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ORIGINAL RESEARCH ARTICLE

Cost-Neutral Optimization of Pazopanib Exposure by Splitting Intake Moments: A Prospective Pharmacokinetic Study in Cancer Patients

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Abstract

Background and Objective Pazopanib is an oral tyrosine kinase inhibitor used in the treatment of renal cell carcinoma and soft-tissue sarcoma. At the approved dose of 800 mg once daily (QD), 16–20% of patients are being underdosed and at risk of decreased efficacy. This study aimed to show whether splitting intake moments, as a cost-neutral alternative to a dose increase, leads to an increased exposure.

Methods We performed a cross-over trial comparing the pharmacokinetics of pazopanib 800 mg QD with pazopanib 400 mg twice daily. Pharmacokinetic sampling was performed at steady-state for both dosing schedules.

Results Nine evaluable patients were included. At the 800 mg QD dosing schedule, median minimum plasma concentration (C_{min}), area under the concentration–time curve from 0 to 24 h ($AUC_{0–24h}$), and maximum plasma concentration (C_{max}) were 23.2 mg/L (interquartile range 18.5–27.6), 773 mg h/L (557–1009), and 40.6 mg/L (36.4–56.4) compared with 41.6 mg/L (30.5–55.8, $p = 0.004$), 942 mg h/L (885–1419, $p = 0.027$), and 50.2 mg/L (46.8–72.5, $p = 0.074$) at 400 mg twice daily. One patient experienced a grade 3 event (i.e., diarrhea).

Conclusions This study demonstrates that splitting intake moments of pazopanib leads to a 79% increase in C_{min}, with acceptable tolerability. Therefore, this new dosing schedule offers a cost-neutral opportunity to optimize treatment in patients with low exposure.

Clinical Trial Registration NL6137 (http://www.trialregister.nl).

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1 Introduction

Pazopanib is an oral tyrosine kinase inhibitor approved for the treatment of advanced renal cell carcinoma (RCC) and soft-tissue sarcoma (STS). Pazopanib is targeted at the vascular endothelial growth factor receptors − 1, − 2 and − 3, platelet-derived growth factor receptors − α and − β, fibroblast growth factor receptor, and stem cell factor receptor (c-Kit) [1]. In the phase III trial in patients with RCC, pazopanib prolonged progression-free survival from 4.2 to 9.2 months compared to placebo [2].

Exposure-response analyses by Suttle et al. revealed that patients with RCC with a minimum plasma concentration (C_{min}) ≥ 20.5 mg/L had a significantly longer progression-free survival than patients with a C_{min} below this threshold (19.6 vs 52.0 weeks, $p = 0.004$) [3]. This exposure-efficacy threshold has been confirmed in the adjuvant setting and in a real-life patient cohort of patients with RCC [4, 5]. A similar

Key Points

Simulations with a population pharmacokinetic model predicted that splitting intake moments of pazopanib from 800 mg once daily into 400 mg twice daily would lead to an increase in the minimum plasma concentration (C_{min}) and area under the concentration–time curve (AUC), due to an increase in the relative bioavailability of pazopanib dosed at 400 mg compared with 800 mg

This prospective cross-over study demonstrated that pharmacokinetic exposure to pazopanib can be boosted by splitting intake moments, leading to a significant increase in C_{min} of 79% with acceptable tolerability

Splitting intake moments offers a simple, effective, and cost-neutral strategy to optimize treatment in the significant subset of 16–20% of patients with a low pazopanib exposure

trend was found for patients with STS as well, although not statistically significant [5].

