JAASP http://www.aaspjournal.org
Journal of Asian Association of Schools of Pharmacy 2020; 9: 1–9

Review

Personalized pharmacotherapy with sunitinib and pazopanib for Asian patients

Satoshi Noda, Shin-ya Morita and Tomohiro Terada*

Department of Pharmacy, Shiga University of Medical Science Hospital, Otsu, Japan

Received November 29, 2019
Revised January 23, 2020
Accepted January 28, 2020

* Corresponding author
Department of Pharmacy, Shiga University of Medical Science Hospital, Otsu City, Shiga 520-2192, Japan
E-mail: teradat@belle.shiga-med.ac.jp

ABSTRACT

In Asia, molecular-targeted therapies using tyrosine kinase inhibitors (TKIs) have achieved a significant increase in the overall survival of cancer patients. These agents are mainly administrated orally at a fixed dose, which often causes large interindividual variability of clinical pharmacokinetic and/or pharmacodynamic (PK/PD) parameters. In particular, Asian patients experience more drug toxicity in response to certain TKIs compared to non-Asian patients. This often results in dose reduction or complete termination of treatment, which has initiated efforts to optimize the dosing schedule to improve drug tolerance. To address these issues, therapeutic drug monitoring has been applied in clinical settings. This review article summarizes the pharmacological factors that are known to cause variations in PK/PD parameters, such as genetic polymorphisms of metabolic enzymes and transporters and drug–drug interactions. This review also discusses the possibility of dose individualization in Asian patients during TKI therapy, primarily focusing on sunitinib or pazopanib.

Key words: tyrosine kinase inhibitors, individual dosing, therapeutic drug monitoring, Asians

1. Introduction

Recent progress in the development of molecular-targeted agents has expanded treatment options for patients with various carcinomas, such as renal cell carcinoma (RCC) (Motzer et al., 2007, 2013) and soft tissue sarcoma (van der Graaf et al., 2012). Molecular-targeted therapies using tyrosine kinase inhibitors (TKIs) are designed to disrupt tumor-related signaling pathways, such as those involved in angiogenesis, tumor proliferation, and cell apoptosis. In contrast to most traditional chemotherapeutic agents, certain TKIs are initially administered orally at a fixed dose. Certain TKIs show an exposure–response and exposure–toxicity relationship and exposure highly vary between patients (Verheijen et al., 2017). In general, drug efficacy and safety are determined by the interplay of multiple processes that regulate pharmacokinetics (e.g., absorption, distribution, metabolism, and excretion) and pharmacodynamics (e.g., mechanism of drug action). For orally administered drugs, pharmacological action is dependent on their adequate intestinal absorption and distribution to other tissues before their elimination via metabolic and excretory pathways (Klümpen et al., 2011). Although drug-metabolizing enzymes are established as key determinants of pharmacokinetic parameters, membrane transport processes mediated by drug transporters also play an important role in determining pharmacokinetic properties (Terada et al., 2015).

In clinical practice, TKIs are given orally on a daily basis (with or without a drug holiday) at fixed doses, which may cause significant variation between individuals in terms of clinical efficacy and toxicity (Gao et al., 2012). Considering that the body size of Asian patients is smaller than that of western countries patients, the fixed dosage of TKIs based on clinical trial developed by western countries tends to be too high for Asian patients. However, there is little evidence that adjusting for body weight is useful for TKIs (Gao et al., 2012). Consequently, weight-based strategy has not implemented for Asian patient treated with TKIs in clinical settings. It is also widely recognized that renal and/or hepatic functions, genetic background, adherence to treatment, and nongenetic factors (drug–drug interactions and drug-food interactions) can cause pharmacokinetic variation of TKIs by altering drug exposure (Klümpen et al., 2011). Among these factors, genetic polymorphisms of the breast cancer resistance protein (BCRP/ABCG2) have been reported to have a major impact on the drug exposure of certain TKIs (Hira and Terada, 2018; Mizuno et al., 2010, 2012, 2014).

Sunitinib is an oral TKI that targets multiple receptors such as the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors (PDGFR),

and stem-cell factor receptor. Similarly, pazopanib is an oral TKI that targets VEGFR, PDGFR, and c-Kit tyrosine kinases. Sunitinib is used as first-line therapy to treat patients with RCC and gastrointestinal stromal tumors (Adams and Leggas, 2007; Motzer et al., 2007), and pazopanib is approved for first-line therapy of advanced RCC and as a second-line treatment for non-adipocytic soft tissue sarcoma (Motzer et al., 2013; van der Graaf et al., 2012). Although sunitinib and pazopanib are effective drugs, patients often experience certain adverse drug side effects such as hypertension, thrombocytopenia, hand-foot syndrome (HFS), hepatotoxicity, and fatigue. Because drug toxicities are difficult to anticipate and reduce the quality of life of patients, dose reduction or discontinuation is often required in clinical settings. In fact, due to drug toxicity, 28%–38% of sunitinib-treated patients and 16%–24% pazopanib-treated patients experienced dose interruptions in a pivotal phase III trial (Demetri et al., 2006; Escudier et al., 2014; Motze et al., 2007, 2013). Interestingly, Asian patients exhibited a higher frequency of adverse events compared to non-Asian patients following sunitinib and pazopanib treatment. For example, as compared to RCC patients in Western countries, Asian patients show an increased frequency of thrombocytopenia and HFS induced by sunitinib. For this reason, about 80% of Japanese and Korean patients are forced to discontinue or reduce the dose of sunitinib during treatment (Hong et al., 2009; Uemura et al., 2010). Recent meta-analysis demonstrated that the efficacy of sunitinib in Asian patients was similar to that of Caucasian patients and that Asian patients showed a higher incidence of all grades of toxicity of HFS, >grade 2 fatigue, >grade 2 HFS, and >grade 2 thrombocytopenia (Liu et al., 2017). Similarly, in response to pazopanib treatment Asian patients had a higher incidence of all grades of palmar-plantar erythrodysesthesia, increased AST, proteinuria, neutropenia, leukopenia, thrombocytopenia, increased ALT, increased bilirubin, and grade 3 hypertension (Guo et al., 2018). These findings demonstrate there is a need to establish individualized pharmacotherapy of sunitinib and pazopanib in Asian patients.

