Relation between plasma trough concentration of Pazopanib and progression free survival in metastatic soft tissue sarcoma patients.

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Abstract

Background. Pazopanib is an oral angiogenesis inhibitor approved to treat soft tissue sarcoma (STS) but associated with large interpatient pharmacokinetic (PK) variability and narrow therapeutic index. In order to improve its clinical use, this study aimed to define specific threshold of pazopanib trough concentration (Cmin) associated with better progression free survival in STS patients. Methods. In this observational study, pazopanib Cmin was monitored over the treatment course. For the primary endpoint, the 3-month PFS in STS was analyzed with logistic regression. Secondary, we performed exposure–overall survival (OS) in STS (Cox model plus Kaplan–Meier analysis/ log-rank test) and exposure-toxicity analyses. Results. One hundred eighteen patients (95 STS and 23 BS) were eligible for PK/PD assessment. In multivariable analysis, pazopanib Cmin < 27 mg/L was independently associated with a risk of progression at 3 months (OR 4.21, 95% CI [1.47-12.12], p = 0.008). OS was not statistically longer between patients with Cmin > 27 mg/L and those with Cmin < 27 mg/L (log-rank p = 0.07). A higher average of PAZ Cmin over the first 3 months of treatment was associated with a higher risk of grades 3-4 toxicities (40.0 vs 30.5 mg/L (OR 1.05, IC95 [1.01-1.09], p = 0.01) Conclusion. Pazopanib Cmin [?] 27 mg/L was independently associated with improved 3-month PFS in a large cohort of STS patients. Pharmacokinetically-guided dosing could be helpful to optimize clinical management of STS patients in daily clinical practice.

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Keywords (MeSH terms):

Pazopanib; pharmacokinetics; soft-tissue sarcoma; progression-free survival; toxicity.

Bullet point summary:

What is already known about this subject:

- The large interpatient pharmacokinetic variability and narrow therapeutic index of pazopanib are complicated to manage in clinical practice.
- A through pazopanib concentration of 20 mg/L in renal cancer has been shown to improve efficacy.
- No consistent cohort of patients treated with pazopanib in sarcoma has been studied.

What this study adds:

- A through pazopanib concentration of 27 mg/L in soft-tissue sarcoma is associated with improved progression-free survival (efficacy).
- Toxicity is also associated with the plasma concentration of pazopanib.
- Therapeutic drug monitoring should be required for all patients treated with pazopanib.

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Ethics approval statement & clinical trial registration: The study was approved by institutional review board for non-interventional research (Approval ID 20210429175029).

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Abstract :

Background. Pazopanib is an oral angiogenesis inhibitor approved to treat soft tissue sarcoma (STS) but associated with large interpatient pharmacokinetic (PK) variability and narrow therapeutic index. In order to improve its clinical use, this study aimed to define specific threshold of pazopanib trough concentration (C_{min}) associated with better progression free survival in STS patients.

Methods. In this observational study, pazopanib C_{min} was monitored over the treatment course. For the primary endpoint, the 3-month PFS in STS was analyzed with logistic regression. Secondary, we performed exposure–overall survival (OS) in STS (Cox model plus Kaplan–Meier analysis/ log-rank test) and exposure-toxicity analyses.

Results. One hundred eighteen patients (95 STS and 23 BS) were eligible for PK/PD assessment. In multivariable analysis, pazopanib $C_{min} < 27$ mg/L was independently associated with a risk of progression at 3 months (OR 4.21, 95% CI [1.47-12.12], p = 0.008). OS was not statistically longer between patients with

C_{min} > 27 mg/L and those with C_{min} < 27 mg/L (log-rank p = 0.07). A higher average of PAZ C_{min} over the first 3 months of treatment was associated with a higher risk of grades 3-4 toxicities (40.0 vs 30.5 mg/L (OR 1.05, IC95 [1.01-1.09], p = 0.01)

Conclusion. Pazopanib C_{min} [?] 27 mg/L was independently associated with improved 3-month PFS in a large cohort of STS patients. Pharmacokinetically-guided dosing could be helpful to optimize clinical management of STS patients in daily clinical practice.

