Dose optimization of oral targeted therapies in oncology

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Therapeutic drug monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study

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ABSTRACT

Background Patients treated with the standard dose of pazopanib show a large inter-patient variability in drug exposure defined as the area under the plasma concentration time curve ($AUC_{0\text{-}24}$). The primary objective of this study was to evaluate the feasibility of pharmacokinetics (PK)-guided individualized dosing to reduce the inter-patient variability in pazopanib exposure.

Patients and Methods Thirteen patients were treated with pazopanib for 3 consecutive periods of 2 weeks. During the first period, all patients received 800 mg of pazopanib once daily to reach steady-state exposure. During the second period, patients either received a PK-guided individualized pazopanib dose or the registered fixed 800 mg dose. During the third period, these 2 dosing regimens were switched.

Results The inter-patient variability in pazopanib $AUC_{0\text{-}24}$ during fixed dosing (27.3 CV%) was not significantly different when compared with the variability in $AUC_{0\text{-}24}$ during PK-guided dosing (24.8 CV%). The percentage of patients within the target window during PK-guided dosing (53.9%) was not significantly different from the percentage during fixed dosing (46.2%). Both C_{trough} and C_{24} were significantly ($P < 0.001$) correlated to pazopanib $AUC_{0\text{-}24}$ ($r^2 = 0.596$ and $r^2 = 0.940$, respectively). Pazopanib $AUC_{0\text{-}24}$ decreased 17% over time.

Conclusion PK-guided dosing did not reduce the inter-patient variability in pazopanib exposure. In this study, the intra-patient variability in pazopanib exposure was relatively large compared with inter-patient variability. This makes it challenging to achieve a target exposure within a predefined window. The causes of intra-patient variability must first be better understood and controlled, before PK-guided dosing can reduce the inter-patient variability.

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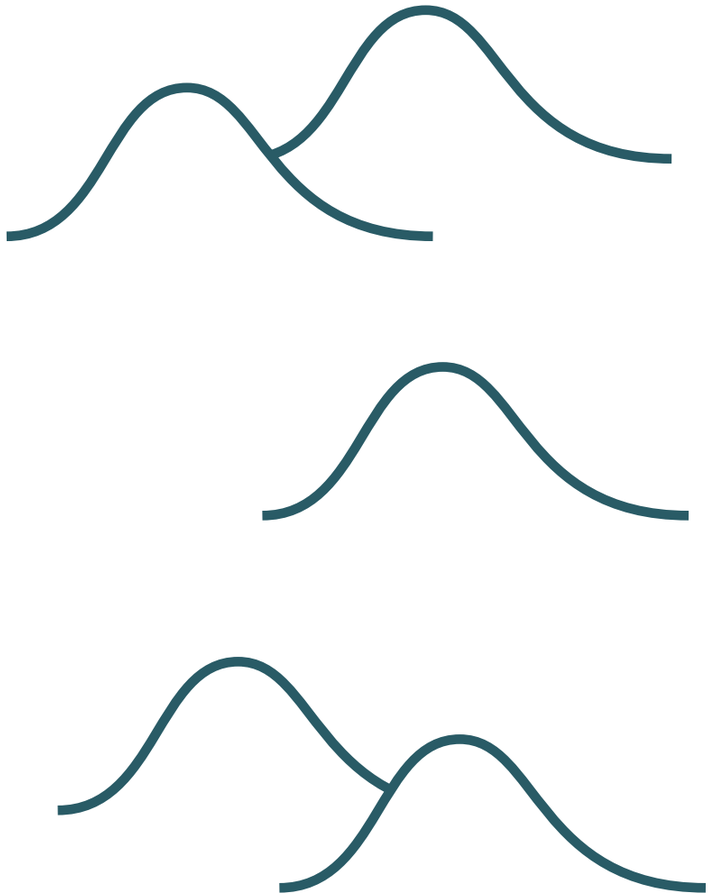


Introduction

Pazopanib hydrochloride (Votrient, GlaxoSmithKline; GW786034) is an oral multi-targeted tyrosine kinase inhibitor (TKI) with activity against vascular endothelial growth factor receptors 1-3, platelet-derived growth factor receptors α and β, and c-KIT [1-3]. Pazopanib is approved for the treatment of metastatic renal cell carcinoma (mRCC) and metastatic non-adipocytic soft tissue sarcoma [1-3].