At the currently used fixed dose of 800 mg once daily (QD), interindividual variability in pharmacokinetic exposure is high (40–70%) [5–7] and about 16–20% of patients do not reach the efficacy threshold of $C_{min} \geq 20.5$ mg/L [3, 5]. These patients are thus underdosed and potentially at risk of decreased antitumor efficacy. This provides a strong rationale for therapeutic drug monitoring, which is individualized dosing based on measured drug concentrations [8]. In a previous prospective clinical trial ($n = 30$) by Verheijen et al., it has been demonstrated that pharmacokinetically guided pazopanib dosing is feasible and results in an increased proportion of patients with adequate pharmacokinetic exposure. To achieve this, pazopanib dosages needed to be increased up to 1800 mg QD in some cases [9]. However, because of the non-linear absorption of pazopanib, which is plateauing at dosages above 800 mg, absolute dose increments are not an efficient strategy to increase pharmacokinetic exposure for pazopanib [10]. Furthermore, it leads to an increase in treatment costs.

Previously, we have developed a population pharmacokinetic model based on three clinical trials ($n = 96$) and have shown that the relative bioavailability of pazopanib dosed at 400 mg is estimated to be 59% higher than at 800 mg [10]. Therefore, we hypothesized that splitting intake moments would be a convenient and cost-neutral option for dose optimization. The aim of this pharmacokinetic cross-over trial was to demonstrate whether switching patients from an 800 mg QD to a 400 mg twice daily (BID) dosing schedule leads to a significant increase in pharmacokinetic exposure, in particular C_{min}.

2 Methods

2.1 Study Design

We performed a prospective multi-center clinical trial with a cross-over design. Figure 1 provides a schematic overview of the study design. First, pharmacokinetic exposure was determined at the 800 mg QD dosing schedule. Subsequently, patients switched to a 400 mg BID schedule for 7 days, after which the pharmacokinetic exposure was determined again at this new dosing schedule. As the elimination half-life ($t_{1/2}$) of pazopanib is 31 h, 7 days was accepted to be sufficient to attain steady-state concentrations at the 400 mg BID dosing schedule (i.e., more than four to five times $t_{1/2}$). Patients were instructed to take pazopanib at approximately 8.00 a.m., and 8.00 p.m. at the BID dosing schedule, in a modified fasting state, meaning no food 2 h before and 1 h after drug intake. Patients requiring a dose interruption or dose reduction or who discontinued treatment during the study were considered non-evaluable for the pharmacokinetic analysis and were replaced. At the end of the trial, pazopanib treatment was continued as part of standard care.

2.2 Patient Population

Patients with histological or cytological proof of cancer with an indication for treatment with pazopanib (i.e., advanced RCC or STS) were eligible for inclusion. Since evidence suggests pazopanib exposure may drop during the first weeks of treatment, all patients needed to be on pazopanib 800 mg QD treatment ≥ 3 weeks prior to start of the study [10]. Further inclusion criteria were age ≥ 18 years, World Health Organization performance status of 0, 1 or 2, and adequate organ function per judgment of the treating physician.

Patients were excluded in case of a (calculated) $C_{min} > 33$ mg/L at screening, as by expecting an increase in C_{min} of at least 50% after splitting intake moments based on previous simulations [10], C_{min} is expected to rise above 50 mg/L in these patients, which is associated with an increased risk of toxicity [9]. Another exclusion criterion was concomitant use of medication that could influence the pharmacokinetics of pazopanib within 14 days or five half-lives of the drug (whichever was shorter) before the start of the study, consisting of (but not limited to) gastric acid-suppressing agents, cytochrome P450 3A4 inhibitors/inducers, P-glycoprotein, and/or breast cancer resistance protein modulators.