INTRODUCTION

Soft-tissue sarcomas (STS) are a group of rare mesenchymal cancers that include about 70 histological types, and account for 1% of adult cancers. In Europe, the estimated yearly incidence is five per 100 000 (1). The prognosis of metastatic and unresectable stages remains poor and has been only slightly improved by doxorubicin and ifosfamide in first-line treatment (2).

Pazopanib is an angiogenesis inhibitor that targets the tyrosine kinase domain of vascular endothelial growth factor receptors 1, 2 and 3, platelet-derived growth factor receptors and c-kit (3,4). Pazopanib is approved in the treatment of advanced renal cell carcinoma (RCC) and chemotherapy-pretreated STS (5). In the PALETTE trial, pazopanib showed a clinical benefit with a longer Progression Free Survival (PFS) compared to placebo (median PFS 4.6 (95% CI 3.7–4.8) versus 1.6 months (0.9–1.8), respectively; hazard ratio (HR) 0.31, p<0.0001) but without overall survival improvement (6). Pazopanib have also demonstrated activity for advanced bone sarcoma (BS) (7,8).

Pazopanib is administered orally at a flat-fixed dose despite a large interpatient pharmacokinetic (PK) variability and a low therapeutic index (4,9–12). Pharmacokinetic/pharmacodynamic (PK/PD) studies have reported relationships between exposure and treatment outcomes (efficacy and toxicity) for several TKI suggesting a potential interest of drug monitoring (9,13–16). Regarding pazopanib, a trough plasma concentration (C_{min}) [?] 20.5 mg/L was associated with both improved PFS (19.6 vs. 52.0 weeks, p=0.004) and tumour shrinkage in RCC patients (9). This efficacy threshold was later confirmed in a real-life RCC cohort (10). No threshold value for pazopanib C_{min} (PAZ C_{min}) has been clearly identified for the occurrence of severe toxicity regardless the tumour type.

From an exploratory study including 34 STS patients, we previously proposed a PAZ C_{min} threshold of 27 mg/L for efficacy (17). In the present study, we aimed to confirm this threshold in a larger cohort of unselected STS patients, then to explore the exposure-response relationship for toxicity in an extended cohort including both STS and BS patients.

MATERIEL AND METHODS

Study design and Patients.

Between December 2013 and October 2020, all patients with metastatic or unresectable STS or BS treated with pazopanib in Cochin-Port Royal hospital (Paris, France) were eligible for this observational study. Patients were considered for the main analysis if at least one plasma concentration of pazopanib was available at steady state (after at least 15 days of treatment) (figure 1). Informed consent was obtained from all patients prior to inclusion. The study was approved by institutional review board for non-interventional research (Approval ID 20210429175029).

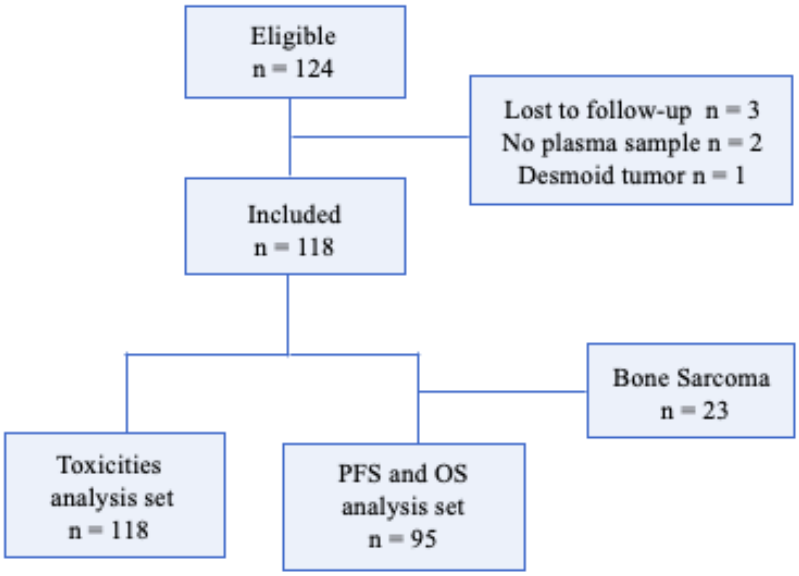

Figure 1. Flowchart.