Similar to other TKIs, pazopanib shows a large inter-patient variability in drug exposure of 40-70 coefficient of variation (CV%) [4-6]. Despite this large inter-patient variability in pharmacokinetics (PK), pazopanib is approved at a fixed oral dose of 800 mg once daily. In addition, a correlation between pazopanib exposure and efficacy and toxicity in mRCC has been demonstrated [7,8]. Subsequently, the reported variability in PK can potentially result for some patients in subtherapeutic exposure levels leading to decreased therapeutic effects. For other patients, the reported variability could result in supratherapeutic drug exposure levels with an increased incidence of adverse events. If this variability in PK can be controlled, the individual benefit – risk ratio for patients treated with pazopanib could be optimized.

The use of therapeutic drug monitoring (TDM) could potentially lower the inter-patient variability in pazopanib area under the plasma concentration time curve (AUC). TDM is the measurement of plasma drug concentrations to individualize the dosage to achieve a target plasma concentration. This individualized dose will ultimately result in an optimal exposure to a predefined target drug level with maximal therapeutic effects and minimal toxicity. TDM has already shown to be of value for the dose individualization of different drugs including antibiotics, antiretroviral drugs, immunosuppressive agents, and anti-epileptics [9-12]. However, for the new orally administered targeted anticancer agents used in oncology, it has not yet been demonstrated whether the use of TDM is feasible or whether it will result in exposures within a predefined target window. This must be demonstrated first, before PK-guided dosing of pazopanib can be recommended.

Clinically, the main prerequisites for TDM are a proven drug exposure-response relationship, a large inter-patient variability in PK, and a well-defined narrow therapeutic window [13,14]. For pazopanib, a drug exposure-response relationship seems to be present, and the reported inter-patient variability is large. This makes it seem likely that TDM is suitable for the individualization of pazopanib therapy. TDM of pazopanib could thereby ultimately result in more efficacy and less toxicity of therapy.

We conducted a prospective study to evaluate the feasibility of PK-guided individualized dosing of pazopanib in patients with cancer. The primary objective of this study was to assess whether individualized PK-guided dosing could reduce the inter-patient variability in pazopanib exposure and whether a predefined target exposure could be achieved. This study was also used to determine the correlation between pazopanib C_{trough} levels (plasma concentration just before pazopanib intake), C_{24} (plasma concentration 24 hours after pazopanib intake), and pazopanib exposure. These analyses may justify the use of trough level measurement for monitoring and guiding pazopanib therapy in clinical practice. Further, we explored whether there is a change in pazopanib exposure over time, which has been shown for other TKIs [15,16].

Patients and Methods

Patients

Patients eligible for this study were 18 years or older with progressive disease from an advanced solid tumor with a World Health Organization performance status ≤ 2 and for whom no standard treatment options were available. All patients had adequate hematologic, renal, and liver function reserves as defined by a hemoglobin ≥ 5.6 mmol/L, absolute neutrophil count ≥ 1.5 × 10^9/L, platelets ≥ 100 ×10^9/L, creatinine clearance ≥ 50 mL/min, total bilirubin ≤ 1.5 × the upper limit of institutional normal value, alanine aminotransferase, and aspartate aminotransferase ≤ 2.5 × upper limit of the institutional normal value.

Cytotoxic chemotherapy or radiation therapy for a period of 4 weeks before entering the study was not allowed. Further, patients receiving concurrent study treatment, patients with clinical evidence of central nervous system metastases or with poorly controlled hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) were not eligible for study entry. Patients were not allowed to use substances known or likely to interfere with the PK of pazopanib, which included CYP3A4 inhibitors (eg, ritonavir, clarithromycin) or inducers (eg, phenytoin, rifampicin) within 14 days or 5 half-lives of the substance (whichever was longer) before study entry. This study was approved by the Institutional Ethics Committee (Leiden University Medical Center, The Netherlands), and all patients gave written informed consent before entering the study.