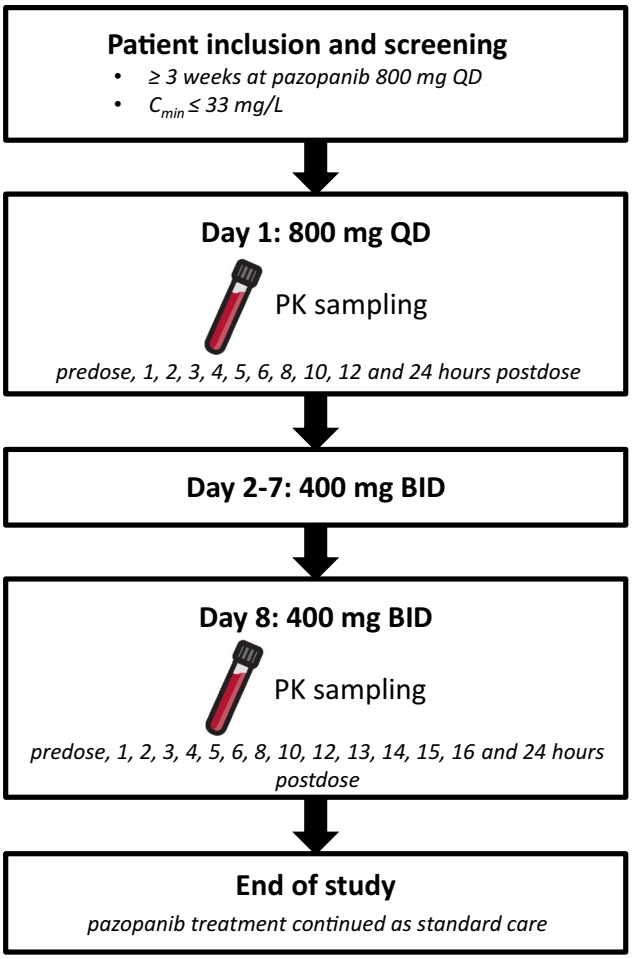

Fig. 1 Schematic overview of clinical trial design. At the 400 mg twice daily (BID) dosing schedule, the second dose of pazopanib was taken 12 h after the first dose. Sampling time points are relative to the first dose. C_{min} minimum plasma concentration, *PK* pharmacokinetic, *QD* once daily

2.3 Pharmacokinetics

At screening, either an actual trough concentration was drawn or C_{min} was calculated using the following formula [11]:

$$C_{min} = C_{measured} \times 0.5^{\frac{\text{dosing interval - TAD}}{t_{1/2}}}$$

where C_{min} is the calculated minimum plasma concentration, $C_{measured}$ is the measured plasma concentration, dosing interval is the time between two consecutive administrations of the drug (i.e., 24 h for pazopanib), TAD is the time after the dose (i.e., the time between the last drug intake and collection of the pharmacokinetic sample), and $t_{1/2}$ is the average elimination half-life of the drug (i.e., 31 h for pazopanib [1]).

At day 1 and day 8 of the study, patients were admitted to the hospital and blood samples were collected for pharmacokinetic analysis. Time points at day 1 (800 mg QD) were pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post-dose. Time points at day 8 (400 mg BID) were pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 16, and 24 h post-dose. Sampling time points were relative to the first dose, the second dose was taken after collection of the 12 h post-dose sample. At each time point, blood samples were collected in 3-mL K_2 EDTA tubes and centrifuged directly after collection (1500G, 5 minutes, 4 °C). Plasma was stored at – 20 °C until analysis. Plasma pazopanib concentrations were measured using a validated liquid chromatography-tandem mass spectrometry method [12].

2.4 Study Endpoint

The primary endpoint of this study was to evaluate whether switching patients from an 800 mg QD to a 400 mg BID dosing schedule would lead to an increase in pharmacokinetic exposure, measured as C_{min} and area under the concentration–time curve from zero to 24 h ($AUC_{0–24h}$). The secondary endpoint was to compare adverse events between the two dosing schedules. As an exploratory endpoint, the cost effectiveness of this intervention compared with QD dose increments was evaluated.

2.5 Safety Assessments

Recording of adverse events (AEs), vital signs, and hematology and blood chemistry assessments was performed at day 1 and day 8 of the study. The incidence, severity, and start and end dates of all AEs were recorded and graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Toxicity at the 800 mg QD dosing schedule was assessed at screening and at day 1. Only toxicities that were present at that time, were taken into account. Toxicity at the 400 mg BID dosing schedule was assessed at day 8.