Procedures.

A comprehensive clinical assessment was systematically performed before treatment start.

During the treatment period, clinical assessment of toxicities as well as blood count, liver, renal and thyroid functions were assessed every 2 weeks for the first 3 months and then monthly. Patients were instructed to monitor blood pressure at home (18,19). All adverse events were prospectively graded according to the National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 (20). In case of grade 3 or 4 toxicity, pazopanib was suspended until improvement to grade 1-2. CT scan and/or MRI tumour evaluations were recommended every three months until progression.

The recommended starting dose of pazopanib was 800 mg/day. However, for patients with a higher risk of toxicities (ECOG PS [?] 2, age [?] 75 years old, albumin $<$ 30 g/L, cardiovascular background), a lower starting dose (200 to 600 mg/day) could be prescribed at the discretion of physician. Subsequently, doses could be adjusted in 200 mg increments or decrements based on tolerance (21).

Pharmacokinetic assessments.

Blood samples were drawn at steady state every two weeks for the first three months and then monthly. Blood was collected into 5 ml lithium heparinized Vacutainer tubes at any time over the administration interval. Samples were centrifuged at 3,000 rpm for five minutes at 4°C and transferred to polypropylene tubes and kept at -20°C until assay. Plasma pazopanib concentration was measured using high-performance liquid chromatography coupled with UV detection. The intra- and inter-assay coefficients of analytical variability were less than 8% and 10%, respectively. The lower quantification limit was 1.2 mg/L. The PAZ C_{min} was estimated using a Bayesian method. The population PK model of Yu et al. (11) was implemented in the Bayesian estimator.

Study endpoints.

Regarding efficacy, the primary endpoint was PFS at 3 months in STS patients. The main objective was to determine whether PAZ C_{min} [?] 27 mg/L at day 15 (D15) was associated with a longer PFS at 3 months. PFS was calculated as the time between the first day of pazopanib to tumour progression or death. Tumour progression was assessed using RECIST 1.1 criteria when measurable lesions were present or was established by the referent oncologist based on clinical findings, with retrospective confirmation by two oncologists (PBR and JA). The cut-off of 3 months for the PFS was chosen for two reasons. First, it corresponded to the first radiologic assessment, secondly it was in accordance with the primary endpoint of PALETTE trial (6).

The secondary endpoints were overall survival (OS) in STS patients and incidence of dose-limiting toxicity (DLT) during the first three months in both STS and BS patients. OS was calculated as the time between the first day of pazopanib to death (all causes included). DLT was defined as any clinical or biological grade 3 or 4 toxicity leading to treatment dose reduction, interruption (temporary stop) or permanent discontinuation.

Statistical analysis.

Statistical analyses were performed with the software R (version 4.0.3). Groups were compared with a Student's t-test for quantitative variables, and Chi2-test for qualitative variables. Based on the results of our exploratory study and the PALETTE trial (6), we calculated that we would need to enrol 82 patients to show a 35% difference of 3-month PFS (70% vs 35% in patients with a C_{min} [?] 27 and $<$ 27 mg/L respectively) with a two-sided 5% significance level and an 80% statistical power. Univariate and multivariable logistic regression models were used to test the association of bio-clinical variables with 3-month PFS. Variables associated with significant p-value in univariate analyses and potential confounders (initial daily dose, histological subtype) were included into multivariable models, except tumour grade (not applicable to some histological subtypes). Interaction tests revealed no significant subgroup differences. Survival curves were obtained with Kaplan-Meier estimates and compared with log-rank test. Univariate and multivariable Cox proportional hazards regression was used to identify variables associated with OS. The proportional hazards assumption was checked for each model using graphical methods based on Kaplan-Meier curves and the scaled Schoenfeld residuals. Univariate logistic regression models were used to test the association of bio-clinical variables with DLT.

All p-values were two-sided, and the level of significance was set at $p < 0.05$.

Our cohort study fulfils the STROBE criteria for the reporting of observational studies in epidemiology (22).