Study design and treatment

This study was a multicenter, open-label, 3-period, randomized, 2-sequence, crossover pharmacokinetic study. Pazopanib (Votrient) was supplied as 200 mg tablets for oral administration 1 hour before or 2 hours after food intake. The study was performed over a timeframe of 6 weeks. Within these 6 weeks, the patients received pazopanib at the registered dose of 800 mg once daily for 4 weeks and a PK-guided individualized dose for 2 weeks. This PK-guided individualized dose was based on

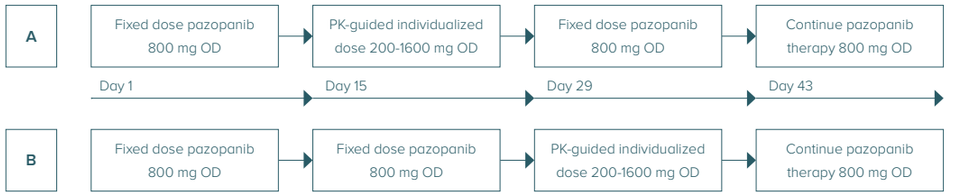
the deviation from a predefined target and measured exposure. Because a therapeutic window with an optimal balance between exposure (AUC) and efficacy on the one hand and toxicity on the other hand was lacking for pazopanib, a safe and effective target exposure had to be established first. For this, we used the results of 2 previous phase I studies in which the median steady-state AUCs for 800 mg of pazopanib were determined with non-compartmental methods. With the results from these trials, we defined a target exposure of 805 mg·hr/L (range 715 - 920 mg·hr/L) [4,17].

At study entry, patients were allocated to treatment group A or B (Figure 1). All patients started with the fixed pazopanib dose of 800 mg once daily for a period of 2 weeks to reach steady-state PK. After 2 weeks, pazopanib AUCs were assessed. Thereafter, patients allocated to treatment group A switched over to a PK-guided individualized dose (based on measured pazopanib exposure on day 14), and patients in treatment group B continued with the fixed 800 mg dose. After a further 2 weeks of pazopanib therapy and having reached a new steady state, the AUCs of pazopanib were assessed on day 28. Patients in treatment group A returned to the fixed 800 mg pazopanib, and patients in treatment group B switched over to the PK-guided individualized dose (based on pazopanib exposure on day 28). After another 2 weeks of pazopanib therapy and a third PK assessment on day 42, all patients returned to the standard dose of 800 mg of pazopanib once daily. This crossover design was chosen to test for changes in pazopanib exposure over time.

Patients were instructed to take pazopanib at the same time and under the same conditions (1 hour before or 2 hours after breakfast) every day. The exact time of pazopanib intake was recorded for the 3 days preceding PK assessment.

On days 14, 28, and 42, adverse events were monitored using the Common Terminology Criteria for Adverse Event version 4.0. Radiological response was determined by computed tomography scan using Response Evaluation Criteria in Solid Tumors version 1.1, at 7 weeks after the start of treatment with pazopanib and reassessed thereafter at 8- to 12-week intervals. Patients were withdrawn from the study if the disease progressed

Figure 1 Study design



Abbreviations: OD, once daily.

or if toxicity was unacceptable. This trial was registered at www.trialregister.nl under the ID: NTR3967.

Pazopanib pharmacokinetics

For pazopanib PK assessment, EDTA-blood samples were collected on 3 days (ie, days 14, 28, and 42 after the start of treatment) at pre-dose (C_{trough}) and 1, 2, 3, 4, 6, 8, 10, and 24 (C_{24}) hours after pazopanib intake. Samples were centrifuged at 1000 relative centrifugal force (RCF) for 5 minutes at room temperature; plasma was split into 2 aliquots and stored at -20 °C until analysis. Pazopanib plasma concentrations were measured within 3 days of the last sample being collected. Pazopanib plasma concentrations were determined using a validated ultraperformance liquid chromatography – tandem mass spectrometric method [18]. The calibration line of this method was linear over the range from 1.0 to 50.0 mg/L of pazopanib. The within- and between-day imprecisions were 2.4% and 4.1%, respectively, and the within- and between-day inaccuracies were 11% and 9%, respectively. Pazopanib exposures were calculated using a non-compartmental trapezoidal approach (Phoenix WinNonlin v6.3).

Sample size calculation

In this study design, patients served as their own control. We hypothesized that the inter-patient variability (SD) in pazopanib exposure could be reduced by 50%, in other words that the variance ratio (SD^2 of fixed dosing relative to SD^2 of PK-guided dosing) would equal 4 by introducing individualized PK-guided dosing. Because the intra-patient variability was unknown, we assumed that the correlation between the AUC measurements within patients equals 0.5, or in other words, that the intra-patient variability in AUC was 50% of the inter-patient variability as has been shown for other TKIs. We used simulation (sampling 100,000 times) in SPSS (version 20.0) to calculate the power of the appropriate F test taking into account this assumed correlation of 0.5 between the 2 variances [19]. A sample size of 13 resulted in a power of at least 80% to reject the null hypothesis of equal variances.