Various efforts to achieve optimal dosing have been attempted. These include dose individualization of TKIs, such as phenotype-guided dosing, genotype-guided dosing, toxicity-adjusted dosing and therapeutic drug monitoring (TDM) (Klümpen et al., 2011). Considering applications in clinical practice, TDM is a very promising strategy and recent evidence indicates that certain pharmacokinetic parameters, including trough levels, are correlated with clinical outcomes for certain TKIs, such as imatinib, sunitinib, and pazopanib (Gao et al., 2012; Verheijen et al., 2017; Yu et al., 2014). Furthermore, it is recognized that there are ethnic differences between Asian and non-Asian patients in terms of genetic polymorphisms of drug-metabolizing enzymes and drug transporters.

Pharmacotherapy of TKIs is continuously evolving by adopting current basic and clinical pharmacological evidence in an effort to resolve the clinical problems observed in daily practice. In this article, we review the most recent advances in basic and clinical research of factors that affect the pharmacokinetics/pharmacodynamics of sunitinib and pazopanib. Also, we summarize the extensive information on the role of drug transporters in affecting pharmacokinetic variation that has recently been published.

2. Genetic polymorphisms of drug-metabolizing enzymes and transporters and their effects on pharmacokinetic parameters

Most TKIs are administered orally and at a fixed dose. Orally administered drugs are absorbed by the intestine through influx and efflux steps, which may be mediated by drug transporters. Although it is not necessary to consider this process for classical injectable anticancer agents, the intestinal absorption of orally administered drugs may cause large pharmacokinetic variability, likely due to the fat content of food, coadministration with gastric acid-reducing drugs, and the functional role of intestinal drug transporters. In this section, we first summarize the pharmacokinetic factors that regulate the drug disposition of sunitinib and pazopanib, focusing on the effects of genetic polymorphisms of drug-metabolizing enzymes and transporters.

2.1. Sunitinib

Sunitinib is primarily metabolized by CYP3A4 to the equally active metabolite SU12662. SU12662 is further metabolized to inactive moieties by CYP3A4 (Adams and Leggas, 2007). *In vitro* transport studies have demonstrated that sunitinib is a substrate for ABCB1 and ABCG2 (Hu et al., 2009; Mizuno et al., 2010). A pharmacokinetic/pharmacogenomics study showed that the *ABCG2* c.421C>A polymorphism was associated with increased sunitinib exposure in RCC patients (Mizuno et al., 2012). Furthermore, a population pharmacokinetic analysis demonstrated that the *ABCG2* 421C>A polymorphism is a significant covariate for the prediction of oral clearance of sunitinib (Mizuno et al., 2014). A previously report had an RCC patient who experienced certain severe adverse events (facial acne, hypothyroidism, and thrombocytopenia) early after the start of sunitinib therapy (Mizuno et al., 2010). Pharmacokinetic analyses revealed that this patient had been exposed to concentrations of sunitinib (Area under the blood concentration-time curve [AUC] on day 8 after the initiation of sunitinib 50 mg daily) that were 2.5-fold higher compared to four other patients. No remarkable difference was observed in nongenetic factors such as concomitant medications and patient characteristics. Interestingly, this patient was homozygous for the *ABCG2* c.421C>A polymorphism, whereas the other patients were heterozygous or wild-type. Mizuno et al., also reported that the dose-adjusted $AUC_{0\text{-}24}$ of sunitinib was significantly higher in patients with a

heterozygous variant for *ABCG2 421 C>A* than in wild-type patients and one homozygous patient showed the highest dose-adjusted AUC_{0-24} in the expanded sunitinib metastatic RCC Japanese cohort (Mizuno et al., 2012). These results were further confirmed in Korean metastatic RCC patients in a pharmacodynamic/pharmacogenomic study (Kim et al., 2013). Another pharmacogenomics study indicated that the homozygous variant of *ABCG2* c.421C>A was associated with severe thrombocytopenia in 219 Japanese patients with RCC (Low et al., 2016). These pharmacogenomic studies, together with the *in vitro* and *in vivo* sunitinib transport studies, revealed that sunitinib is a substrate of ABCG2 and decrease of its function due to the *ABCG2* c.421C>A polymorphism can lead to an increase in systemic exposure to sunitinib.

Sunitinib-related toxicity is observed more frequently in Asian patients than in non-Asian patients (Gore et al., 2009; Hong et al., 2009; Motzer et al., 2007; Uemura et al., 2010; Yoo et al., 2010). In contrast to Asian patients, the impacts of the *ABCG2* c.421C>A genotype on sunitinib efficacy and toxicity have not been identified in European patients (Diekstra et al., 2014; Garcia-Donas et al., 2011; van der Veldt et al., 2011; van Erp et al., 2009). Interestingly, the *ABCG2* c.421C>A genotype appears to be more common in Asians (allele frequency, 26.6%–35.0%), whereas this allele is very rare in sub-Saharan Africans (1.0%) and Caucasian populations (7.4%–11.1%) (Giacomini et al., 2013). A population pharmacokinetic analysis indicated that Asian patients is significantly associated with decreased oral clearance of sunitinib compared to western country patients (Houk et al., 2009). These results suggest that *ABCG2* c.421C>A is one of the reasons contributing to the ethnic differences in sunitinib pharmacokinetics and toxicity. From these results, the *ABCG2* c.421C>A genotype was identified as a significant covariate for the prediction of the oral clearance of sunitinib, suggesting that the assessment of the *ABCG2* variant could help to identify patients at high risk of increased exposure to sunitinib. *ABCG2 376C>T* introduce a stop codon resulting in a non-functional ABCG2 and is present at low frequencies in Japanese (Kobayashi et al., 2005). However, an association of other ABCG2, including ABCG2 376C>T, with the PK of sunitinib has not been reported.