RESULTS

Patients and treatment.

One hundred and eighteen patients, mostly with STS (81%), were eligible for statistical analysis. Their baseline characteristics are outlined in Table 1. The median treatment duration was 3.9 months (range 0.4-51.0). At least one dose change was performed in 51 patients (43%), mainly within the first 3 months (36%).

Variable	
Sexe, n (%) Male	62 (53%)
Median age, years (range)	52 (17 – 83)
Age, n (%) [?] 70 years	13 (11%)
Performance status, n (%) 0-1 [?] 2	89 (75%) 29 (25%)
Body Mass Index, n (%) $<$ 25 [?] 25	64 (54%) 54 (46%)
Primitive, n (%) Soft tissue sarcoma Bone sarcoma	95 (81%) 23 (19%)

Variable	
Subtypes, n (%) Leiomyosarcoma Synovial sarcoma Malignant solitary fibrous tumour Epithelioid and clear cell sarcoma Myxofibrosarcoma Undifferentiated pleomorphic and fusiform cell sarcoma Others*	28 (30%) 14 (15%) 12 (13%) 8 (9%) 7 (8%) 6 (6%) 13 (13%)
Site of primitive tumour, n (%) Lower member Upper member Trunk (thorax, abdomen, head and neck) Uterus	43 (45%) 11 (11%) 30 (32%) 11 (11%)
Histological grade, n (%) 1 2 3 Not concerned**	4 (4%) 27 (29%) 40 (42%) 24 (25%)
Pazopanib metastatic line, n (%) First Second [?] Third	31 (26%) 44 (37%) 43 (37%)
Initial daily dose of pazopanib, n (%) 200 mg 400 mg 600 mg 800 mg	2 (2%) 17 (14%) 30 (25%) 69 (59%)
Albumin, n (%) < 35 [?] 35	17 (14%) 101 (86%)
SGOT - SGPT, n (%) [?] ULN ([?] 40) > ULN (> 40)	97 (82%) 21 (18%)
C Reactive Protein, n (%) < 10 [?] 10 NA	72 (61%) 43 (37%) 3 (2%)
Neutrophils/Lymphocytes Ratio (NLR) < 3.5 [?] 3.5	70 (59%) 48 (41%)

Table 1. Patient characteristics (n = 118).

* Less than 5 each: Rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, malignant Peripheral Nerve Sheath Tumour, extraskeletal osteosarcoma, desmoplastic small round cell tumour, dermatofibrosarcoma

** Grading system does not apply to bone sarcoma, liposarcoma, clear cell sarcoma, alveolar sarcoma, epithelioid sarcoma, desmoplastic small round cell tumour<;

n: number

ULN: upper limit of normal

Plasma concentration of pazopanib

Five hundred and twenty-nine samples were assayed with a median of 3 (range 1-20) samples per patient. The target C_{min} [?] 27 mg/L was not reached in 45% of the samples at the first sampling and in 40% in the whole cohort. The initial daily dose of pazopanib was 800 mg/day in 69 patients (58.5%). In this subgroup, the inter-individual variability in PAZ C_{min} was 47.4% at D15. No baseline characteristic was associated with PAZ C_{min} (data not shown). PAZ C_{min} at D15 was significantly higher for patients treated with 800 mg/day compared with those treated at lower dosage (34.6 ± 16.4 vs 26.4 ± 11.8 mg/L; p=0.002). Among patients who received 800 mg/day over the whole sampling period (n = 23), no variation with time in PAZ C_{min} was observed.

Efficacy of pazopanib in STS cohort

Ninety-five STS patients were eligible for the analysis of survival-exposure relationship.

The median follow-up was 11.4 months (95% CI 1.4-41.1). At data cut-off in November 2020, 13 STS patients (14%) were still treated with pazopanib.

The median PFS was 3.30 months (95% CI 2.56-5.06). In univariate analysis, PAZ C_{min} < 27 mg/L at D15 was associated with a higher risk of progression at 3 months (OR 3.09, 95% CI [1.31-7.28], p=0.01) unlike to

the initial daily dose (table 2). The multivariate analysis identified PAZ C_{min}< 27 mg/L as an independent risk factor of progression (OR 4.21, 95% CI [1.47-12.12], p=0.008), with other bio-clinical factors (table 2).