Statistical analysis

The inter-patient variability in $AUC_{0\text{-}24}$ was evaluated by determining the sample variances from the fixed and individualized PK-guided dosing regimen (σ^2). To calculate the limits of a 95% confidence interval (CI) for the population variance ratio, we used likelihood-ratio tests in linear mixed models (profile likelihood-like analysis, SAS, version 9.2). To calculate the intra-patient variability in exposure, the 2 $AUCs_{0\text{-}24}$ during fixed 800 mg dosing (PK day 14 and PK day 28 or 42) were used. When there was no dose adjustment during PK-guided dosing and patients were dosed with

800 mg, this third AUC_{0-24} was also included to calculate the individual intra-patient variability. The mean biases from the target AUC_{0-24} (ie, individual AUC_{0-24} values minus the target AUC_{0-24}) during fixed and PK-guided dosing were compared using a paired sample t-test.

The relationship between pazopanib C_{trough} and C_{24} and AUC_{0-24} was examined by Pearson correlation analysis.

To test for changes in pazopanib AUC_{0-24} over time, we used the statistical method described for the assessment of bioequivalence because these studies also determine possible differences in exposure [20]. We calculated the 90% CI of the geometric mean ratios AUC_{fixed} on day 28 (treatment arm B) or 42 (treatment arm A): AUC_{fixed} on day 14. The CI of this ratio should be between 0.80 and 1.25 to conclude the absence of a decrease or increase of pazopanib exposure over time. Statistical calculations were performed with SPSS, version 20.0 and SAS version 9.2.

Table 1 Patient baseline characteristics

Characteristic	Treatment Arm A	Treatment Arm B	Total
N	7	6	13
Age (years)	58 (23 - 68)	45 (30 - 60)	48 (23 - 68)
Sex (n)			
Male	6 (86%)	6 (100%)	12 (92%)
Female	1 (14%)	0 (0%)	1 (8%)
Length (cm)	182 (168 - 183)	182 (170 - 184)	182 (168 - 184)
Weight (kg)	84 (62 - 101)	90 (77 - 98)	89 (62 - 101)
ECOG PS (n)			
0	1 (14%)	2 (33%)	3 (23%)
1	5 (71%)	4 (67%)	9 (69%)
2	1 (14%)	0 (0)	1 (8%)
Hematology			
ANC ($\times 10^9$/L)	4.9 (3.1 - 6.0)	4.4 (2.5 - 6.4)	4.4 (2.5 - 6.4)
Platelets ($\times 10^9$/L)	278 (158 - 651)	261 (150 - 394)	271 (150 - 651)
Hemoglobin (mmol/L)	9.2 (6.8 - 9.9)	8.8 (7.8 - 9.9)	9.0 (6.8 - 9.9)
Chemistry			
AST (U/L)	22 (17 - 33)	25 (17 - 32)	22 (17 - 33)
ALT (U/L)	17 (12 - 26)	23 (12 - 33)	20 (12 - 33)
Creatinine (µmol/L)	70 (63 - 88)	77 (71 - 86)	73 (64 - 88)
Total bilirubin (µmol/L)	7 (5 - 11)	10 (7 - 12)	10 (5 - 12)
Blood pressure (mmHg)			
Systolic	129 (112 - 142)	129 (113 - 138)	129 (112 - 142)
Diastolic	77 (60 - 93)	80 (70 - 88)	79 (60 - 93)
Tumor type (n)			
Chordoma	3	1	4
Sarcoma	2	1	3
mRCC	1	0	1
Pancreas carcinoma	1	0	1
Schwannoma	0	2	2
Ganglioneuroma	0	1	1
Granulair cell myoblastoma	0	1	1

Data are presented as median (range) unless stated otherwise. Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance score; mRCC, metastatic Renal Cell Carcinoma; WBC, white blood count.

Results

Patient characteristics

Between July 2012 and June 2013, 14 patients were enrolled in the study. One patient withdrew informed consent before starting pazopanib therapy. Seven patients were assigned to group A, and 6 patients were assigned to group B. Baseline patient characteristics are summarized in Table 1.

