Clinical Cancer Research

Individualized Pazopanib Dosing: A Prospective Feasibility Study in Cancer Patients

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Abstract

Purpose: Pazopanib is a tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and soft tissue sarcoma. Retrospective analyses have shown that an increased median progression-free survival and tumor shrinkage appear in patients with higher plasma trough levels (C_{min}). Therefore, patients with low C_{min} might benefit from pharmacokinetically guided individualized dosing.

Experimental Design: We conducted a prospective multicenter trial in 30 patients with advanced solid tumors. Pazopanib C_{min} was measured weekly by LC-MS/MS. At weeks 3, 5, and 7, the pazopanib dose was increased if the measured C_{min} was <20 mg/L and toxicity was <grade 3.

Results: In total, 17 patients had at least one C_{min} <20 mg/L at weeks 3, 5, and 7. Of these, 10 were successfully treated with a pharmacokinetically guided dose escalation, leading to daily dosages ranging from 1,000 to 1,800 mg. C_{min} in these patients increased significantly from 13.2 (38.0%) mg/L [mean (CV%)] to 22.9 mg/L (44.9%). Thirteen patients had all C_{min} levels ≥20.0 mg/L. Of these, 9 patients with a high C_{min} of 51.3 mg/L (45.1%) experienced ≥grade 3 toxicity and subsequently required a dose reduction to 600 or 400 mg daily, yet in these patients, C_{min} remained above the threshold at 28.2 mg/L (25.3%).

Conclusions: A pharmacokinetically guided individualized dosing algorithm was successfully applied and evaluated. The dosing algorithm led to patients being treated at dosages ranging from 400 to 1,800 mg daily. Further studies are needed to show a benefit of individualized dosing on clinical outcomes, such as progression-free survival. *Clin Cancer Res; 22(23); 5738–46. ©2016 AACR.*

See related commentary by Ornstein and Rini, p. 5626

Introduction

Pazopanib is a tyrosine kinase inhibitor targeting VEGFR-1,2,3; PDGFR α/β; FGFR; and c-Kit (1). Pazopanib increased progression-free survival (PFS) from 4.2 to 9.2 months in renal cell carcinoma (RCC) and from 1.6 to 4.6 months in soft tissue sarcoma (STS) compared with placebo (2, 3).

A retrospective analysis in 177 RCC patients by Suttle and colleagues showed an increased tumor shrinkage and longer PFS in patients with plasma trough levels (C_{min}) ≥20.5 mg/L compared with patients with a C_{min} below this threshold (4). Median PFS was found to be 50.2 weeks in patients with higher pazopanib C_{min} versus 19.6 weeks in patients with lower C_{min}. Median tumor shrinkage was 37.9% in the high versus 6.9% in the low exposure group. No further increase in PFS or tumor shrinkage was found above a pazopanib plasma concentration of 20.5 mg/L.

This threshold for efficacy seems to be in accordance with preclinical data showing optimal VEGFR2 inhibition by pazopanib *in vivo* at a concentration of ≥17.5 mg/L (40 μmol/L) in mouse models (5). Additionally, in the phase I trial, hypertension, a pharmacodynamic biomarker for response to antiangiogenic agents, correlated with C_{24h} values above 15 mg/L at day 22 (6). Plasma concentrations were also correlated with radiographic response in a phase II study of patients with progressive, radioiodine-refractory, metastatic differentiated thyroid cancers treated with pazopanib (7). The above indicates that efficacy of pazopanib is strongly associated with pharmacokinetic (PK) exposure in many tumor types.

Pazopanib PK has shown significant interindividual variability in plasma exposure (6, 8, 9) and may be affected by various factors, such as concomitant medication (e.g., drugs increasing gastric pH or inhibiting/inducing CYP3A4), intake of food, patient compliance, and (exact) time of tablet ingestion and blood sampling (9–12).

Despite the large variability in exposure, pazopanib is currently still administered at a fixed dose of 800 mg daily. This may, however, result in suboptimal treatment in a subset of patients who have a low C_{min}. In a retrospective analysis performed by the manufacturer of pazopanib, 20% of patients had a C_{min} below 20.5 mg/L and might have benefited from an increased dose (4).

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Translational Relevance

Pharmacokinetic exposure to pazopanib, measured as C_{min}, has been linked to treatment efficacy. As pazopanib pharmacokinetics display large interpatient variability, some patients may be at risk of suboptimal treatment outcomes on the currently approved fixed dose. An individualized dosing algorithm was applied and evaluated in patients with advanced solid tumors. C_{min} was measured weekly, and the dose was increased if C_{min} was <20 mg/L and toxicity <grade 3. The dosing algorithm led to patients receiving dosages of 400 to 1,800 mg daily. Patients whose dose was increased had a significant increase in exposure. Patients who required a dose reduction for toxicity could, in many cases, be treated at a reduced dose while maintaining adequate exposure. Individualized pazopanib dosing was feasible and safe. Future randomized clinical trials are needed to investigate the effect of individualized dosing on a clinical endpoint such as progression free or overall survival.