2.2. Pazopanib

Pazopanib is mainly metabolized by CYP3A4 (minor metabolism by CYP1A2 and CYP2C8), in the liver and excreted in the feces, with <4% being extracted by the kidney. Pazopanib is a substrate for P-glycoprotein (P-gp/ABCB1) and the breast cancer resistance protein (BCRP/ABCG2) (Keisner and Shah, 2011). However, the relationships between pazopanib PK and the polymorphism of ABCB1 and ABCG2 have not been reported. Pazopanib is known to inhibit the organic anion transporter 1B1 (OAT1B1) and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), with IC_{50} values of 0.79 and 1.2 mmol/L (Keisner and Shah, 2011). Recently, Ellawatty et al. suggested that the organic cation transporter-1 (OCT1) is responsible for hepatocellular uptake of pazopanib in both *in vitro* and *in vivo* studies (Ellawatty et al., 2018). A population pharmacokinetic analysis reported that *CYP3A4*22* resulted in a 35% low clearance of pazopanib (Bins et al., 2019).

Analysis of previous pazopanib clinical trials found that *UGT1A1*28* was associated with increased hyperbilirubinemia (Xu et al., 2010). A recent pharmacogenomics study suggested that the mechanism of pazopanib-induced hepatotoxicity is related to genetic mutations in the human leukocyte antigen (HLA-B*57:01), suggesting that hepatotoxicity is mediated by an immunologic reaction (Xu et al., 2016). In addition, pazopanib-associated ALT elevations are associated with polymorphisms in HFE (rs2858996 and rs707889), which suggests a mechanism involving perturbation of iron metabolism in the liver (Xu et al., 2011).

3. Other factor that influence pharmacokinetic parameters

Sunitinib clearance is reported to be affected by body weight and gender (Chae et al., 2016; Houk et al., 2009; Narjoz et al., 2015). The effects of body weight and gender on sunitinib PK is limited, so starting dose of sunitinib is not recommended base on these characteristics in clinical settings (Westerdijk et al., 2019). Certain studies explore the effect of body composition parameters on severe toxicity of sunitinib. Cancer Cachexia is a dramatic wasting syndrome and causes reduced physical function and quality of life, partly resulting in sarcopenia (the condition of low muscle mass) (Fearon et al., 2011). In fact, RCC patients frequently developed cancer cachexia, and approximately 50% of RCC patients was found to be sarcopenia (Antoun et al., 2010). Interestingly, a previous study reported that sarcopenia and low body mass index (BMI) predict sunitinib-induced early dose-limiting toxicities in patients with RCC (Huillard et al., 2013). Therefore, this study suggests that RCC patients with sarcopenia and low BMI should be monitored carefully early sunitinib-induced severe toxicities. No sunitinib concentrations were measured, however, sarcopenia might result in alterations in the PK parameters (e.g. distribution, metabolism and clearance) of sunitnib. Actually, AUC of sorafenib, another TKI, was significantly higher in sarcopenic patients with hepatocellular carcinoma (Mir et al., 2012). Further PK studies are needed in sarcopenic patients treated with sunitinib. Sunitinib PK is not reported to be different in patients with normal hepatic function, mild, or moderate hepatic impairment (Bello et al., 2010). Therefore, dose adjust is not necessary for sunitinib treatment in patients with mild to moderate hepatic impairment.

The influence of hepatic impairment on the PKs of pazopanib has been clarified (Pick and Nystrom, 2012).

Pazopanib clearance is decreased by 50% in patients with pre-existing moderate hepatic impairment, defined as total bilirubin between 1.5 and 3 times the upper limit of normal. A daily dose of 200 mg is recommended for patients with moderate hepatic impairment. Pazopanib should be avoided in patients with severe hepatic impairment (total bilirubin >3 the upper limit of normal with any elevation of alanine aminotransferase levels). Regarding pazopanib, the relationship between body weight or sarcopenia and PK has not been reported.

4. Pharmacokinetic drug-drug interactions

Drug interactions in oncology are of particular importance due to their narrow therapeutic index and the inherent toxicity of anticancer agents (Scripture and Figg, 2006). As such, drug–drug interactions have become a serious issue in chemotherapy. In most pharmacokinetic drug interactions, drug metabolites and/or transporters are involved in the underlying mechanisms (Scripture and Figg, 2006). Some examples of typical drug–drug interactions for sunitinib and pazopanib are shown in Table 1. As the solubility of oral TKIs depends on the gastric pH, we also summarized the influences of concomitant food intake and histamine H_2-receptor antagonists (H_2 blockers)/proton pump inhibitors (PPIs) for sunitinib and pazopanib in Table 1.

Drug–drug interactions with a CYP3A4 inducer or inhibitor caused a notable change in the AUC of sunitinib (Adams and Leggas, 2007). Because the solubility of sunitinib does not decline until pH6.8, no effect on sunitinib would be expected during treatment with H_2 blockers or PPIs (van Leeuwen et al., 2014). Additionally, there were no effects of food intake on the AUC of sunitinib or the pharmacokinetics of sunitinib and its metabolite SU12662 (Bello et al., 2006). However, we should be aware that the AUC of sunitinib increased by 11% in combination with grapefruit juice, which is a known inhibitor of intestinal CYP3A4 (van Erp et al., 2011).

In combination with the CYP3A4 inhibitor ketoconazole, the AUC and C_{max} of pazopanib were increased by 66% and 45%, respectively (Tan et al., 2013). Similarly, coadministration with pazopanib at 400 and 800 mg/day increased the AUC of SN-38, an active metabolite of irinotecan by 38% and 89%, respectively (Bennouna et al., 2015). This interaction may be because SN-38 is primarily taken up by OATP1B1 (Fujita et al., 2014). Daily administration of pazopanib (800 mg) with the CYP3A4 and CYP2C8 substrate paclitaxel (80 mg/m^2) increased the paclitaxel AUC and C_{max} by 26% and 31%, respectively (Sanford and Keating, 2010). Pazopanib also increased the AUC of docetaxel, perhaps because it inhibited CYP3A and OATP1B1 (Hamberg et al., 2015).