Table 2 Summary of pazopanib PK parameters during individualized and fixed dosing

Parameter	Fixed dose D14	PK-guided dose D28/42	Fixed dose D28/42
AUC_{0-24} (mg·hr/L)			
Mean	1087	838	881
SD	349	207	241
CV%	32.1	24.8	27.3
ln AUC_{0-24} (mg·hr/L)			
Mean	6.94	6.70	6.75
SD	0.33	0.29	0.26
C_{trough} (mg/L)			
Mean	32.3	25.9	29.0
SD	11.7	9.6	9.2
CV%	36.2	36.9	31.7
ln C_{trough} (mg/L)			
Mean	3.41	3.18	3.30
SD	0.39	0.41	0.41

Abbreviations: D14/D28/D42, treatment day 14, 28 and 42, respectively; ln AUC_{0-24}, natural log-transformed AUC_{0-24}; ln C_{trough}, natural log-transformed C_{trough}.

Pharmacokinetics

Pazopanib pharmacokinetic data were obtained from all 13 patients on days 14, 28, and 42 of treatment. Table 2 summarizes the pharmacokinetic parameters of pazopanib during the fixed and individualized PK-guided dosing regimens.

The mean exposures (AUC_{0-24}) were 881 mg·hr/L (range, 600 - 1296 mg·hr/L) and 838 (range, 361 - 1191 mg·hr/L) during, respectively, fixed dosing and PK-guided dosing with accompanying SDs of 241 and 207 mg·hr/L, respectively. The corresponding inter-patient variability (CV%) in AUC_{0-24} was 27.3% for fixed dosing and 24.8% for PK-guided dosing. The inter-patient variability in AUC_{0-24} was not significantly reduced with the introduction of PK-guided dosing; the ratio of variance (σ^2)

Figure 2 AUC_{0-24} during individualized and fixed pazopanib dosing

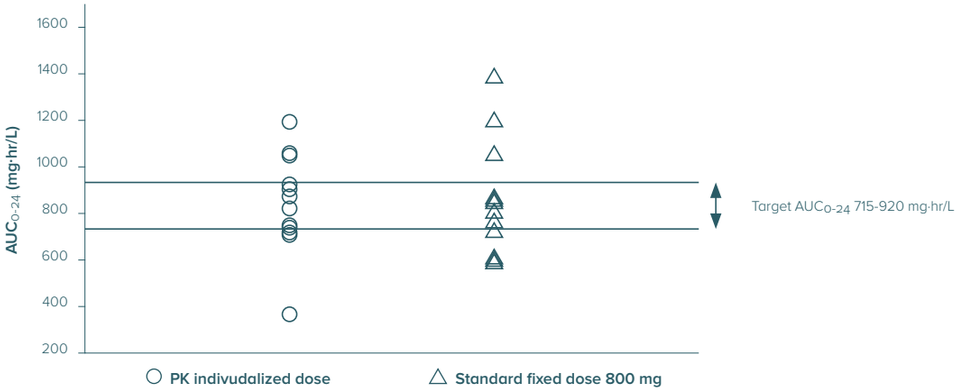
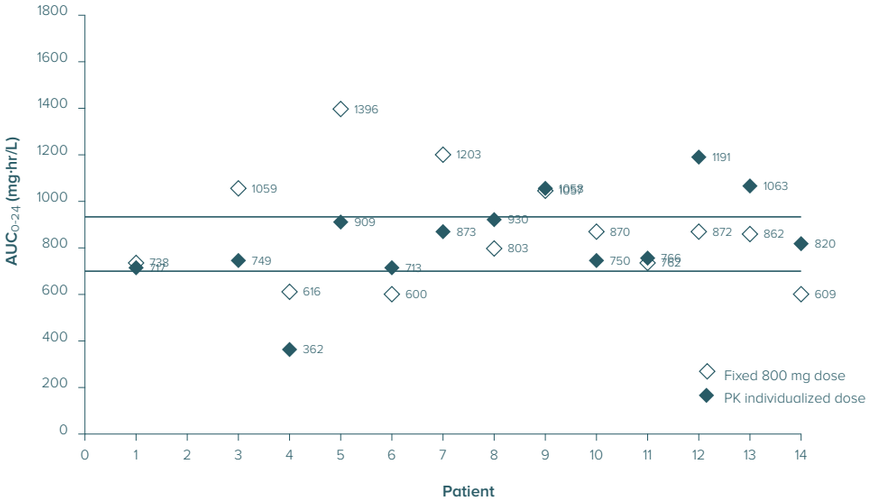


Figure 3 AUC_{0-24} per subject



during fixed dosing relative to PK-guided dosing was 1.35 (95%-CI: 0.48 - 3.9) (Figure 2). Individual intra-patient variability was calculated based on 3 AUCs for 6 patients and based on 2 AUCs for 7 patients; the mean intra-patient variability in AUC_{0-24} was 24.7 CV% (range, 8.3 - 48.7 CV%).

