imatinib exposure. *Invest New Drugs*. 2012;30(4):1703-1708. <https://doi.org/10.1007/s10637-011-9633-5> Epub 2011 Jan 14.
98. Judson I, Ma P, Peng B, et al. Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC soft tissue and bone sarcoma group. *Cancer Chemother Pharmacol*. 2005;55(4):379-386. <https://doi.org/10.1007/s00280-004-0876-0> Epub 2004 Dec 9
99. Schmidli H, Peng B, Riviere GJ, et al. Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study. *Br J Clin Pharmacol*. 2005;60(1):35-44. <https://doi.org/10.1111/j.1365-2125.2005.02372.x>
100. Petain A, Kattygnarath D, Azard J, et al. Population pharmacokinetics and pharmacogenetics of imatinib in children and adults. *Clin Cancer Res*. 2008;14(21):7102-7109. <https://doi.org/10.1158/1078-0432.CCR-08-0950>
101. Menon-Andersen D, Mondick JT, Jayaraman B, et al. Population pharmacokinetics of imatinib mesylate and its metabolite in children and young adults. *Cancer Chemother Pharmacol*. 2009;63(2):229-238. <https://doi.org/10.1007/s00280-008-0730-x> Epub 2008 Apr 9.
102. Yamakawa Y, Hamada A, Nakashima R, et al. Association of genetic polymorphisms in the influx transporter SLCO1B3 and the efflux transporter ABCB1 with imatinib pharmacokinetics in patients with chronic myeloid leukemia. *Ther Drug Monit*. 2011;33(2):244-250. <https://doi.org/10.1097/FTD.0b013e31820beb02>
103. Adeagbo BA, Olugbade TA, Durosini MA, Bolarinwa RA, Ogunbenro K, Bolaji OO. Population pharmacokinetics of Imatinib in Nigerians with chronic myeloid Leukemia: clinical implications for dosing and resistance. *J Clin Pharmacol*. 2017;57(12):1554-1563. <https://doi.org/10.1002/jcph.953> Epub 2017 Jun 15.
104. Gurney H, Wong M, Balleine RL, et al. Imatinib disposition and ABCB1 (MDR1, P-glycoprotein) genotype. *Clin Pharmacol Ther*. 2007;82(1):33-40. <https://doi.org/10.1038/sj.cpt.6100201> Epub 2007 May 9.
105. Gibbons J, Egorin MJ, Ramanathan RK, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: a study by the National Cancer Institute organ dysfunction working group. *J Clin Oncol*. 2008;26(4):570-576. <https://doi.org/10.1200/JCO.2007.13.3819>
106. Liu J, Chen Z, Chen H, et al. Genetic polymorphisms contribute to the individual variations of Imatinib Mesylate plasma levels and adverse reactions in Chinese GIST patients. *Int J Mol Sci*. 2017;18(3pii: ijms18030603):1-14. <https://doi.org/10.3390/ijms18030603>
107. Verboom MC, Kloth JSL, Swen JJ, et al. Genetic polymorphisms in ABCG2 and CYP1A2 are associated with imatinib dose reduction in patients treated for gastrointestinal stromal tumors. *Pharmacogenomics J*. 2019;4(10):019-0079.