The feasibility of pharmacokinetically guided dosing has already been shown in prospective clinical trials for tamoxifen (13) and another tyrosine kinase inhibitor with similar properties, sunitinib (14). Therefore, we conducted a prospective feasibility trial to investigate whether the dose of pazopanib could be safely increased in patients who have a low C_{min} on the fixed 800-mg dose of pazopanib and whether this led to increased drug exposure without intolerable toxicity.

Materials and Methods

Patient population

Cancer patients for whom pazopanib was considered standard of care or for whom no remaining standard treatment options were available were eligible for enrollment. Patients also had to be at least 18 years of age; had to have a World Health Organization (WHO) performance status score of 0 or 1; had to have evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and had to have an adequate organ function at baseline, defined as absolute neutrophil count $\geq 1.5 \times 10^9$/L, hemoglobin $\geq$5.6 mmol/L, platelets $\geq 100 \times 10^9$/L, prothrombin time or international normalized ratio $\leq 1.2 \times$ ULN, activated partial thromboplastin time $\leq 1.2 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN, alanine amino transferase and aspartate aminotransferase $\leq 2.5 \times$ ULN, serum creatinine $\leq$133 μmol/L or if >133 μmol/L, a calculated creatinine clearance of 30 to 50 mL/minute and urinary protein (on dipstick) <2+ or <1 g in 24-hour urine.

Exclusion criteria were corrected QT interval (QTc) >480 milliseconds, history of any relevant cardiovascular conditions, cerebrovascular accidents, transient ischemic attack, pulmonary embolisms or untreated deep venous thrombosis (DVT) within the past 6 months, poorly controlled hypertension [defined as systolic blood pressure (SBP) of $\geq$140 mm Hg or diastolic blood pressure (DBP) of $\geq$90 mm Hg], clinically significant gastrointestinal abnormalities that might increase the risk for gastrointestinal bleeding, major surgery or trauma within 28 days prior to first pazopanib dose, evidence of active bleeding or bleeding diathesis, known endobronchial lesions and/or lesions infiltrating major pulmonary vessels, recent hemoptysis within 8 weeks before first pazopanib dose, any anticancer therapy within 14 days or five half-lives of the previous anticancer drug (whichever was longer) prior to first pazopanib dose, and any ongoing toxicity from prior anticancer therapy that was grade >1 and/or that was progressing in severity, except for alopecia.

Pharmacokinetically guided dosing

All patients started at the approved pazopanib dose of 800 mg once daily (QD). Plasma samples for C_{min} measurements were collected weekly in the first 8 weeks of pazopanib treatment and every 4 weeks thereafter. Pazopanib concentrations were measured using a validated LC-MS/MS assay.

A 10-μL plasma aliquot was used, to which 500 μL of methanol containing $^{13}C,^{2}H_3$-pazopanib as internal standard and 500 μL of 10 mmol/L ammonium hydroxide in water were added. This solution was then centrifuged at 15,000 rpm, and 5 μL of the supernatant was injected into the LC-MS/MS system (LC-system from Agilent Technologies and API3000 MS by AB Sciex). Elution was performed using an isocratic gradient of 45% 10 mmol/L ammonium hydroxide in water and 55% methanol on a Gemini C18 column, 2.0 × 50 mm, 5 μm by Phenomenex. This assay was validated and fulfilled all requirements of the U.S. Food and Drug Administration and the European Medicines Agency guidelines for bioanalytical method validation. C_{min} results were reported to the treating physician within 1 week.

At day 15 (week 3, day 1), day 29 (week 5, day 1), and day 43 (and week 7, day 1), the dose could be adapted, based on the measured C_{min} collected a week earlier, and observed toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.02).

The target exposure for efficacy used during this trial was a C_{min} $\geq$20.0 mg/L. Patients with a C_{min} <15.0 mg/L received a dose increase of 400 mg daily in the absence of $\geq$grade 2 toxicity or 200 mg daily when experiencing grade 2 toxicity, but not $\geq$grade 3 adverse events (AE). Patients with a C_{min} of 15.0 to 19.9 mg/L received a 200-mg dose increase if toxicity was below grade 3. No patients would be treated above the prespecified dose limit of 2,000 mg QD, as this was the highest dose previously tested in humans (6). In case of severe ($\geq$grade 3) treatment-related toxicity, the dose was lowered by 1 dose level or to the previous dose level in case of an earlier dose increment.

Safety assessments

Recording of AEs, physical examination, and hematology and blood chemistry assessments were performed weekly during the first 8 weeks after initiation of therapy and monthly thereafter. The incidence, severity, and start and end dates of all serious AEs (SAE) and of nonserious AEs related to pazopanib were recorded.

Efficacy assessments

CT scan and/or MRI scans were performed every 8 weeks after initiation of therapy until documented disease progression according to RECIST version 1.1. Data on best response and time to progression were collected.