Variable	Univariate analysis		Multivariable analysis	
	OR [95 CI]	p-value	OR [95 CI]	p-value
Initial daily dose				
< 800 vs 800 mg	1.95 [0.85-4.5]	0.12	2.15 [0.71-6.57]	0.18
PAZ C_{min} at D15				
< 27 vs [?] 27 mg/L	3.09 [1.31-7.28]	0.01	4.21 [1.47-12.12]	0.008
Histological subtype				
Leiomyosarcoma vs other	1.22 [0.48-3.07]	0.68	1.99 [0.62-6.40]	0.25
Synovial sarcoma vs other	0.54 [0.15-1.99]	0.35	0.67 [0.14-3.26]	0.62
Tumour grade*				
Grade 3 vs 1-2	2.91 [1.03-8.20]	0.04		
Metastatic sites				
Bone metastasis	2.85 [1.15-7.06]	0.02	2.63 [0.87-7.95]	0.09
Lymph node metastasis	2.78 [1.16-6.70]	0.02	4.55 [1.43-14.46]	0.01
ECOG PS				?¿?
2 vs 0-1	3.10 [1.16-8.32]	0.02	1.89 [0.55-6.55]	0.31
Previous treatments				?¿?
2 vs 0-1 previous lines	0.93 [0.40-2.18]	0.87		
BMI				
> 25 vs [?] 25 kg/m^2	2.63 [1.13-6.13]	0.03	3.05 [1.02-9.15]	0.046
Albumin				?¿?
35 vs < 35 g/L	0.77 [0.25-2.41]	0.66		
NLR				?¿?
3.5 vs < 3.5	0.40 [0.17-0.95]	0.04	0.31 [0.10-0.93]	0.04

Table 2. Univariate and multivariate Cox proportional hazard analysis of risk factors for 3-month progression.

** Not included in multivariable analysis (not evaluable for some histological subtypes) Abbreviations: PAZ C_{min} at D15: pazopanib Cmin at day 15 ;PS : Performance Status; BMI : Body Mass Index ; NLR : Neutrophil-Lymphocytes Ratio.*

Overall survival in STS cohort

The median OS in the STS cohort was 13.9 months (95% CI 11.4-20.1).

Over the whole duration of follow-up, patients with PAZ C_{min} > 27 mg/L at D15 tended to have a longer OS than other patients: 17.7 (12.0-27.6) vs 11.4 months (7.1-18.8) (log-rank p=0.07) (Figure 2). In multivariate analysis, only ECOG PS [?] 2 was identified as an independent risk factor for OS (HR 2.31 [1.26-4.23], p=0.007) (table3).

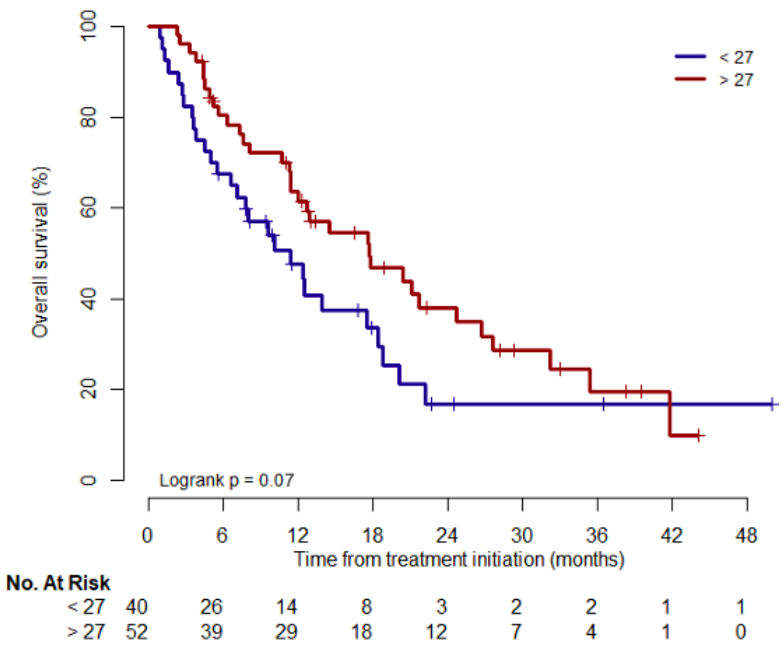

Figure 2. Kaplan-Meier analysis for OS according to trough pazopanib concentration at day 15.