Concomitant use of pazopanib and simvastatin has been shown to significantly increase the risk of the incidence of ALT ≥ 3 × upper limit of normal (ULN) in patients with cancer (Xu et al., 2012). Exploratory pharmacogenetic analyses revealed that the *ABCG2* c.421C>A polymorphism may be associated with ALT elevation in patients treated with pazopanib and simvastatin. Patients with the *ABCG2* c.421C>A allele had a higher incidence of ALT ≥ 3 × ULN compared to patients with the wild-type allele. This polymorphism was not associated with ALT elevations in pazopanib-treated patients without concurrent use of statins.

Pazopanib should be taken at least 1 hour before or 2 hours after a meal, as administration with a low- or high-fat meal is associated with a >2-fold increase in the C_{max} and AUC of pazopanib (Sanford and Keating, 2010). Lubberman et al. indicated that a 600 mg dose of pazopanib taken with a continental breakfast is bioequivalent to an 800 mg dose of pazopanib taken in a fasted state (Lubberman et al., 2019).

The solubility of pazopanib decreases above pH 4 (Budha et al., 2012), indicating that a decrease in acid secretion could contribute to decreased solubility and absorption of pazopanib. As expected, concomitant use of pazopanib with a PPI, which inhibits gastric secretion for >24 hours, resulted

Table 1. Factors causing pharmacokinetic variation of sunitinib and pazopanib.

	Sunitinib	Pazopanib
SNPs*	*ABCG2* c.421C>A 2.5-fold higher concentration [a, b, c]	
CYP3A4 inhibitors/inducers*	Rifampicin AUC 54%, C_{max} 77%[d]	Phenytoin or carbamazepine AUC 70%, C_{max} 50% [h]
	Ketoconazole AUC 151%, C_{max}149% [d]	Ketoconazole AUC 166%, C_{max}145% [i]
	grapefruit juice AUC 111% [e]	
PPIs/H_2 inhibitors*	No effect [f]	Esomeprazol AUC 60%, C_{max} 58% [i]
Fasting/Fed*	No effect [g]	AUC 219%, C_{max} 213% (high fat meal in take) [j]

*compared with control.
PPIs: proton pump inhibitors, H_2 inhibitors: histamine H_2-receptor antagonists, AUC: area under the curve.
Fasting is the condition that the drug is administered on an empty stomach.
Fed is the condition that drug is administered shortly after a meal.
Data compiled from a, Mizuno, et al., 2010; b, Mizuno, et al., 2012; c, Mizuno, et al., 2014; d, Adams & Leggas, 2007; e; van Erp et al., 2011; f, Budha, et al. 2012; g, Bello et al., 2006; h, van Leeuwen et al. 2014; i, Tan et al., 2013; j, Heath et al., 2010.

in a marked decrease in the absorption and bioavailability of pazopanib (Tan et al., 2013; Warrington et al., 2002). Therefore, the current recommendation is to avoid the use of gastric acid-reducing agents and, if unavoidable, take pazopanib without food once daily in the evening concomitantly with a PPI (Verheijen et al., 2017). If concomitant use of an H_2-receptor antagonist is necessary, pazopanib could be given without food for 2 hours within 10 hours following administration of an H_2-receptor antagonist, which starts to reduce gastric secretion 2.5 hours after doing, and lasts up to 10 hours. Interestingly, a recent clinical study suggested that coadministration of long-term gastric acid-suppressive (GAS) agent therapy (e.g., PPI) with pazopanib was associated with significantly shortened -progression-free survival and Overall survival in patients with advanced soft tissue carcinoma. Withdrawal of GAS agents must be considered whenever possible. TDM of pazopanib plasma concentrations may be helpful for patients on pazopanib and GAS therapy (Mir et al., 2019).

5. TDM

Retrospective studies have shown that targeted drug exposure, reflected in the AUC, correlates with treatment response (efficacy/toxicity) in various cancers (de Wit et al., 2015; Verheijen et al., 2017). However, the levels of evidence for TDM are heterogeneous among these agents, and TDM is still uncommon for the majority of them. Current evidence suggests a benefit of using TDM to guide dosing of imatinib, while this idea is just emerging for sunitinib and pazopanib (Verheijen et al., 2017). TDM during oral targeted therapies might only be useful for particular situations including a lack of therapeutic response, severe or unexpected toxicities, unanticipated drug–drug interactions and/or concerns over adherence to treatment (Terada et al., 2015).

5.1. Current dose

Table 2 describes the current dose of approved indications. As indicated below, the initial doses of these TKIs are fixed. Sunitinib is initially administered orally at 50 mg per day for a cycle of 4 weeks on and 2 weeks off in patients with RCC. Dose reductions to either 37.5 mg or 25 mg per day are permitted based on individual tolerability. Pazopanib treatment begins with a daily 800 mg dose. Because the pharmacokinetic variability of these drugs is very high, fixed dose regimens result in variation of the efficacy and adverse side effects. The interpatient variability of these drugs is presented in Table 2.