Statistical methods

All statistical analyses were performed in R version 3.2.2 (15). For exposure–response relationships, the mean of all measured C_{min} levels for each patient during the entire treatment period (from start of treatment to discontinuation) was

Table 1. Demographics of included patients

Characteristic	Patients ($N = 30$)
Gender, *n* (%)	
Male	14 (47)
Female	16 (53)
Age, median (range)	58 (33–88)
Steady-state C_{min} (mg/L) at 800-mg dose (W2D1), mean (CV %)	30.0 (71.9)
Performance status, *n* (%)	
0	7 (23)
1	23 (77)
Previous lines of systemic therapy, median (range)	2 (1–5)
Type, *n* (%)	
Chemotherapy	24 (80)
Targeted therapy	7 (23)
Endocrine therapy	3 (10)
Primary tumor, *n* (%)	
Soft tissue sarcoma	7 (23)
Colorectal carcinoma	6 (20)
Cancer of unknown primary	4 (13)
Neuroendocrine carcinoma	2 (6)
Miscellaneous[a]	11 (33)

[a]Hepatocellular carcinoma, ovarian carcinoma, mesothelioma, esophageal carcinoma, meningioma, perivascular epithelial tumor, renal cell carcinoma, choroidal melanoma, endometrial carcinoma, cholangiocarcinoma, and thymus carcinoid (all $n = 1$).

used as the measure of pazopanib exposure. For the purpose of exposure–toxicity relationships, the C_{min} measurement closest to the first presentation of the toxicity was used. Unless otherwise specified, hypotheses were tested using a two-sided, independent sample *t* test. *P* values of <0.05 were considered statistically significant.

Study conduct and registry

This trial was conducted in accordance with the World Medical Organization declaration of Helsinki, compliant with Good Clinical Practice, and approved by the Medical Ethics Committee of each of the participating medical centers. All patients provided written informed consent before enrollment. This trial was registered in the EudraCT database (2013-001567-24) and the Netherlands Trial Registry (NTR3967).

Results

Patient population

A total of 30 patients were included from September 2013 until March 2014 in three Dutch cancer centers. Characteristics of the included patients are shown in Table 1. Tumor types of included patients were soft tissue sarcoma ($n = 7$); colorectal carcinoma ($n = 6$); cancer of unknown primary ($n = 4$); neuroendocrine carcinoma ($n = 2$); and thymus carcinoid, hepatocellular carcinoma, ovarian carcinoma, mesothelioma, esophageal carcinoma, meningioma, perivascular epithelial tumor, renal cell carcinoma, choroidal melanoma, endometrial carcinoma, and cholangiocarcinoma (all $n = 1$).

All patients received at least one dose of pazopanib, underwent at least one C_{min} measurement, and were eligible for PK evaluation. Median study follow-up was 34 weeks.

Pharmacokinetically guided dosing

Based on treatment outcome, patients were divided into four groups (Fig. 1). Patients who had at least one C_{min} below 20.0 mg/L at day 15, 29, or 43 were classified as group 1; patients who had all these C_{min} measurements above the target were classified as group 2. Patients who did not experience any toxicity requiring a dose reduction or interruption during the dose-escalation period (the first 8 weeks of treatment) were classified as group a (no severe toxicity), whereas those who did were classified as group b (severe toxicity). Based on these classifications, the distribution of patients was 10 in group 1a (eligible for a dose escalation), 7 in 1b (no dose escalation possible due to toxicity), 4 in group 2a (adequate C_{min}, no toxicity), and 9 in group 2b (adequate C_{min}, severe toxicity; Fig. 1). A full overview of treatment outcomes (C_{min} measurements, dose received, and percentage of patients above the C_{min} target) is provided in Table 2. Plots of the C_{min} over time per treatment outcome group are shown in Fig. 2.

Group 1a: This group (patients with low drug exposure and no severe toxicity) consisted of 10 patients who were sustainably treated at an increased dose. The C_{min} in this group increased from 13.2 (CV 38.0%) mg/L in week 2 to 22.9 (CV 44.9%) mg/L in week 8 ($P = 0.02$). Only 2 patients did not show an increase in C_{min} after the dose escalation. Four patients reached the target at the end of the dose-escalation period (week 8), and 7 patients reached the target exposure of $\geq$20 mg/L within 3 months of treatment. After the last dose escalation (day 43), patients in group 1a were treated at a mean dose of 1,378 mg, ranging from 1,000 to 1,800 mg. One patient was treated with 1,800 mg QD for over 33 weeks, with acceptable (<grade 3) toxicity.

Group 1b: This group (patients with low drug exposure but with toxicity requiring a dose interruption or reduction) consisted of 7 patients who had a stable C_{min} during the dose-escalation phase. In this group, 1 patient could not have a dose escalation due to toxicity [aspartate aminotransferase/alanine aminotransferase (ASAT/ALAT) increase] at the prespecified dose-escalation moments. Another patient required a dose interruption but could later continue treatment on 800 mg QD. Five patients experienced toxicity after an initial escalation and required a subsequent dose reduction. Four of these five could thereafter be treated successfully until disease progression at a dose of 800 mg ($n = 3$) or 1,000 mg ($n = 1$) daily. One patient discontinued treatment due to toxicity after dose escalation (fatigue, grade 3). The patients' C_{min} was 19.7 (CV 56.6%) mg/L at week 2 and 18.9 (CV 40.5%) mg/L at week 8 ($P = 0.89$).