2.6 Statistics

Splitting intake moments was considered to result in an increase in C_{min} and $AUC_{0–24h}$ of at least 50%, based on previous simulations [10]. By assuming an intra-individual standard deviation of the difference between the two dosing schedules of 50%, ten evaluable patients had to be included to obtain 80% power (two-sided $\alpha = 0.05$) to detect this increase of ≥ 50%. Pharmacokinetic parameters were calculated using non-compartmental analysis. C_{min} was defined as the median value of the pre-dose and 24 h post-dose sample for the 800 mg QD dosing schedule, and of the pre-dose, 12 and 24 h post-dose sample for the 400 mg BID dosing schedule. $AUC_{0–24h}$ was calculated using the linear/log trapezoidal method. C_{max} was defined as the highest measured

concentration for each dosing schedule. Minimum plasma concentration, $AUC_{0–4h}$, and C_{max} of the two dosing schedules were compared using two-sided Wilcoxon signed rank tests. All statistical analyses were performed using R version 3.3.2 (R Project, Vienna, Austria) [13].

2.7 Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee of The Netherlands Cancer Institute-Antoni van Leeuwenhoek. Participating centers were The Netherlands Cancer Institute-Antoni van Leeuwenhoek and the Erasmus MC Cancer Institute. Local approval was obtained in each participating center. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to enrollment in the study. This trial was registered in the Netherlands Trial Register (http://www.trialregister.nl, NL6137) and the EudraCT database (2016-005252-21). The full trial protocol can be accessed upon reasonable request by contacting the corresponding author.

3 Results

3.1 Patient Characteristics

In total, 11 patients were enrolled in the study from June 2017 until January 2019, of which nine patients were evaluable for pharmacokinetic analyses. In one patient, pazopanib treatment was interrupted because of toxicity before all pharmacokinetic measurements were completed and one patient did not take pazopanib according to the protocol. Both of these patients were excluded. Initially, unevaluable patients were replaced according to the protocol. However, the last patient was unevaluable after the study had been closed. As the study was already positive on its primary endpoint of change in C_{min}, it was decided not to replace this patient. Baseline characteristics of all patients are provided in Table 1. The majority of patients were female (73%), and the median age was 61 years. Six patients were diagnosed with RCC and five patients with STS. Median time on pazopanib treatment before enrollment in the study was 4.5 months.

3.2 Pharmacokinetics

Figure 2 shows the pazopanib concentration–time curves at both dosing schedules. An overview of the pharmacokinetic parameters for each of the dosing schedules is provided in Table 2. In Fig. 3, plots of C_{min}, $AUC_{0–24h}$, and C_{max} at both dosing schedules are shown. Using the 800 mg QD dosing schedule, median C_{min}, $AUC_{0–24h}$, and C_{max} were 23.2 mg/L (interquartile range [IQR] 18.5–27.6), 773 mg h/L (IQR 557–1009), and 40.6 mg/L (IQR 36.4–56.4), respectively. Switching to the 400 mg BID dosing schedule resulted in an increase in C_{min}, $AUC_{0–24h}$, and C_{max} to 41.6 mg/L (IQR 30.5–55.8, 79% increase, $p = 0.004$), 942 mg h/L (IQR 885–1419, 22% increase, $p = 0.027$), and 50.2 mg/L (IQR 46.8–72.5, 19% increase, $p = 0.074$), respectively.