5.2. Target concentration

5.2.1. Sunitinib target concentration

Sunitinib inhibits VEGFR-2 and PDGF-β phosphorylation in tumor-bearing mice when administered at a dose of 50 to 100 ng/ml (Mendel et al., 2003). A clinical trial (Faivre et al., 2006) reported that the total sunitinib trough concentration (sunitinib + SU12662) obtained following a daily dose of 50 mg ranged from 50 to 100 ng/ml. The results from a case study of three patients in this trial indicated that total sunitinib trough concentrations ≥ 100 ng/mL might be associated with dose-limiting toxicities (Faivre et al., 2006). A phase II study also reported that total sunitinib was effective at plasma trough concentrations ≥ 50 ng/ml in Japanese patients with metastatic RCC (Uemura et al., 2010). Additionally, Mizuno et al. showed that dose-limiting toxicities were often observed in Japanese RCC patients with total sunitinib trough concentrations >90 ng/mL (Mizuno et al., 2012). We reported that patients with concentrations ≥ 100 ng/mL of total sunitinib (n = 8), compared to patients with <100 ng/mL (n = 13), had a higher incidence of grade ≥ 3 toxicities (75% vs. 23%), resulting in shortened progression-free survival (Noda et al., 2015). Furthermore, Nagata et al indicated that the required total trough level of sunitinib to avoid severe thrombocytopenia should be <100 ng/mL using a PK/PD model simulation (Nagata et al., 2015). Therefore, the target range could be a total sunitinib trough concentration of 50–100 ng/mL during therapy. Recently, Lankheet et al. reported that a pharmacokinetic-guided dosing strategy could be effective during treatment of advanced solid tumors (Lankheet et al., 2014). In their study, patients were treated with a daily dose of 37.5 mg of sunitinib. Plasma trough levels of total sunitinib were measured on days 15 and 29 following the initiation of treatment. If the trough levels were <50 ng/ml and the patient did not show any grade 3 toxicity, the daily sunitinib dose was increased by 12.5 mg per day. If the patient suffered from grade 3 toxicity, the dose was lowered by 12.5 mg per day. With the starting dose, the total sunitinib concentrations were below the target range in 15 patients (52%). Of these, five patients (17%) reached the target level after their dose was increased without any

Table 2. Current doses, interpatient pharmacokinetic variations, and target concentration of sunitinib and pazopanib.

Drug	Recommended starting dose (Indications)	Interpatient variation (coefficient of variation)		Proposed target trough	References
		AUC	C_{trough}		
Sunitinib	50 mg (RCC, GIST)	41%	54%	50–100 ng/mL	Britten et al., 2008; Noda et al., 2015
Pazopanib	800 mg (RCC, STS)	19–73%	11–90%	20–50 μg/mL	de Wit et al., 2015; Noda et al., 2019

RCC: renal cell carcinoma, GIST: gastrointestinal stromal tumor, STS: soft tissue sarcoma.

additional toxicity. Therefore, pharmacokinetic-guided dosing may lead to safer and more effective treatment of sunitinib. From these findings, TDM service for sunitinib has been covered by the national health insurance in Japan since April 2018 in Japan. In Singapore, sunitinib 50 mg daily once daily 4/2 regimen is also high incidence of severe toxicity. Based on this observation, patients in Singapore have been routinely prescribed with attenuated doses of sunitinib at 37.5 mg once daily 4/2 regimen (referred to as attenuated dosing, AD) as the first-line therapy for treatment of metastatic RCC. The AD regimen of sunitinib in Singapore metastatic RCC patients provided sufficient drug exposure (>50 ng/ml of total sunitinib concentration) with a lower incidence of toxicity, with higher drug exposure (>100 ng/ml) being observed in patients who experienced toxicity (Teo et al., 2015).

Certain studies suggest that a dosing schedule consisting of 2 weeks on and 1 week off (2/1 regimen) is associated with decreased sunitinib toxicity without reduced efficacy in patients with metastatic RCC, when compared to a 4 weeks on and 2 weeks off schedule (4/2 regimen) (Atkinson et al., 2014; Bjarnason et al., 2014; Kondo et al., 2014; Najjar et al., 2014). Furthermore, using mechanism-based and semi mechanistic PK/PD models in patients with RCC and GIST Khosravan et al. suggested that the efficacy of sunitinib administered on a 2/1 regimen would be comparable to a 4/2 regimen, but thrombocytopenia would be less severe in patients on a 2/1 regimen (Khosravan et al., 2016). Therefore, in the case of severe toxicity induced by sunitinib when a patient is following a 4/2 regimen, a 2/1 regimen was proposed to reduce adverse effects while maintaining clinical efficacy using a PK assessment.

We summarize the guidance of TDM for sunitinib. Serum or plasma trough concentration of sunitnib is used in order to assess sunitinib PK. Semi-physiological pharmacokinetic model for sunitinib and SU12662 reported that the time to reach >90% of the theoretical steady-state concentration was approximately 6 days for sunitinib and 8 days for SU12662 (Yu et al., 2014). Therefore, the sunitinib and SU12662 concentration from day 8 could be almost an alternative indicator of sunitinib and SU12662 concentration at a steady state (day 10–14). Therefore, we propose that sunitnib and SU12662 trough serum concentration start to monitor on day 8.

5.2.2. Pazopanib target concentration

Preclinical studies demonstrated that pazopanib is effective at plasma concentrations of 17.5 μg/mL (Kumar et al., 2007). In a clinical trial, Suttle et al. reported that metastatic RCC patients with a trough concentration ≥ 20.5 μg/mL showed significantly improved clinical outcomes than those with a trough concentration <20.5 μg/mL (Suttle et al., 2014). Furthermore, Sternberg et al. reported that pazopanib was effective at plasma concentrations >20.5 μg/mL in RCC patients receiving adjuvant therapy (Sternberg et al., 2018). In Japanese patients with RCC, we reported that 88.9% (24/27) of patients had pazopanib concentrations >20.5 μg/mL, and these patients showed either a complete response, partial response, or stable disease as the best response (Noda et al., 2019). Therefore, the target range could be a trough concentration of >20.5 μg/mL during pazopanib therapy. Importantly, information regarding the exposure–toxicity relationship is currently lacking. Recently, we reported that the threshold value of trough pazopanib concentration for predicting grade ≥ 3 toxicities was 50.3 μg/mL based on the receiver operating characteristic curve (Noda et al., 2019). In agreement with our study, Verheijen et al. reported that a high pazopanib trough concentration of 51.3 μg/mL resulted in grade ≥ 3 toxicity and a subsequent dose reduction in the PK-guided study of patients with an advanced solid tumor (Verheijen et al., 2016). These findings suggest that a pazopanib trough concentration >50 μg/mL may be a limiting factor in treatment discontinuation.

Recently, a prospective PK-guided study of patients with solid tumors was conducted. In this study, the pazopanib dose was increased at weeks 3, 5, and 7, if the C_{min} was <20 μg/L and toxicity was <grade 3 (Verheijen et al., 2016). This algorism successfully modified pazopanib dosage without any severe toxic side effects. This individualized pharmacokinetically-guided dosing study could provide evidence of the benefits of TDM.