Group 2a: This group (patients with high drug exposure and no severe toxicity) consisted of 4 patients who could be treated on the fixed 800-mg dose with adequate C_{min} without the need for a dose reduction or interruption in the first 8 weeks. Surprisingly, the C_{min} decreased in these patients from 37.4 mg/L (CV 19.4%) at week 2 to 25.9 mg/L (CV 18.8%) at week 8 ($P = 0.04$).

Group 2b: This group (patients with a high drug exposure but also severe toxicity) consisted of 9 patients who had a decrease in C_{min} from week 2 to week 8, from 51.3 mg/L (CV 45.1%) to 28.2 mg/L (CV 25.3%; $P = 0.04$). The mean dose was reduced from 800 mg to 600 mg in the same interval.

Use of gastric acid–reducing agents was discouraged, but not prohibited during this trial. Nine patients in the low exposure groups (7 in group 1a and 2 in group 1b) and 4 in the high exposure groups (all in group 2b) used a proton pump inhibitor (PPI) at any point during treatment. Patients were instructed to take the PPI concomitantly with pazopanib, as recommended in the summary of product characteristics.

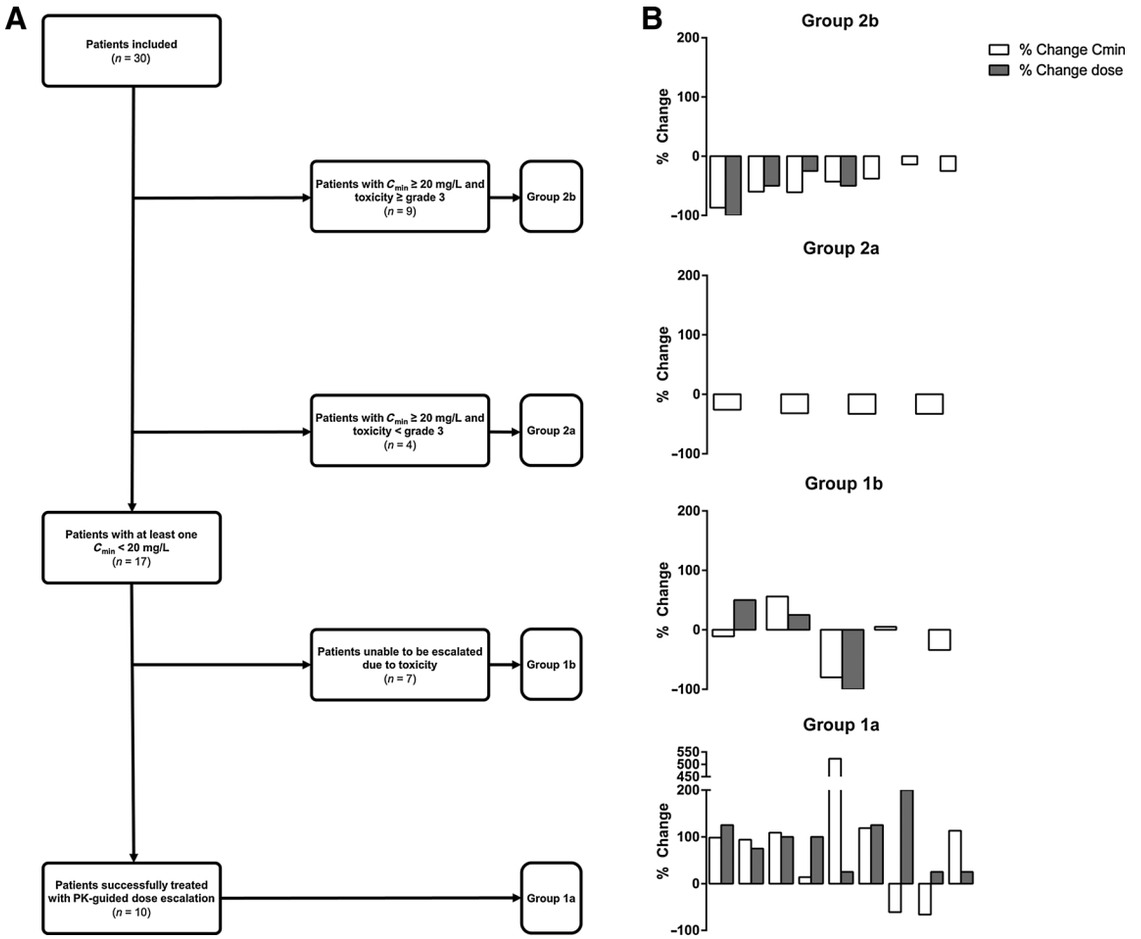

Figure 1.

A, Trial outcome flowchart. Toxicity, for the purpose of this chart, is defined as any AE requiring a dose interruption or reduction in the first 8 weeks of treatment. C_{min} below or above the target of ≥20.0 mg/L is based on samples from week 2, 4, or 6, as per protocol. Dose escalations were based on these samples. **B,** Percentage change in dose from baseline (steady state at W2D1) to the end of the dose algorithm period [last dose change (W7D1) and corresponding steady state C_{min} W8D1]. Gray bars represent percentage change in pazopanib dose (mg QD); white bars represent percentage change in pazopanib C_{min} (mg/L). Each patient is represented by adjacent bars, plotted per treatment outcome group; only patients evaluable at both weeks 2 and 8 are shown.