108. Chatelut E, Gandia P, Gotta V, Widmer N. Long-term prospective population PK study in GIST patients—letter. *Clin Cancer Res.* 2013; 19(4):949–949. <https://doi.org/10.1158/1078-0432.CCR-12-3445> Epub 2013 Feb 5.
109. Bins S, Eechoute K, Kloth JS, et al. Prospective analysis in GIST patients on the role of Alpha-1 acid glycoprotein in Imatinib exposure. *Clin Pharmacokinet.* 2017;56(3):305-310. <https://doi.org/10.1007/s40262-016-0441-0>
110. Yoo C, Ryu MH, Kang BW, et al. Cross-sectional study of imatinib plasma trough levels in patients with advanced gastrointestinal stromal tumors: impact of gastrointestinal resection on exposure to imatinib. *J Clin Oncol.* 2010;28(9):1554-1559. <https://doi.org/10.1200/JCO.2009.26.5785> Epub 2010 Feb 22.
111. Wu X, Li J, Zhou Y, et al. Relative factors analysis of Imatinib trough concentration in Chinese patients with gastrointestinal stromal tumor. *Chemotherapy.* 2018;63(6):301-307. <https://doi.org/10.1159/000493195> Epub 2019 Mar 5.
112. Franke RM, Sparreboom A. Inhibition of imatinib transport by uremic toxins during renal failure. *J Clin Oncol.* 2008;26(25):4226-4227author reply 7-8. <https://doi.org/10.1200/JCO.2008.18.4390>
113. Houk BE, Bello CL, Kang D, Amantea M. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. *Clin Cancer Res.* 2009;15(7):2497-2506. <https://doi.org/10.1158/1078-0432.CCR-08-1893> Epub 2009 Mar 3.
114. Kloth JS, Klumpen HJ, Yu H, et al. Predictive value of CYP3A and ABCB1 phenotyping probes for the pharmacokinetics of sunitinib: the ClearSun study. *Clin Pharmacokinet.* 2014;53(3):261-269. <https://doi.org/10.1007/s40262-013-0111-4>
115. Mizuno T, Fukudo M, Fukuda T, et al. The effect of ABCG2 genotype on the population pharmacokinetics of sunitinib in patients with renal cell carcinoma. *Ther Drug Monit.* 2014;36(3):310-316. <https://doi.org/10.1097/FTD.0000000000000025>
116. Khosravan R, Motzer RJ, Fumagalli E, Rini BI. Population pharmacokinetic/pharmacodynamic modeling of sunitinib by dosing schedule in patients with advanced renal cell carcinoma or gastrointestinal stromal tumor. *Clin Pharmacokinet.* 2016;55(10):1251-1269. <https://doi.org/10.1007/s40262-016-0404-5>
117. Chae JW, Teo YL, Ho HK, et al. BSA and ABCB1 polymorphism affect the pharmacokinetics of sunitinib and its active metabolite in Asian mRCC patients receiving an attenuated sunitinib dosing regimen. *Cancer Chemother Pharmacol.* 2016;78(3):623-632. <https://doi.org/10.1007/s00280-016-3104-9> Epub 2016 Aug 2.
118. Zhang Y, Mai H, Guo G, et al. Association analysis of SNPs present in plasma with adverse events and population pharmacokinetics in Chinese sunitinib treated patients with renal cell carcinoma. *Oncotarget.* 2018;9(18):14109-14123. <https://doi.org/10.18632/oncotarget.23881> eCollection 2018 Mar 6.
119. Narjoz C, Cessot A, Thomas-Schoemann A, et al. Role of the lean body mass and of pharmacogenetic variants on the pharmacokinetics and pharmacodynamics of sunitinib in cancer patients. *Invest New Drugs.* 2015;33(1):257-268. <https://doi.org/10.1007/s10637-014-0178-2> Epub 2014 Oct 25.
120. Diekstra MH, Klumpen HJ, Lolkema MP, et al. Association analysis of genetic polymorphisms in genes related to sunitinib pharmacokinetics, specifically clearance of sunitinib and SU12662. *Clin Pharmacol Ther.* 2014;96(1):81-89. <https://doi.org/10.1038/clpt.2014.47> Epub Feb 24.