We summarize the guidance of TDM for pazopanib. Serum or plasma trough concentration of pazopanib is used in order to assess pazopanib PK. We propose pazopanib trough concentration start to monitor on day 8 at a steady state.

Table 2 describes the therapeutic target concentrations for sunitinib and pazopanib. However, these studies were analysis of a small number of patients. Therefore, these results need to be validated in a large prospective study.

5.3. PK/PD analysis of TKIs in patients with hemodialysis

TDM could also be helpful in patients with hemodialysis (HD). Most clinical trials indicate renal function impairment as an exclusion criterion, so there is limited data available for HD patients. A lack of information concerning the use of anticancer agents in patients with renal insufficiency led to the inappropriate use of chemotherapeutics and increased fatality in patients (Kitai et al., 2015). We investigated the pharmacokinetics of sunitinib and pazopanib in patients on HD (Noda et al., 2012, 2016). As representative data, we analyzed a hemodialyzed patient treated with 25 mg of sunitinib using a pharmacokinetic approach (Noda et al., 2012). There were limited differences in the $AUC_{0-24\ h}$ of sunitinib and its major active metabolite SU12662 on day 17 (on HD) and day 18 (off HD) of the first cycle. We also showed that there were few differences between the pazopanib concentrations before and after HD, suggesting that pazopanib is not removed or accumulated by HD in patients with RCC (Noda et al., 2016). Collectively, we

identified that sunitinib and pazopanib may be one of the treatment options for hemodialyzed patients because the pharmacokinetics of these agents is not affected by HD. This is because these agents have similar characteristics, such as being metabolized by the liver, and a high protein binding.

6. Conclusions and future perspectives

In this commentary, we described the recent data on the oral TKIs sunitinib and pazopanib, primarily focusing on their drug-metabolizing enzymes and transporters, factors causing pharmacokinetic variation, and TDM. The pharmacokinetic parameters of these TKIs are known to be associated with drug efficacy and toxicity. Additionally, these pharmacokinetic variations may be caused by genetic variants of ABCG2, which is observed more frequently in Asians compared to non-Asians. Thus, pharmacokinetic and pharmacogenomic assessment of TKIs could be useful for the evaluation and prediction of their outcomes, adverse effects, and drug–drug interactions. Especially in Asians, TDM is considered to be helpful to determine the optimal dosage, as the toxicity profile in Asians is different from non-Asians. In the near future, the information summarized here could play a prominent role in personalized medicine in TKI treatment.

Conflict of interest statement

All authors have declared no potential conflicts of interest.

Acknowledgments

This work was supported in part by grants from JSPS KAKENHI Grant Numbers JP15H0499 and JP17H00493 (Japan), from the Research Foundation for Pharmaceutical Science (Japan), and from the Nakatomi Foundation (Japan).

References

Adams VR and Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clin Ther 2007; 29: 1338-1353.

Antoun S, Baracos VE, Birdsell L, Escudier B and Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol 2010; 21: 1594-1598.

Atkinson BJ, Kalra S, Wang X, Bathala T, Corn P, Tannir NM, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. J Urol 2014; 191: 611-618.

Bello CL, Garrett M, Sherman L, Smeraglia J, Ryan B and Toh M. Pharmacokinetics of sunitinib malate in subjects with hepatic impairment. Cancer Chemother Pharmacol 2010; 66: 699-707.

Bello CL, Sherman L, Zhou J, Verkh L, Smeraglia J, Mount 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: 353-358.

Bennouna J, Deslandres M, Senellart H, de Labareyre C, Ruiz-Soto R, Wixon C, et al. A phase I open-label study of the safety, tolerability, and pharmacokinetics of pazopanib in combination with irinotecan and cetuximab for relapsed or refractory metastatic colorectal cancer. Invest New Drugs 2015; 33: 138-147.

Bins S, Huitema ADR, Laven P, Bouazzaoui SE, Yu H, van Erp N, et al. Impact of CYP3A4*22 on Pazopanib Pharmacokinetics in Cancer Patients. Clin Pharmacokinet 2019; 58: 651-658.

Bjarnason GA, Khalil B, Hudson JM, Williams R, Milot LM, Atri M, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: correlation with dynamic microbubble ultrasound data and review of the literature. Urol Oncol 2014; 32: 480-487.

Britten CD, Kabbinavar F, Hecht JR, Bello CL, Li J, Baum C, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. Cancer Chemother Pharmacol 2008; 61: 515-524.

Budha NR, Frymoyer A, Smelick GS, Jin JY, Yago MR, Dresser MJ, et al. Drug absorption interactions between oral targeted anticancer agents and PPIs: is pH-dependent solubility the Achilles heel of targeted therapy? Clin Pharmacol Ther 2012; 92: 203-213.

Chae JW, Teo YL, Ho HK, Lee J, Back HM, Yun HY, 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: 623-632.

Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-1338.

de Wit D, van Erp NP, den Hartigh J, Wolterbeek R, den Hollander-van Deursen M, Labots M, et al. Therapeutic drug monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study. Ther Drug Monit 2015; 37: 331-338.

Diekstra MH, Klümpen HJ, Lolkema MP, Yu H, Kloth JS, Gelderblom H, et al. Association Analysis of Genetic Polymorphisms in Genes Related to Sunitinib Pharmacokinetics, Specifically Clearance of Sunitinib and SU12662. Clin Pharmacol Ther. 2014; 96: 81-89.

Ellawatty WEA, Masuo Y, Fujita KI, Yamazaki E, Ishida H, Arakawa H, et al. Organic Cation Transporter 1 Is Responsible for Hepatocellular Uptake of the Tyrosine Kinase Inhibitor Pazopanib. Drug Metab Dispos 2018; 46: 33-40.

Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 2014; 32: 1412-1418.

Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006; 24: 25-35.

Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12: 489-495.