During PK-guided dosing, patients received daily doses ranging from 400 to 1200 mg of pazopanib. Seven of 13 patients received an adjusted dose during PK-guided dosing; 6 patients received a lowered

dose, and 1 patient an increased pazopanib dose. Dose reduction resulted in a dose-proportional decrease in pazopanib AUC_{0-24} in 4 of 6 patients. The only patient with an increased dose showed a dose-proportional increase in AUC_{0-24}. The percentage of patients with an AUC_{0-24} within the target window was not significantly different during PK-guided dosing when compared with that in fixed dosing (7 versus 6 out of 13 patients, 53.9% and 46.2%, respectively) (Figure 3). The biases from the target AUC in the fixed dosing arm and in the individualized arm were 75.9 mg·hr/L (95%-CI: 254.9 - 206.7) and 33.1 mg·hr/L (95%-CI: 297.7 - 145.8), respectively ($P = 0.538$).

Correlation between C_{trough}, C_{24} and AUC_{0-24}

Both C_{trough} and C_{24} were significantly associated with pazopanib AUC_{0-24} as shown in Figures 4A and 4B ($r^2 = 0.596$, $P < 0.001$ for C_{trough} and $r^2 = 0.940$, $P < 0.001$ for C_{24}, respectively). C_{trough} levels were taken after an uncontrolled pazopanib intake at home the day before hospital admission for PK sampling. The C_{trough} levels that were taken earlier or later than 24 hours after the previous dose tended to be, respectively, higher and lower than the controlled intake C_{24} levels (which is the same as a C_{trough} level taken exactly 24 hours after in-hospital pazopanib administration) (Figure. 4C).

Figure 4 Correlation between (A) pazopanib C_{trough} and AUC_{0-24}; (B) pazopanib C_{24}, and AUC_{0-24}; (C) time after prior dose at C_{trough} sampling and difference between C_{trough} and C_{24}

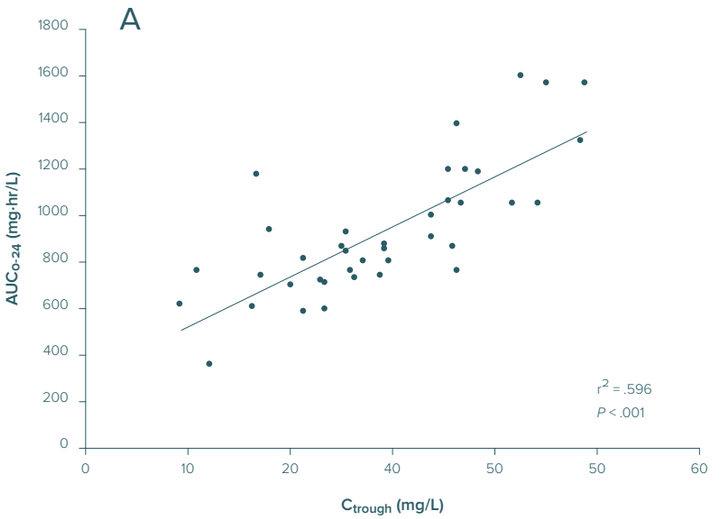
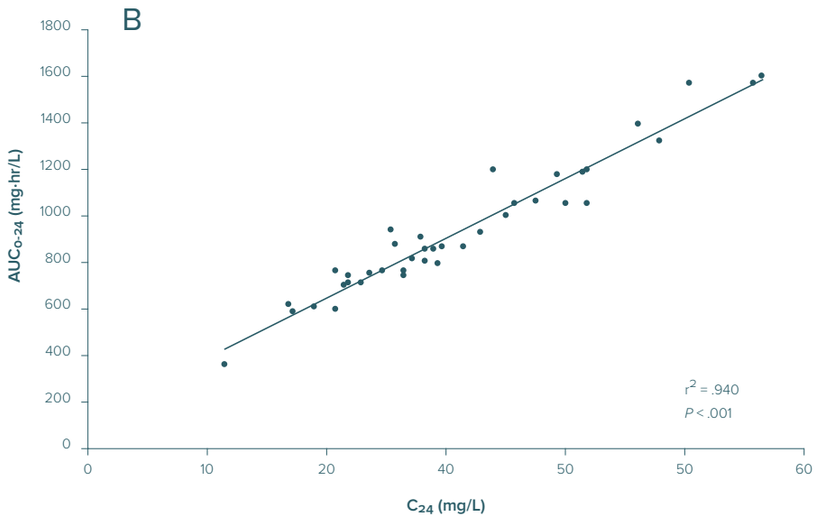