Adverse events

An overview of the observed AEs related to pazopanib with a frequency of ≥10% is shown in Table 3. The most common severe (≥grade 3) AEs were hypertension, fatigue, and ASAT/ALAT increase.

Fewer patients experienced ≥grade 3 AEs in the low exposure groups (1a and 1b), with 41.2% of patients experiencing at least one ≥grade 3 AE, compared with 76.9% in the high exposure groups (2a and b). The percentage of patients discontinuing due to toxicity was similar between the high and low exposure groups: 11.8% in 1a plus 1b and 15.4% in 2a plus 2b.

Of patients with a high exposure requiring a dose reduction (group 2b, $n = 9$), all but 2 (both cases grade 3 fatigue) could be successfully treated at a lower dose until disease progression.

Overall, events causing the discontinuation were fatigue ($n = 3$) and ASAT/ALAT increase ($n = 1$). Remarkably, C_{min} at week 2 appeared higher in patients in group 1 experiencing toxicity (1b) than those who did not experience toxicity (1a) [19.7 mg/L vs. 13.2 mg/L ($P = 0.19$), respectively]. The same trend was observed in group 2 [37.4 mg/L for patients without toxicity (2a) vs. 51.3 mg/L for patients with toxicity (2b; $P = 0.27$), respectively].

Patients who experienced fatigue ($n = 3$) or ASAT/ALAT increase ($n = 2$) had a C_{min} (at first presentation of grade 3 toxicity) of 51.4 mg/L (range, 21.4–98.1) and 8.9 mg/L (range, 7.3–10.5), respectively. Patients with grade 3 hypertension ($n = 11$) had a C_{min} at presentation of 37.3 mg/L (range, 7.0–76.5), whereas patients with grade 2 hypertension ($n = 10$) had a C_{min} of 27.8 mg/L (range, 16.7–43.8).

Efficacy

From 27 patients, at least one response evaluation was available. Of these, 3 patients had a partial response (perivascular epithelial tumor, renal cell carcinoma, and soft tissue sarcoma, all $n = 1$), 18 had stable disease, and 6 had progressive disease as best response.

The mean of all measured C_{min} levels per patient (from start of treatment to discontinuation) was calculated as a measure of

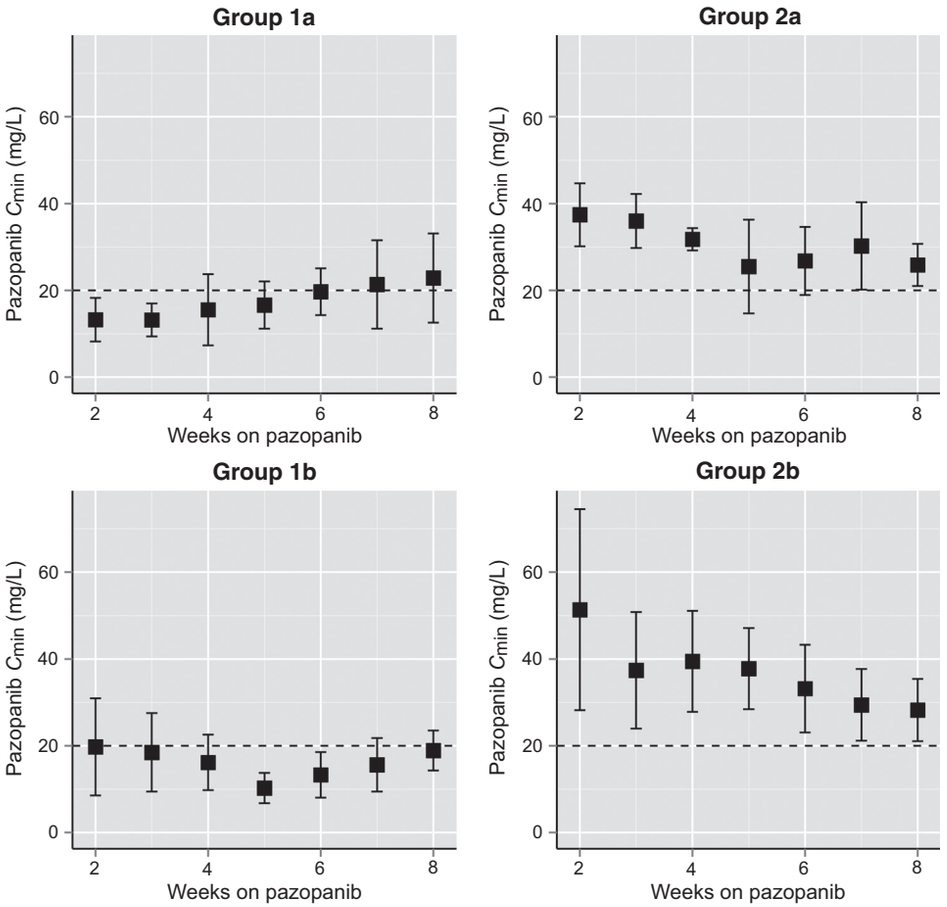

Figure 2.
Pazopanib exposure over time per outcome group (mean C_{min} ± standard deviation). The dotted line indicates the threshold of 20 mg/L. C_{min} did not change in group 1b ($P = 0.89$). In groups 2a and 2b, C_{min} declined significantly ($P = 0.04$ and 0.04, respectively). Group 1a showed a significant increase in C_{min}, from 13.2 mg/L to 22.9 mg/L ($P = 0.02$).