121. de Jong FA, Marsh S, Mathijssen RH, et al. ABCG2 pharmacogenetics: ethnic differences in allele frequency and assessment of influence on irinotecan disposition. *Clin Cancer Res.* 2004; 10(17):5889-5894. <https://doi.org/10.1158/1078-0432.CCR-04-0144>
122. Garcia-Donas J, Esteban E, Leandro-Garcia LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. *Lancet Oncol.* 2011;12(12):1143-1150. [https://doi.org/10.1016/S1470-2045\(11\)70266-2](https://doi.org/10.1016/S1470-2045(11)70266-2) Epub 2011 Oct 17.
123. Diekstra MH, Swen JJ, Boven E, et al. CYP3A5 and ABCB1 polymorphisms as predictors for sunitinib outcome in metastatic renal cell carcinoma. *Eur Urol.* 2015;68(4):621-629. <https://doi.org/10.1016/j.eururo.2015.04.018> Epub Apr 27.
124. van Erp NP, Baker SD, Zandvliet AS, et al. Marginal increase of sunitinib exposure by grapefruit juice. *Cancer Chemother Pharmacol.* 2011;67(3):695-703. <https://doi.org/10.1007/s00280-010-1367-0> Epub 2010 May 29.
125. Bello CL, Garrett M, Sherman L, Smeraglia J, Ryan B, Toh M. Pharmacokinetics of sunitinib malate in subjects with hepatic impairment. *Cancer Chemother Pharmacol.* 2010;66(4):699-707. <https://doi.org/10.1007/s00280-009-1213-4> Epub 2010 Jan 5.
126. Khosravan R, Toh M, Garrett M, et al. Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. *J Clin Pharmacol.* 2010;50(4):472-481. <https://doi.org/10.1177/0091270009347868> Epub 2009 Sep 24.
127. de Wit D, van Erp NP, den Hartigh J, et al. Therapeutic drug monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study. *Ther Drug Monit.* 2015;37(3):331-338. <https://doi.org/10.1097/FTD.0000000000000141>
128. Imbs DC, Negrier S, Cassier P, et al. Pharmacokinetics of pazopanib administered in combination with bevacizumab. *Cancer Chemother Pharmacol.* 2014;73(6):1189-1196. <https://doi.org/10.1007/s00280-014-2455-3> Epub 2014 Apr 6.
129. Baneyx G, Combes FP, Huang PH, Elmeliegy M. Population pharmacokinetic modeling of pazopanib in healthy volunteers and patients with advanced renal cell carcinoma, 2017 [Available from: <https://www.page-meeting.org/default.asp?abstract=7105>.
130. Bins S, Huitema ADR, Laven P, et al. Impact of CYP3A4 22 on Pazopanib pharmacokinetics in cancer patients. *Clin Pharmacokinet.* 2018;27(10):018-0719.
131. Heath EI, Chiorean EG, Sweeney CJ, et al. A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat meal in patients with advanced solid tumors. *Clin Pharmacol Ther.* 2010;88(6):818-823. <https://doi.org/10.1038/clpt.2010.199> Epub Oct 27.
132. Shibata SI, Chung V, Synold TW, et al. Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute organ dysfunction working group study. *Clin Cancer Res.* 2013;19(13):3631-3639. <https://doi.org/10.1158/1078-0432.CCR-12-3214> Epub 2013 May 7.
133. Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. Pazopanib summary of product characteristics. 2013 [Available from: https://www.ema.europa.eu/documents/product-information/votrient-epar-product-information_en.pdf.
134. Tan AR, Gibbon DG, Stein MN, et al. Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. *Cancer Chemother Pharmacol.* 2013;71(6):1635-1643. <https://doi.org/10.1007/s00280-013-2164-3> Epub 2013 May 1.
135. Groenland SL, Mathijssen RHJ, Beijnen JH, Huitema ADR, Steeghs N. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. *Eur J Clin Pharmacol.* 2019;7(10):019-02704.
136. Lankheet NA, Kloth JS, Gadellaa-van Hooijdonk CG, et al. Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. *Br J Cancer.* 2014;110