Figure 4 [Continued]



Change in pazopanib exposure over time

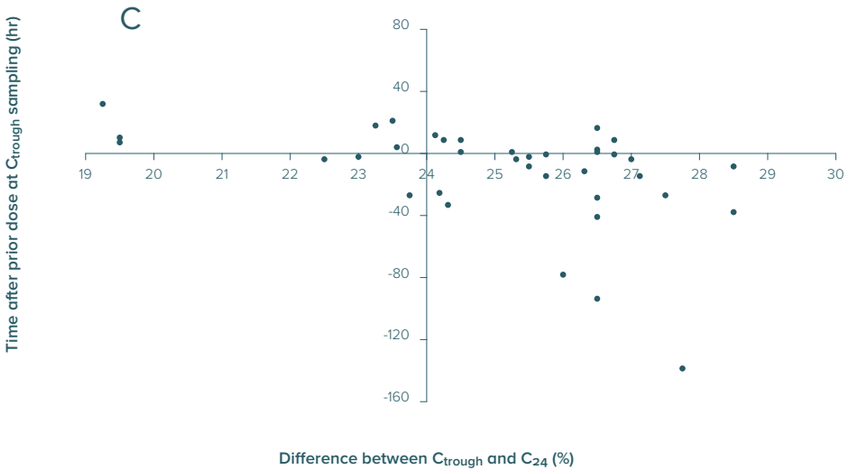
The ratio of the fixed dose pazopanib $AUC_{0\text{-}24}$ (day 28 or 42) versus fixed dose pazopanib $AUC_{0\text{-}24}$ (day 14) was 0.83 (90%-CI: 0.69-0.99) indicating a significant decrease in pazopanib $AUC_{0\text{-}24}$ of 17% over time.

Discussion

The reported large inter-patient variability in pazopanib PK may result in subtherapeutic or supratherapeutic exposure, which could potentially lead to either decreased efficacy or increased toxicity. In this study, we assessed whether individualized PK-guided dosing could reduce the inter-patient variability. The primary aim was to decrease the inter-patient variability in pazopanib $AUC_{0\text{-}24h}$ by 50%. This aim was not achieved; the results of our study indicate that PK-guided dosing to reach a pazopanib exposure within a predefined target window is not yet feasible.

Because the intra-patient variability in exposure has not been described before, we hypothesized this to be approximately 50% of the inter-patient variability. This is comparable with the results seen for other TKIs [21-23]. However, in this study, we found that the intra-patient variability was actually within the same range (24.7%) as that of the inter-patient variability (27.3%). Moreover, the inter-patient variability in exposure was much lower than that reported in the literature. The relatively large intra-patient variability described for the first time here is the main reason why

Figure 4 [Continued]



this study could not show the feasibility of TDM for the dose individualization of pazopanib therapy.

According to the Biopharmaceutics Classification System, pazopanib is a class II active substance and characterized by poor water solubility and low oral bioavailability of 14% to 39% [24]. These physicochemical properties, when combined with oral administration, cause variability in the absorption of pazopanib within and between individuals as shown in this study. However, other factors influencing the exposure cannot be completely ruled out.