exposure during pazopanib therapy for the purpose of exposure–response relationships. Overall, the average of the mean C_{min} of each patient was 24.4 mg/L (CV 39.1%). In total, 19 patients had a mean C_{min} above and 11 below the target of 20 mg/L. A waterfall plot of the maximum decrease in tumor size from baseline is shown in Fig. 3. All three patients who had a partial response had a mean C_{min} above the 20 mg/L threshold [with an average of 27.6 mg/L (CV 14.4%)]. In non-prespecified,

Table 2. Pazopanib C_{min}, percentage of patients above target, and dose per treatment outcome group[a]

Outcome	Group 1a TOX − C_{min} <20.0 mg/L $n = 10$	Group 1b TOX + C_{min} <20.0 mg/L $n = 7$	Group 2a TOX − C_{min} ≥20.0 mg/L $n = 4$	Group 2b TOX + C_{min} ≥20.0 mg/L $n = 9$	Total $N = 30$
Mean pazopanib C_{min}, mg/L (CV %)					
W2D1	13.2 (38.0)	19.7 (56.6)	37.4 (19.4)	51.3 (45.1)	30.0 (71.9)
W4D1	15.5 (52.8)	16.2 (39.6)	31.8 (8.1)	39.4 (29.5)	24.8 (54.8)
W6D1	19.7 (27.4)	13.3 (39.6)	26.8 (29.2)	33.2 (30.5)	22.8 (43.2)
W8D1	22.9 (44.9)	18.9 (40.5)	25.9 (18.8)	28.2 (25.3)	24.1 (33.9)
Percentage of patients above the target C_{min} of ≥20.0 mg/L[b]					
W2D1	10.0	42.8	100.0	100	56.7
W4D1	20.0	14.3	100.0	88.6	50.0
W6D1	40.0	14.3	100.0	66.6	50.0
W8D1	40.0[c]	28.6	100.0	55.6	50.0
Mean daily pazopanib dose (mg)					
W3D1	1,040	933	800	725	893
W5D1	1,280	1,000	800	667	1,000
W7D1	1,378	950	800	633	1,009

[a]Toxicity, for the purpose of grouping, is defined as any adverse event requiring a dose interruption or reduction in the first 8 weeks of treatment. C_{min} below or above the target of ≥20.0 mg/L is based on samples from week 2, 4, or 6.
[b]Patients for whom no C_{min} was available or who discontinued treatment are scored as below the target.
[c]40% of patients in group 1a achieved the target in week 8. During study follow-up, 7 patients in group 1a (70%) achieved target exposure of >20.0 mg/L within 3 months since start of treatment.

Table 3. Toxicity data per outcome group[a]

	Group 1a TOX − C_{min} ↓ $n = 10$		Group 1b TOX + C_{min} ↓ $n = 7$		Group 2a TOX − C_{min} ↑ $n = 4$		Group 2b TOX + C_{min} ↑ $n = 9$		Total $N = 30$	
Adverse event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Hypertension	4	2[b]	3	2	1	1[b]	7	6	15	11
Fatigue	3	0	3	1	1	0	6	2	13	3
Diarrhea	4	1[b]	4	0	2	0	2	0	12	1
Nausea	2	0	0	0	1	0	6	0	9	0
Rash	2	0	3	1	0	0	3	0	8	1
Hair depigmentation	3	0	2	0	3	0	0	0	8	0
ASAT increase	1	0	2	2	2	0	1	0	6	2
ALAT increase	1	0	2	2	0	0	2	0	5	2
Anorexia	2	0	1	0	0	0	1	0	4	0
Weight loss	1	0	1	0	0	0	2	0	4	0
Dysgeusia	0	0	0	0	2	0	2	0	4	0
Vomiting	1	0	0	0	1	0	2	0	4	0
Edema	0	0	1	0	1	0	1	0	3	0
Proteinuria	1	0	0	0	0	0	2	0	3	0
Dyspnea	1	0	0	0	1	0	1	0	3	0

NOTE: Only toxicities related to pazopanib with a frequency of 10% are shown. Data are presented as number of patients (*n*).

[a]Toxicity, for the purpose of grouping, is defined as any adverse event requiring a dose interruption or reduction in the first 8 weeks of treatment. C_{min} below or above the target of ≥20.0 mg/L is based on samples from week 2, 4, or 6.