3.3 Adverse Events

An overview of all treatment-related AEs is provided in Table 3. All but one patient experienced treatment-related

Table 1 Baseline characteristics of all patients ($n = 11$) and evaluable patients ($n = 9$)

Characteristic	All patients ($n = 11$)	Evaluable patients ($n = 9$)
Sex, female	8 (73%)	7 (78%)
Age (years)	61 [42–78]	55 [42–78]
Tumor type		
Renal cell carcinoma	6 (55%)	6 (67%)
Soft-tissue sarcoma	5 (45%)	3 (33%)
WHO performance status		
0	6 (55%)	5 (56%)
1	4 (36%)	4 (44%)
2	1 (9%)	0 (0%)
Number of previous lines of systemic treatment	0 [0–2]	0 [0–2]
Previous systemic treatment		
Chemotherapy	4 (36%)	3 (33%)
Targeted therapy	1 (9%)	0 (0%)
Time taking pazopanib (months)	4.5 [0.7–28.7]	4.5 [0.7–23.7]

Data are expressed as *n* (%) or median [range], as appropriate

WHO World Health Organization

AEs. No patients discontinued treatment and none required a dose reduction because of an adverse event. A single patient experienced a grade 3 event of diarrhea at the 400 mg BID dosing schedule, for which pazopanib treatment was interrupted at day 6 of the study. Calculated C_{min} at this time was high (72.9 mg/L). Treatment was resumed after 5 days at 800 mg QD, without toxicity. This patient was excluded from the pharmacokinetic analysis, because no pharmacokinetic samples were available at the 400 mg BID dosing schedule.

4 Discussion

In this prospective multi-center cross-over trial, we evaluated the effect of splitting intake moments of pazopanib from 800 mg QD into 400 mg BID on the pharmacokinetic exposure. This intervention resulted in a significant increase in C_{min} and $AUC_{0–24h}$ of 79% and 22%, respectively, with acceptable tolerability (Figs. 2, 3; Table 2). C_{max} was also numerically higher (19%), although this difference was not statistically significant. Thereby, splitting intake moments offers a convenient strategy to optimize pazopanib treatment for patients with a low pharmacokinetic exposure.

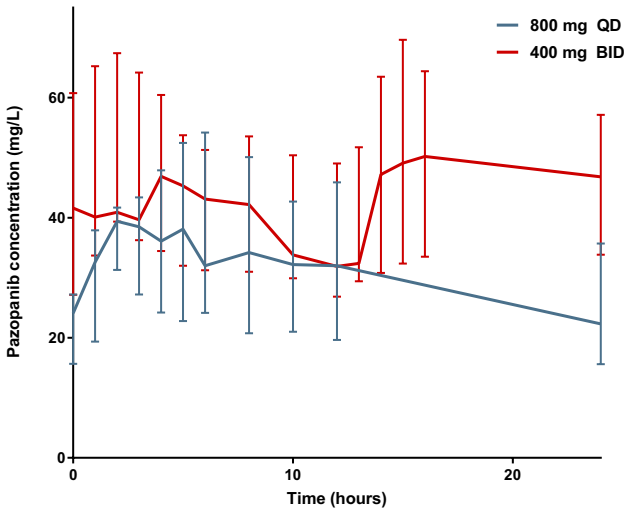

Fig. 2 Pazopanib plasma concentration–time curves (median plus interquartile range) of the 800 mg once-daily (QD) and 400-mg twice-daily (BID) dosing schedule ($n=9$)

As the number of doses increases, C_{min} is expected to increase as well, even if the bioavailability would remain equal. However, the increased bioavailability is reflected by the significant increase in AUC of 22%, which demonstrates the proof of principle of splitting intake moments for pazopanib. The efficacy threshold of $C_{min} \geq 20.5$ mg/L is determined for an once daily dosing schedule and reflects a certain total exposure (i.e., AUC). As AUC does not increase to the same extent as C_{min} when splitting intake moments, the same C_{min} value at a twice daily dosing schedule reflects a lower total exposure. In general, if a certain total exposure is needed for efficacy, using the same C_{min} target for a twice daily dosing schedule could result in a potential risk of underdosing. Therefore, for pazopanib it should be further investigated if the target of $C_{min} \geq 20.5$ mg/L also applies for the twice daily dosing schedule or that a higher threshold should be used. Since exposure-efficacy analyses were only performed for C_{min} and not for AUC, it is unknown which parameter most accurately predicts clinical response. However, C_{min} is the most pragmatic predictor, as only a single plasma sample is needed.