Administration of pazopanib with both low and high fat meals has been shown to increase the $AUC_{0\text{-}24}$ by approximately 2-fold compared with that in a fasted condition [17]. Although in this study the intake of pazopanib has been standardized to the advised administration of 1 hour before or 2 hours after the intake of food, the intra-patient variability is relatively large. Possibly, this time interval of no food intake around pazopanib administration is insufficient to prevent an effect of food on pazopanib absorption. In addition, we did not standardize diet composition, and this could also have influenced the results. A possible option to reduce the intra-patient variability could be to increase the interval between food consumption and pazopanib intake. An alternative approach could be the administration of pazopanib at a lower dose in combination with a standardized meal to regulate the factors that influence its absorption. An additional benefit of this approach would be decreased costs of thera-

py with pazopanib [25]. The lower inter-patient variability found in this study, when compared with what is reported in the literature, is possibly the result of the inclusion and exclusion criteria used, controlled drug adherence, and the standardized intake of pazopanib [4].

Of the 13 patients included, 7 received an adjusted dose during PK-guided dosing. Dose reduction resulted in a dose-proportional decrease in AUC_{0-24} in 4 of 6 patients. Previous research has suggested that the steady-state exposure to pazopanib seems to plateau at 800 mg. However, in this study, the increased dose from 800 to 1200 mg in 1 patient did result in a dose-proportional increase in AUC_{0-24} [4].

The pazopanib plasma concentration at 24 hours after pazopanib intake (C_{24}) was much better correlated with the AUC_{0-24} than C_{trough} levels. Besides the intra-patient variability, 2 other reasons could possibly explain this finding; First, C_{trough} levels were taken around 24 hours (19.5 - 28.5 hours) after pazopanib intake, whereas C_{24} levels were taken exactly 24 hours after pazopanib intake. When C_{trough} levels were drawn > 24 hours after pazopanib intake, C_{trough} was lower than C24 and vice versa supporting our hypothesis. Second, C_{trough} levels reflected an at home - uncontrolled - pazopanib administration, whereas C_{24} levels were drawn after in hospital - controlled - administration of pazopanib. However, these findings are the reality of clinical practice and should be kept in mind when interpreting pazopanib C_{trough} levels in the clinic. A possible option to address this issue may be dry blood spot sampling. Patients could then take samples at home at exactly 24 hours after their last pazopanib intake. However, the feasibility and accuracy of this at home approach needs prospective validation.

A decrease of 17% in pazopanib exposure over time was observed. Similar decreases have been shown for imatinib and sorafenib [15,16]. Changes in the activity or expression of drug transporters or upregulation of liver enzymatic function might explain our observation. However, due to the small number of patients, this finding should be regarded as hypothesis generating and needs to be confirmed in a larger group of patients.

Although this study could not show the feasibility of TDM to reach a target exposure, measuring of pazopanib plasma concentrations may still be of clinical importance. A plasma concentration of 20.5 mg/L is retrospectively defined as the threshold for improved efficacy of pazopanib therapy in patients with mRCC [8]. In this study, 20% of the patients had C_{trough} levels below this threshold (data not shown). However, the incidence of different pazopanib-induced toxicities has also shown to be concentration dependent; there was a ≥ 2-fold increase in the incidence of hypertension, diarrhea, hair color change, alanine aminotransferase increase, and stomatitis when C_{trough} increased from 12.6 to 46 mg/L [7].

Although the problem of intra-patient variability remains to be solved, threshold-driven dosing might be beneficial and safe because target levels are much cruder. The concentration window between efficacy and toxicity seems to be much larger (> 2-fold (20.5 - 46 mg/L)) than the target window used in this study (~1.25-fold (715 - 920 mg·hr/L)). Therefore, it seems justified to target a C_{trough} level > 20.5 mg/L in clinical practice to prevent under dosing and unjustified discontinuation of treatment. Additionally, in patients that experience pazopanib-induced toxicity, measurement of pazopanib concentrations could help to determine whether the dose can be reduced or an alternative therapy should be initiated.

Conclusion

In this study, the feasibility of PK-guided dosing to reduce the inter-patient variability in pazopanib exposure could not be shown due to the relatively large intra-patient variability. The causes of the intra-patient variability must first be better understood and controlled, before PK-guided dosing will result in less inter-patient variability. Further research is needed to confirm whether there is a decrease in pazopanib exposure over time. Measuring of pazopanib plasma concentrations may still be of clinical benefit, especially to target a threshold pazopanib exposure with increased efficacy and limited risk to toxicity. For the interpretation of these plasma concentrations in the clinic, samples for C_{trough} levels are preferably taken exactly 24 hours after pazopanib intake.

Acknowledgment

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