[b]These grade 3 toxicities did not result in a dose reduction or discontinuation, or they occurred after the 8-week dose-escalation period.

exploratory analyses of all evaluable patients ($n = 27$), tumor response was associated with mean C_{min} of pazopanib. An average change from baseline for patients above and below the PK threshold of −6.49% and +14.6% respectively ($P = 0.01$). In soft tissue sarcoma patients ($n = 7$), mean change from baseline was −6.01% ($n = 5$) for patients above the threshold and +13.5% for patients below ($n = 2$; $P = 0.28$). In patients with sarcoma, PFS was 49.9 weeks (range, 8–60, $n = 5$) for patients above and 11.5 weeks (range, 7–16, $n = 2$) for patients below the PK threshold ($P = 0.06$, log-rank test).

Discussion

We performed a prospective, multicenter clinical trial to assess the safety and feasibility of pharmacokinetically guided individualized dosing of pazopanib in 30 patients with advanced solid tumors.

With the pharmacokinetically guided dosing algorithm, 33.3% of all patients could be treated at a higher dose (1,000–1,800 mg daily) with acceptable toxicity (Fig. 1). Most of these patients achieved the target C_{min} of 20.0 mg/L within study follow-up. Furthermore, overall variability in pazopanib C_{min} was reduced from 71.9% before the dose-escalation period to 33.9% thereafter (Table 2).

An equal number of patients discontinued treatment in the low C_{min} versus the high C_{min} group, and only 1 patient discontinued treatment after a dose escalation. This suggests that PK-guided increasing of the dose does not lead to more severe toxicity or higher rates of treatment discontinuation. Meanwhile, a reduction of the dose in case of very high systemic concentrations may lead to less toxicity and still maintain therapeutic C_{min} levels (group 2b; Fig. 2).

High pazopanib exposure seemed predictive of dose reductions for toxicity in patients not eligible for a dose escalation (groups 2a and 2b). The C_{min} at week 2 was higher (though not significantly) in the patients who would require a dose reduction (2b) than those who would not (2a; mean of 51.3 vs. 37.4 mg/L; Table 2 and Fig. 2). This implies that patients are unlikely to tolerate a very high trough level for a longer period and could support strategies to prevent toxicity by implementing dose reduction in patients with C_{min} >50 mg/L, although this is based on limited data.

No clear relations between C_{min} and specific grade ≥ 3 toxicities were found. The most common severe AE was hypertension. This is thought to be related to higher pazopanib exposure (6); our

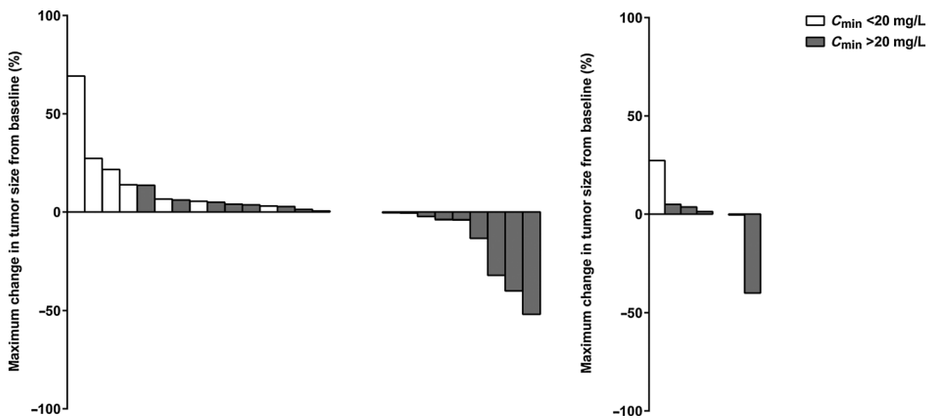

Figure 3.
Left, waterfall plot showing the maximum change in tumor size from baseline in all evaluable patients ($n = 27$). Gray bars represent patients with a mean C_{min} ≥20.0 mg/L ($n = 17$); white bars represent patients with a C_{min} <20.0 mg/L ($n = 10$). Mean change from baseline for all evaluable patients ($n = 27$) above and below the PK threshold was −6.49% and +14.6% ($P = 0.01$). Right, mean change from baseline for soft tissue sarcoma patients ($n = 7$) above and below the PK threshold was −6.01% ($n = 5$) and +13.5% ($n = 2$; $P = 0.28$).

study found a mean C_{min} at occurrence of hypertension of 37.3 and 27.8 mg/L in patients experiencing grade 3 ($n = 11$) and 2 ($n = 10$) hypertension, respectively. But this was not significantly higher than the overall mean C_{min}. It might be the case, however, that another PK parameter (e.g., C_{max}) may be more appropriate to study exposure–toxicity relationships than C_{min}, the parameter used in the current trial.

Two patients experienced severe hepatotoxicity, which in one case led to ASAT and ALAT values of over 13 times the upper limit of normal and discontinuation of treatment. This seemed unrelated to high exposure, as the mean C_{min} of these patients (in the sample closest in time to occurrence) was only 8.9 mg/L. This finding is corroborated by a recent study suggesting that the mechanism of pazopanib hepatotoxicity may be immunologic and, therefore, unrelated to pazopanib PK or dose (16).