Pazopanib shows a complex absorption profile, which has been described by Yu et al. and consists of a sequential fast and slow absorption phase. This is explained by the fact that pazopanib is only water soluble at pH < 4, resulting in a fast absorption at the first part of the intestine (i.e., the duodenum), when pazopanib is still in solution. As the pH rises sharply > 4 in the small intestines, pazopanib precipitates (i.e., speculation based on the above-mentioned physiological considerations [14]) and further absorption becomes dissolution rate limited, which occurs much slower. The

Table 2 Pharmacokinetic (PK) parameters of pazopanib at the 800 mg once daily (QD) and 400 mg twice-daily (BID) dosing schedule ($n=9$)

PK parameter	800 mg QD	400 mg BID	Percentage change (%)	*P* value
C_{min} (mg/L)[a]	23.2 (18.5–27.6)	41.6 (30.5–55.8)	+ 79	**0.004**
$AUC_{0–24h}$ (mg h/L)[b]	773 (557–1009)	942 (885–1419)	+ 22	**0.027**
C_{max} (mg/L)[c]	40.6 (36.4–56.4)	50.2 (46.8–72.5)	+ 19	0.074

Bold values indicate statistically significant *p* values

Data expressed as median (interquartile range)

$AUC_{0–24h}$ area under the plasma concentration–time curve from zero to 24 h, C_{max} maximum plasma concentration, C_{min} minimum plasma concentration

[a] C_{min} was defined as the median value of the pre-dose and 24 h post-dose sample for the 800 mg QD dosing schedule, and of the pre-dose, 12 and 24 h post-dose sample for the 400 mg BID dosing schedule

[b] $AUC_{0–24h}$ was calculated using the linear/log trapezoidal method

[c] C_{max} was defined as the highest measured concentration for each dosing schedule