- (10):2441-2449. <https://doi.org/10.1038/bjc.2014.194> Epub Apr 15.
137. Groenland SL, Katz D, Huitema ADR, Steeghs N. Harnessing soft tissue sarcoma with low-dose pazopanib—a matter of blood levels. *BMC Cancer*. 2018;18(1):1–3. <https://doi.org/10.1186/s12885-018-5043-9>
138. Lubberman FJE, Gelderblom H, Hamberg P, et al. The effect of using pazopanib with food vs fasted on pharmacokinetics, patient safety and preference (DIET study). *Clin Pharmacol Ther*. 2019; 106(5):1076–1082. <https://doi.org/10.1002/cpt.1515>. Epub 2019 Jul 9.
139. Groenland SL, van Eerden RA, Verheijen RB, Huitema A, Mathijssen RH, Steeghs N. Boosting pazopanib exposure by splitting intake moments: A prospective pharmacokinetic study in cancer patients. *J Clin Oncol*. 2019;37(15_suppl):3119–3119.
140. van Leeuwen RW, Peric R, Hussaarts KG, Kienhuis E, NS IJ, de Bruijn P, et al. Influence of the acidic beverage cola on the absorption of Erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol*. 2016;34(12):1309–1314. <https://doi.org/10.1200/JCO.2015.65.2560> Epub 6 Feb 8.
141. Lubberman FJE, Gelderblom H, Wilmer CM, et al. Does a glass of coke boost the exposure to imatinib in gastrointestinal stromal tumour patients after gastrectomy? *Br J Clin Pharmacol*. 2017;83(10):2312–2314. <https://doi.org/10.1111/bcp.13333> Epub 2017 Jul 4.
142. Bertolaso P, Gross-Goupil M, Molimard M, Cochin V, Ravaud A, Daste A. Drug interaction with Sunitinib and the evidence of therapeutic drug monitoring: a case report and review of the literature. *Clin Genitourin Cancer*. 2017;15(5):e885–e887. <https://doi.org/10.1016/j.clgc.2017.05.004> Epub May 10.
143. Da Silva F, Thomas-Schoemann A, Huillard O, Goldwasser F, Blanchet B. Benefit of therapeutic drug monitoring to disclose pharmacokinetic interaction between sunitinib and calcium channel blocker. *Ann Oncol*. 2016;27(8):1651–1652. <https://doi.org/10.1093/annonc/mdw182> Epub 2016 Apr 26.
144. van Kinschot CM, van Erp NP, Feberwee T, Dezentje VO. Sunitinib treatment in a patient with metastatic renal cell carcinoma and bariatric surgery. *Eur J Clin Pharmacol*. 2015;71(10):1279–1281. <https://doi.org/10.1007/s00228-015-1902-3> Epub 2015 Jul 16.
145. Thiery-Vuillemin A, Montange D, Kalbacher E, et al. Impact of sunitinib pharmacokinetic monitoring in a patient with metastatic renal cell carcinoma undergoing hemodialysis. *Ann Oncol*. 2011;22(9):2152–2154. <https://doi.org/10.1093/annonc/mdr343>
146. Moyle GJ, Back D. Principles and practice of HIV-protease inhibitor pharmacoenhancement. *HIV Med*. 2001;2(2):105–113.
147. Reimers MA, Shango MM, Daignault-Newton S, et al. Pazopanib with low fat meal (PALM) in advanced renal cell carcinoma. *Invest New Drugs*. 2018;5(10):018–0692.
148. McAlister RK, Aston J, Pollack M, Du L, Koyama T, Chism DD. Effect of concomitant pH-elevating medications with Pazopanib on progression-free survival and overall survival in patients with metastatic renal cell carcinoma. *Oncologist*. 2018;23(6):686–692. <https://doi.org/10.1634/theoncologist.2017-0578> Epub 2018 Feb 27.
149. Mir O, Touati N, Lia M, et al. Impact of concomitant Administration of Gastric Acid-Suppressive Agents and Pazopanib on outcomes in soft-tissue sarcoma patients treated within the EORTC 62043/62072 trials. *Clin Cancer Res*. 2019;25(5):1479–1485. <https://doi.org/10.1158/1078-0432.CCR-18-2748> Epub 019 Feb 14.
150. Heath EI, Forman K, Malburg L, et al. A phase I pharmacokinetic and safety evaluation of oral pazopanib dosing administered as crushed tablet or oral suspension in patients with advanced solid tumors. *Invest New Drugs*. 2012;30(4):1566–1574. <https://doi.org/10.1007/s10637-011-9725-2> Epub 2011 Aug 3.
151. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091–D106. <https://doi.org/10.3/nar/gkx121>
152. Alexander SP, Kelly E, Marrion NV, et al. The Concise Guide to PHARMACOLOGY 2017/18: Overview. *Br J Pharmacol*. 2017Dec; 174(Suppl 1):S1–S16. <https://doi.org/10.1111/bph.13882>

SUPPORTING INFORMATION

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

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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

Leiden University Medical Center, Leiden, the Netherlands

University Medical Center Groningen, Groningen, the Netherlands

Radboud University Medical Center, Nijmegen, the Netherlands

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