A significant reduction in pazopanib C_{min} was seen in patients treated continuously at the 800-mg fixed dose (group 2a; Fig. 2). Although this group consisted of only a small number of patients in our trial, the same effect was observed in a population PK analysis of previously published clinical trials (17). A time-dependent decrease in exposure was also observed for another tyrosine kinase inhibitor, imatinib (18). For imatinib, upregulation of drug transporters or CYP3A4 has been suggested as a possible explanation, which could also be the case for pazopanib, as it is a known substrate of both.

In addition to pharmacokinetically guided dosing of pazopanib, other dose individualization strategies could be explored. Pharmacodynamic biomarkers could be used, for example, such as interleukin 12 (IL12) or soluble VEGFR2 (sVEGFR2; ref. 19). However, given that for pazopanib the relation between C_{min} and PFS was very significant at $P = 0.0038$ and resulted in a remarkable median PFS difference of 32.4 weeks in patients with RCC (4), C_{min} might be a more appropriate biomarker for pazopanib than sVEGFR2 or IL12.

Toxicity-based dosing could also be proposed as a dose individualization approach and has been explored previously for erlotinib (using rash), sorafenib (using hypertension), and axitinib (using hypertension; refs. 20–22). A drawback of this strategy is that it, per definition, would lead to more toxicity. The PK-guided approach applied in this trial with pazopanib did not seem to lead to less tolerability.

Another trial was performed by De Wit and colleagues to assess pharmacokinetically guided dosing of pazopanib (9). In that trial, pazopanib area under the curve ($AUC_{0-24\ h}$) was used as the PK parameter to individualize dosing, and a target window of 715 to 920 $mg{\cdot}h{\cdot}L^{-1}$ (corresponding to C_{min} values of 20.5–46.0 mg/L) was specified. The primary endpoint of that study in 13 patients was a reduction in variability, and, per protocol, only one dose change was allowed. AUC-guided dosing did not significantly reduce interpatient variability, probably due to intrapatient variability or sampling time issues. Based on this trial, the authors concluded that it may be more beneficial to target the C_{min} threshold rather than an AUC window (4, 9).

In addition, dosing based on C_{min} will also be more practical to implement in routine care, as it requires just one instead of multiple samples. Moreover, as target inhibition is thought to be concentration dependent, dosing should strive to keep the drug concentration above a certain minimally efficacious concentration during the whole dose interval, which is most accurately reflected by C_{min}.

Most importantly, studies relating pazopanib exposure to response have used C_{min} rather than AUC, further strengthening the case for C_{min}-threshold monitoring (4, 6).

Finally, self-sampling approaches facilitated by dried blood spot sampling may further enable the use of pharmacokinetically guided dosing in routine care, and several assays have already been developed for this purpose (23, 24).

The number of patients who had a C_{min} below the target at a moment of possible dose modification was 56.7%, which is markedly higher than the 20% found by Suttle and colleagues (4). This may partly be explained by the combination of repeated measurements and relatively large intraindividual variability in C_{min}. The large number of patients with low drug exposure may also partially be caused by use of PPIs, which are known to decrease the pH-dependent absorption of pazopanib (25). Nine patients in the low exposure groups (1a and 1b) used a PPI. The use of gastric pH–increasing agents was discouraged but not prohibited during this trial. On the other hand, it also shows that pharmacokinetically guided dosing may overcome the problem of pH-limited absorption of pazopanib in patients for whom treatment with PPIs is medically necessary.

A drawback of the current study is that dose modification was limited to three prespecified time points. If later dose increments would have been allowed, more patients in the low exposure group might have achieved the target threshold.

Another limitation is that our study was performed in patients with a wide range of advanced solid tumors. Therefore, a satisfying analysis of the effect of individualized dosing on tumor response or PFS is impossible. Nonetheless, all patients who had a partial response had a C_{min} above the 20.0 mg/L threshold and in a non-prespecified analysis, we found significant association between tumor response (measured as maximum change in tumor size from baseline) and pazopanib C_{min}, which would provide further support for targeting a C_{min} of $\geq$20.0 mg/L. Interestingly, in a subgroup analysis of patients with STS ($n = 7$), a trend toward increased response and longer PFS with higher C_{min} was found. Yet, perhaps due to the small size of this subgroup, these results were not significant.

The results of this trial merit further investigation of individualized pazopanib dosing in cancer patients. A similar design to the one that was previously used for axitinib dose titration in patients with RCC could be explored (21, 26). The ideal form for future studies would be a prospective, randomized, placebo-controlled trial in patients with either STS or RCC.

Conclusions

In summary, this prospective, multicenter trial in patients with advanced solid tumors showed that pazopanib dose could safely be escalated in selected patients with a C_{min} <20.0 mg/L and that pazopanib exposure increased significantly in patients whose dose was escalated based on a low C_{min}. Moreover, a significant association between C_{min} and tumor response was found.

The outcomes of this trial support further investigation of individualized pazopanib dosing, using the described dosing

algorithm, ideally in a large, prospective, randomized clinical trial using PFS or overall survival as an endpoint.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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