Variable	Univariate analysis		Multivariable analysis	
	OR [95 CI]	p-value	OR [95 CI]	p-value
Age				?¿?
70 vs < 70 yrs	1.01 [0.99-1.02]	0.58		
Sexe				
Female vs Male	1.02 [0.62-1.68]	0.94		
Initial daily dose				
< 800 vs 800 mg	1.38 [0.83-2.30]	0.22	1.01 [0.58-1.77]	0.97
PAZ C_{min} at D15				
< 27 vs [?] 27 mg/L	1.57 [0.95-2.61]	0.08	1.62 [0.97-2.72]	0.07
Histological subtype				
Leiomyosarcoma vs other	1.08 [0.62-1.87]	0.8	1.19 [0.67-2.13]	0.55
Synovial sarcoma vs other	0.71 [0.30-1.70]	0.45	0.86 [0.35-2.09]	0.74
Tumour grade*				
Grade 3 vs 1-2	1.72 [0.94-3.18]	0.08		
Metastatic sites				
Bone metastasis	1.78 [1.07-2.97]	0.03	1.42 [0.82-2.47]	0.22
Lymph node metastasis	0.98 [0.57-1.67]	0.93		
ECOG PS				?¿?
2 vs 0-1	2.54 [1.49-4.33]	0.0006	2.31 [1.26-4.23]	0.007
Previous treatments				?¿?
2 vs 0-1 previous lines	1.44 [0.86-2.41]	0.17		
BMI				
> 25 vs [?] 25 kg/m^2	1.41 [0.85-2.33]	0.19		
Albumin				?¿?

Variable	Univariate analysis		Multivariable analysis	
35 vs < 35 g/L	1.07 [0.53-2.18]	0.85		
NLR				?¿?
3.5 vs < 3.5	1.00 [0.60-1.67]	0.99		

Table 3. Univariate and multivariate Cox proportional hazard analysis for OS.

** Not included in multivariable analysis (not evaluable for some histological subtypes).*

Dose-limiting toxicity- exposure relationship.

Both STS and BS patients (n=118) were included in the DLT analysis. Overall, 51 DLT events was observed in xx (%) patients during the first 3 months of treatment, including hypertension in 14% of patients (n=17), asthenia 12% (n=14), anorexia 10% (n=12), hepatic cytolysis 6.5% (n=8). Grade 3-4 toxicities led to dose decrease, treatment interruption and discontinuation in 25 patients (21%) (including 19 patients with 800 mg initial dose), 42 patients (35.5%) and 29 patients (24.5%) respectively. Eighteen patients (15%) were able to have a dose increase within the first three months and a further eleven patients (9%) after three months.

Baseline characteristics associated with occurrence of DLT are shown in table 4.

Variable	Univariate analysis	
	OR [95 CI]	p-value
Sexe		
Female vs Male	1.19 [0.57-2.48]	0.65
Age		?¿?
70 vs < 70 years	1.82 [0.57-5.8]	0.31
Initial daily dose		
< 800 vs 800 mg	0.75 [0.36-1.6]	0.46
ECOG PS		?¿?
2 vs 0-1	2.65 [1.12-6.25]	0.03
BMI		
> 25 vs [?] 25 kg/m^2	2.37 [1.12-5.02]	0.02
Previous treatments		?¿?
2 vs 0-1	1.78 [0.83-3.83]	0.14
Albumin		?¿?
35 vs < 35 g/L	1.31 [0.45-3.81]	0.63
NLR		?¿?
3.5 vs < 3.5	0.93 [0.44-1.96]	0.84
SGOT or SGPT		
> 40 vs [?] 40	1.24 [0.47-3.26]	0.67

Table 4. Univariate analysis of factors associated with dose-limiting toxicities.