Fujita K, Sugiura T, Okumura H, Umeda S, Nakamichi N, Watanabe Y, et al. Direct inhibition and down-regulation by uremic plasma components of hepatic uptake transporter for SN-38, an active metabolite of irinotecan, in humans. Pharm Res 2014; 31: 204-215.

Gao B, Yeap S, Clements A, Balakrishnar B, Wong M and Gurney H. Evidence for therapeutic drug monitoring of targeted anticancer therapies. J Clin Oncol 2012; 30: 4017-4025.

Garcia-Donas J, Esteban E, Leandro-García LJ, Castellano DE, del Alba AG, Climent MA, 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: 1143-1150.

Giacomini KM, Balimane PV, Cho SK, Eadon M, Edeki T, Hillgren KM, et al. International Transporter Consortium commentary on clinically important transporter polymorphisms. Clin Pharmacol Ther 2013; 94: 23-26.

Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009; 10: 757-763.

Guo J, Jin J, Oya M, Uemura H, Takahashi S, Tatsugami K, et al. Safety of pazopanib and sunitinib in treatment-naive patients with

metastatic renal cell carcinoma: Asian versus non-Asian subgroup analysis of the COMPARZ trial. J Hematol Oncol 2018; 11: 69.

Hamberg P, Mathijssen RH, de Bruijn P, Leonowens C, van der Biessen D, Eskens FA, et al. Impact of pazopanib on docetaxel exposure: results of a phase I combination study with two different docetaxel schedules. Cancer Chemother Pharmacol 2015; 75: 365-371.

Heath EI, Chiorean EG, Sweeney CJ, Hodge JP, Lager JJ, Forman K, 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: 818-823.

Hira D and Terada T. BCRP/ABCG2 and high-alert medications: Biochemical, pharmacokinetic, pharmacogenetic, and clinical implications. Biochem Pharmacol 2018; 147: 201-210.

Hong MH, Kim HS, Kim C, Ahn JR, Chon HJ, Shin SJ, et al. Treatment outcomes of sunitinib treatment in advanced renal cell carcinoma patients: a single cancer center experience in Korea. Cancer Res Treat 2009; 41: 67-72.

Houk BE, Bello CL, Kang D and 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: 2497-2506.

Hu S, Chen Z, Franke R, Orwick S, Zhao M, Rudek MA, et al. Interaction of the multikinase inhibitors sorafenib and sunitinib with solute carriers and ATP-binding cassette transporters. Clin Cancer Res 2009; 15: 6062-6069.

Huillard O, Mir O, Peyromaure M, Tlemsani C, Giroux J, Boudou-Rouquette P, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. Br J Cancer 2013; 108: 1034-1041.

Keisner SV and Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. Drugs 2011; 71: 443-454.

Khosravan R, Motzer RJ, Fumagalli E and 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: 1251-1269.

Kim HR, Park HS, Kwon WS, Lee JH, Tanigawara Y, Lim SM, et al. Pharmacogenetic determinants associated with sunitinib-induced toxicity and ethnic difference in Korean metastatic renal cell carcinoma patients. Cancer Chemother Pharmacol 2013; 72: 825-835.

Kitai Y, Matsubara T and Yanagita M. Onco-nephrology: current concepts and future perspectives. Jpn J Clin Oncol 2015; 45: 617-628.

Klümpen HJ, Samer CF, Mathijssen RH, Schellens JH and Gurney H. Moving towards dose individualization of tyrosine kinase inhibitors. Cancer Treat Rev 2011; 37: 251-260.

Kobayashi D, Ieiri I, Hirota T, Takane H, Maegawa S, Kigawa J, et al. Functional assessment of ABCG2 (BCRP) gene polymorphisms to protein expression in human placenta. Drug Metab Dispos 2005; 33: 94-101.

Kondo T, Takagi T, Kobayashi H, Iizuka J, Nozaki T, Hashimoto Y, et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma--comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. Jpn J Clin Oncol 2014; 44: 270-277.

Kumar R, Knick VB, Rudolph SK, Johnson JH, Crosby RM, Crouthamel MC, 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: 2012-2021.

Lankheet NA, Kloth JS, Gadellaa-van Hooijdonk CG, Cirkel GA, Mathijssen RH, Lolkema MP, et al. Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. Br J Cancer 2014; 110: 2441-2449.

Liu X, Fiocco M, Swen JJ and Guchelaar HJ. Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis. Acta Oncol 2017; 56: 582-589.

Low SK, Fukunaga K, Takahashi A, Matsuda K, Hongo F, Nakanishi H, et al. Association Study of a Functional Variant on ABCG2 Gene with Sunitinib-Induced Severe Adverse Drug Reaction. PLoS One 2016; 11: e0148177.

Lubberman FJE, Gelderblom H, Hamberg P, Vervenne WL, Mulder SF, Jansman FGA, et al. The Effect of Using Pazopanib With Food vs. Fasted on Pharmacokinetics, Patient Safety, and Preference (DIET Study). Clin Pharmacol Ther 2019; 106: 1076-1082.

Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, 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: 327-337.

Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One 2012; 7: e37563.

Mir O, Touati N, Lia M, Litière S, Le Cesne A, Sleijfer S, 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: 1479-1485.

Mizuno T, Fukudo M, Fukuda T, Terada T, Dong M, Kamba 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: 310-316.

Mizuno T, Fukudo M, Terada T, Kamba T, Nakamura E, Ogawa O, et al. Impact of Genetic Variation in Breast Cancer Resistance Protein (BCRP/ABCG2) on Sunitinib Pharmacokinetics. Drug Metab Pharmacokinet 2012; 27: 631-639.

Mizuno T, Terada T, Kamba T, Fukudo M, Katsura T, Nakamura E, et al. ABCG2 421C>A polymorphism and high exposure of sunitinib in a patient with renal cell carcinoma. Ann Oncol 2010; 21: 1382-1383.

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115-124.

Motzer RJ, McCann L and Deen K. Pazopanib versus sunitinib in renal cancer. N Engl J Med 2013; 369: 1970.