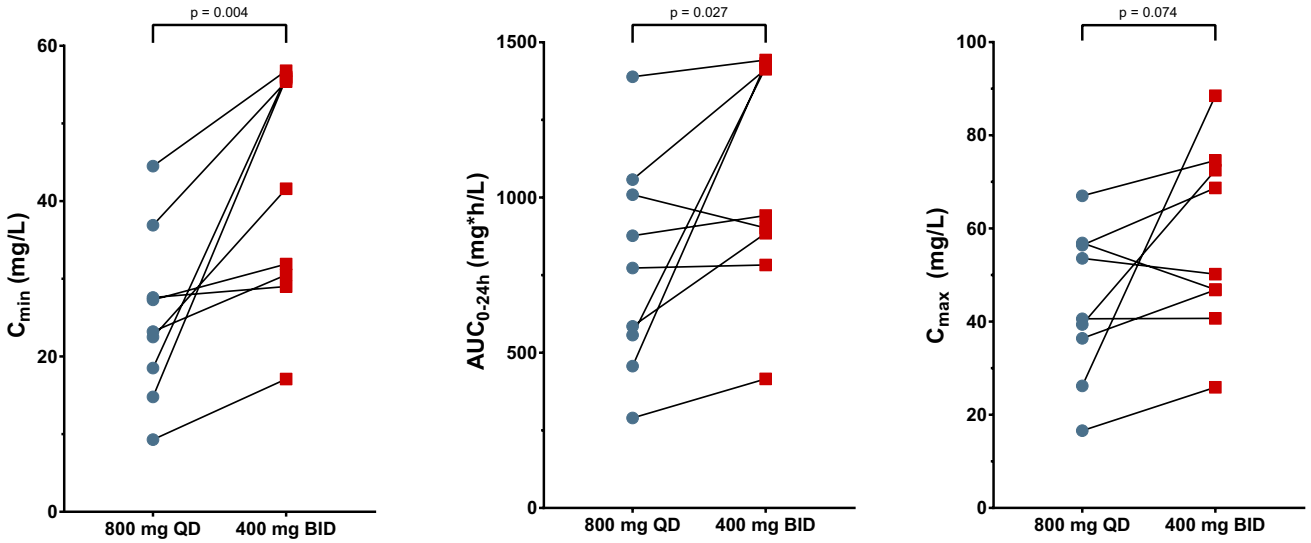

Fig. 3 Plots of pazopanib minimum plasma concentration (C_{min}), area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0–24h}$) and maximum plasma concentration (C_{max}) for both dosing schedules ($n=9$). Minimum plasma concentration was defined as the median value of the pre-dose and 24 h post-dose sample for the 800 mg once-daily (QD) dosing schedule, and of the pre-dose, 12 and 24 h post-dose sample for the 400 mg twice daily (BID) dosing schedule. $AUC_{0–24h}$ was calculated using the linear/log trapezoidal method. C_{max} was defined as the highest measured concentration for each dosing schedule

Table 3 Treatment-related adverse events (AEs) [all patients, $n=11$], according to common terminology criteria for adverse events, version 4.03

AE	800 mg QD		400 mg BID	
	Any grade (*n*)	Grade ≥ 3 (*n*)	Any grade (*n*)	Grade ≥ 3 (*n*)
Diarrhea	4	0	6	1
Fatigue	5	0	8	0
Hypertension	4	0	4	0
Nausea	3	0	4	0
Hypothyroidism	2	0	3	0
Anorexia	2	0	3	0
Dysgeusia	1	0	1	0
Vomiting	0	0	2	0
Myalgia	1	0	1	0
Thrombocytopenia	1	0	1	0
Bilirubin increase	1	0	1	0
Localized edema	1	0	1	0
Hair change	1	0	1	0
Skin hypopigmentation	1	0	1	0
Abdominal pain	1	0	1	0
Headache	1	0	1	0
Generalized muscle weakness	1	0	1	0
Weight loss	1	0	1	0
Total number of patients experiencing AEs	7	0	10	1

BID twice daily, *QD* once daily

poor solubility of pazopanib also explains the previously observed dose dependency in relative bioavailability, which was estimated to be 59% higher at 400 mg compared with 800 mg [10].

In fact, the oral bioavailability of pazopanib at the approved dose of 800 mg is only 14–39%, due to its sub-optimal pharmaceutical formulation [15]. This results in both a high inter- and intra-individual variability in

pharmacokinetic exposure. In a previous study, we have shown that with an improved pharmaceutical formulation with a much better dissolution profile, only 300 mg QD is needed to attain a similar pharmacokinetic exposure as with 800 mg QD of the current formulation [16]. However, this improved formulation is not available in clinical practice.

As the bioavailability increases by splitting intake moments of pazopanib, variability was expected to decline [17]. However, in this study, we still observed a substantial interindividual variability at 400 mg BID. Hence, plasma concentrations and toxicity should still be carefully monitored. In addition, relatively large individual differences in increases were seen between patients (Fig. 3), which could be explained by the relatively high intra-individual variability of pazopanib (i.e., 24.7% [18]) and differences in drug absorption between patients.

In a previous pharmacokinetically guided dosing study of pazopanib, dose increments to dosages ranging from 1000 mg QD to 1800 mg QD were needed to attain adequate exposure [9]. The costs of these additional 200–1000 mg of pazopanib are €873–€4342 per patient per month in The Netherlands, part of which could theoretically be saved when splitting intake moments is used to increase pharmacokinetic exposure. Because dose increments in the case of low exposure are currently not implemented as standard of care, this calculation does not represent an actual cost saving. Instead, it represents a comparison of the costs between absolute dose increments and splitting intake moments. As splitting intake moments does not lead to any additional costs compared to the standard dose of 800 mg QD, it can be concluded that this is a cost-neutral strategy.