Nagata M, Ishiwata Y, Takahashi Y, Takahashi H, Saito K, Fujii Y, et al. Pharmacokinetic-pharmacodynamic analysis of sunitinib-induced thrombocytopenia in Japanese patients with renal cell carcinoma. Biol Pharm Bull 2015; 38: 402-410.

Najjar YG, Mittal K, Elson P, Wood L, Garcia JA, Dreicer R, et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. Eur J Cancer 2014; 50: 1084-1089.

Narjoz C, Cessot A, Thomas-Schoemann A, Golmard JL, Huillard O, Boudou-Rouquette P, 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: 257-268.

Noda S, Hira D, Kageyama S, Jo F, Wada A, Yoshida T, et al. Pharmacokinetic Analysis of a Hemodialyzed Patient Treated with Pazopanib. Clin Genitourin Cancer 2016; 14: e453-456.

Noda S, Kageyama S, Tsuru T, Kubota S, Yoshida T, Okamoto K, et al. Pharmacokinetic/Pharmacodynamic Analysis of a Hemodialyzed Patient Treated with 25 mg of Sunitinib. Case Rep Oncol 2012; 5: 627-632.

Noda S, Otsuji T, Baba M, Yoshida T, Kageyama S, Okamoto K, 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: 350-358.

Noda S, Yoshida T, Hira D, Murai R, Tomita K, Tsuru T, et al. Exploratory Investigation of Target Pazopanib Concentration Range for Patients with Renal Cell Carcinoma. Clin Genitourin Cancer 2019; 17: e306-e313.

Pick AM and Nystrom KK. Pazopanib for the treatment of metastatic

renal cell carcinoma. Clin Ther 2012; 34: 511-520.

Sanford M and Keating GM. Pazopanib: in advanced renal cell carcinoma. BioDrugs 2010; 24: 279-286.

Scripture CD and Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer 2006; 6: 546-558.

Sternberg CN, Donskov F, Haas NB, Doehn C, Russo P, Elmeliegy M, et al. Pazopanib Exposure Relationship with Clinical Efficacy and Safety in the Adjuvant Treatment of Advanced Renal Cell Carcinoma. Clin Cancer Res. 2018; 24: 3005-3013.

Suttle AB, Ball HA, Molimard M, Hutson TE, Carpenter C, Rajagopalan D, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. Br J Cancer 2014; 111: 1909-1916.

Tan AR, Gibbon DG, Stein MN, Lindquist D, Edenfield JW, Martin JC, et al. Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. Cancer Chemother Pharmacol 2013; 71: 1635-1643.

Teo YL, Chue XP, Chau NM, Tan MH, Kanesvaran R, Wee HL, 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: 429-437.

Terada T, Noda S and Inui K. Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors. Pharmacol Ther 2015; 152: 125-134.

Uemura H, Shinohara N, Yuasa T, Tomita Y, Fujimoto H, Niwakawa M, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. Jpn J Clin Oncol 2010; 40: 194-202.

van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379: 1879-1886.

van der Veldt AA, Eechoute K, Gelderblom H, Gietema J, Guchelaar HJ, van Erp NP, et al. Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. Clin Cancer Res 2011; 17: 620-629.

van Erp NP, Baker SD, Zandvliet AS, Ploeger BA, den Hollander M, Chen Z, et al. Marginal increase of sunitinib exposure by grapefruit juice. Cancer Chemother Pharmacol 2011; 67: 695-703.

van Erp NP, Eechoute K, van der Veldt AA, Haanen JB, Reyners AK, Mathijssen RH, et al. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol 2009; 27: 4406-4412.

van Leeuwen RW, van Gelder T, Mathijssen RH and Jansman FG. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014; 15: e315-326.

Verheijen RB, Bins S, Mathijssen RH, Lolkema MP, van Doorn L, Schellens JH, et al. Individualized Pazopanib Dosing: A Prospective Feasibility Study in Cancer Patients. Clin Cancer Res 2016; 22: 5738-5746.

Verheijen RB, Yu H, Schellens JHM, Beijnen JH, Steeghs N and Huitema ADR. Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. Clin Pharmacol Ther 2017; 102: 765-776.

Warrington S, Baisley K, Boyce M, Tejura B, Morocutti A and Miller N. Effects of rabeprazole, 20 mg, or esomeprazole, 20 mg, on 24-h intragastric pH and serum gastrin in healthy subjects. Aliment Pharmacol Ther 2002; 16: 1301-1307.

Westerdijk K, Desar IME, Steeghs N, van der Graaf WTA, van Erp NP and (DPOG) DPaOG. Imatinib, sunitinib and pazopanib: from flat-fixed dosing towards a pharmacokinetically guided personalized dose. Br J Clin Pharmacol 2019.

Xu CF, Johnson T, Wang X, Carpenter C, Graves AP, Warren L, et al. HLA-B*57:01 Confers Susceptibility to Pazopanib-Associated Liver Injury in Patients with Cancer. Clin Cancer Res 2016; 22: 1371-1377.

Xu CF, Reck BH, Goodman VL, Xue Z, Huang L, Barnes MR, et al. Association of the hemochromatosis gene with pazopanib-induced transaminase elevation in renal cell carcinoma. J Hepatol 2011; 54: 1237-1243.

Xu CF, Reck BH, Xue Z, Huang L, Baker KL, Chen M, et al. Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism. Br J Cancer 2010; 102: 1371-1377.

Xu CF, Xue Z, Bing N, King KS, McCann LA, de Souza PL, et al. Concomitant use of pazopanib and simvastatin increases the risk of transaminase elevations in patients with cancer. Ann Oncol 2012; 23: 2470-2471.

Yoo C, Kim JE, Lee JL, Ahn JH, Lee DH, Lee JS, et al. The efficacy and safety of sunitinib in korean patients with advanced renal cell carcinoma: high incidence of toxicity leads to frequent dose reduction. Jpn J Clin Oncol 2010; 40: 980-985.

Yu H, Steeghs N, Nijenhuis CM, Schellens JH, Beijnen JH and Huitema AD. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. Clin Pharmacokinet 2014; 53 :305-325.