A strength of the current study is that full pharmacokinetic curves instead of only trough samples were obtained at both dosing schedules, enabling comparison of C_{max} and $AUC_{0–24h}$ as well. Limitations of this study include the fact that toxicity of the QD and BID schedule could not be reliably compared because of the short duration of BID dosing (i.e., only 7 days) and the fact that only patients who already tolerated the 800 mg QD dose for multiple weeks were eligible for enrollment. Although this was sufficient to reach steady-state concentrations, more time might be needed for adverse events to emerge. Furthermore, only nine evaluable patients were included instead of ten. A post hoc power calculation indicated that nine patients provided 75% power to detect an increase in pharmacokinetic exposure of 50%.

A drawback of switching to a twice daily dosing schedule could be the inconvenience for patients with regard to the modified fasting state in which pazopanib should be administered. An alternative strategy to increase pharmacokinetic exposure to pazopanib could be concomitant intake with food [7, 20]. Both strategies could be applied to reach the predefined target. We are currently performing a prospective study on therapeutic drug monitoring of oral anticancer drugs, including pazopanib, in which we split intake moments as a first step to optimize pazopanib treatment in the case of low pharmacokinetic exposure. As a second step, concomitant intake with food is recommended [8, 21].

The current study demonstrated that previous simulations using a population pharmacokinetic model of pazopanib adequately predicted the effect of splitting intake moments on C_{min} (i.e., 75% vs 79% increase), validating a population pharmacokinetic simulation approach for changes in pazopanib dosing schedules [10]. It has to be noted, though, that the increase in $AUC_{0–24h}$ was less pronounced than the simulations predicted (i.e., 22% vs 59%). However, pazopanib pharmacokinetics shows wide variability, and consequently, comparisons based on a relatively small sample size are difficult. Furthermore, this study illustrates the relevance of population pharmacokinetic simulations in general, which could be applied more often in oncology. These simulations could provide a rationale for proof-of-concept pharmacokinetic studies. The pharmacokinetic data of these clinical studies could then be added to the original population pharmacokinetic model, to further optimize its predictions.

Implications of this study for clinical practice are that patients with pazopanib $C_{min} < 20.5$ mg/L could be switched from an 800 mg QD to a 400 mg BID dosing schedule to improve pharmacokinetic exposure. The feasibility, tolerability, and efficacy of this strategy will now be further studied in a prospective clinical study on therapeutic drug monitoring of oral anticancer drugs (http://www.trialregister.nl; NL6695) [8]. Furthermore, data of the current study could be added to the existing population pharmacokinetic model to better characterize the non-linear pharmacokinetics of pazopanib and to further optimize the dosing schedule.

5 Conclusions

This study demonstrates that pharmacokinetic exposure to pazopanib can be boosted by splitting intake moments from 800 mg QD to 400 mg BID, leading to a significant increase in C_{min} of 79% with acceptable tolerability. This is relevant for the 16–20% of patients who are currently underdosed and therefore have a risk of decreased efficacy. As the observed variability in pazopanib pharmacokinetics is large, also after splitting the dose, this strategy should only be applied for those patients where follow-up blood concentration monitoring is in place. Hence, splitting intake moments offers a simple, effective, and cost-neutral strategy to optimize treatment in the significant subset of patients with a low pazopanib exposure.

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Compliance with Ethical Standards

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Conflict of interest Remy B. Verheijen is currently an employee and shareholder of AstraZeneca, Cambridge, UK. Stijn L.W. Koolen and Ron H.J. Mathijssen received funding and speakers' fees by Novartis on a topic not related to the current study. Jos H. Beijnen is a part-time employee, stock holder, and patent holder of Modra Pharmaceuticals (a spin-out company developing oral taxane formulations, not related to this study). Stefanie L. Groenland, Ruben A.G. van Eerden, Niels de Vries, Bas Thijssen, Hilde Rosing, Alwin D.R. Huitema, and Neeltje Steeghs have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Medical Ethics Committee of The Netherlands Cancer Institute-Antoni van Leeuwenhoek, reference number: METC17.482/N17PSI) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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