We tested the threshold value of 50 mg/L proposed for DLT onset in RCC patients, but it was not statistically significant (data not shown).

However, a higher average of PAZ Cmin over the first 3 months of treatment was associated with a higher risk of grades 3-4 toxicities (40.0 vs 30.5 mg/L (OR 1.05, IC95 [1.01-1.09], p=0.01) (figure 3).

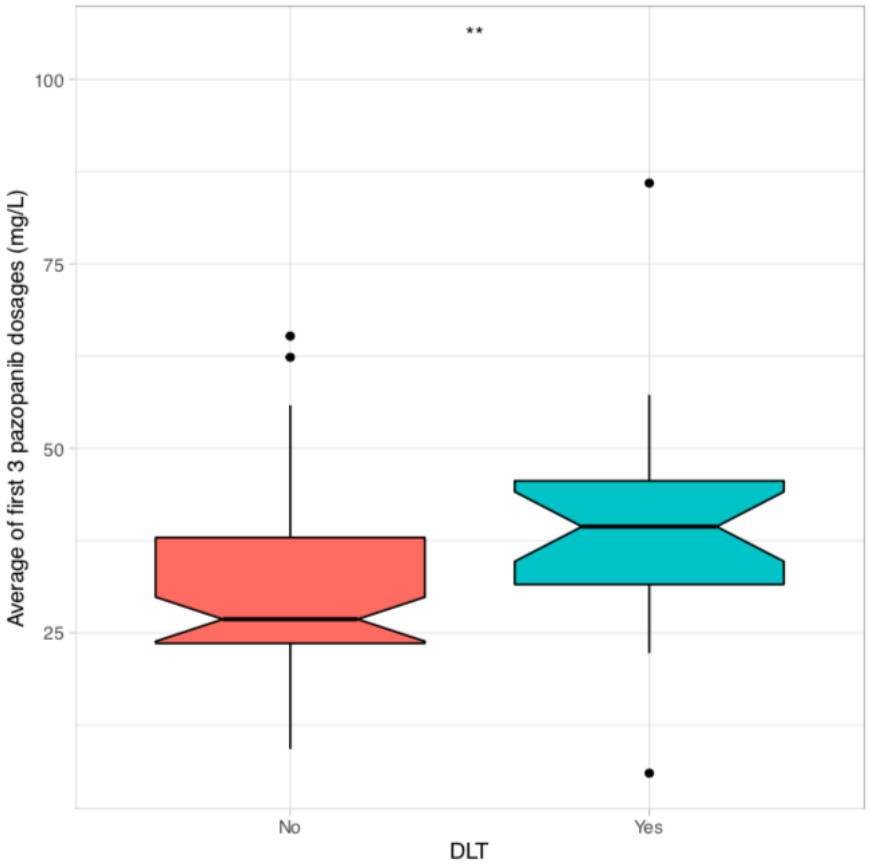

Figure 3. Dose-limiting toxicities (DLT) according to the average of first 3 trough (C_{min}) concentration of pazopanib (n=118).

DISCUSSION

The pivotal PALETTE trial (6) showed a clinical benefit of pazopanib compared to placebo in STS patients treated with 800 mg/day. However, a large interindividual variability in response to pazopanib is observed in STS patients in daily clinical practice, both in terms of efficacy and toxicity. Different clinical and biological parameters can contribute to this variability, especially in unselected STS patients treated outside a clinical trial. In the present study, different parameters such as PS, tumour grade, bone or node metastasis, BMI and NLR were identified as risk factors for 3-month progression. These results are in accordance with those of PALETTE trial.

The main finding of this observational study is that a PAZ $C_{min} < 27$ mg/L at day 15 was an independent risk factor of 3-month PFS while a daily start dosing lower than 800 mg/day was not. A threshold of 20.5 mg/L was previously explored by Verheijen R.B et al and was found significantly associated with PFS in RCC patients but not in STS patients (9,16). This discrepancy could be related to the lower efficacy of pazopanib in STS patients compared to RCC. We also observed OS tended to be shorter in patients with PAZ $C_{min} < 27$ mg/L, but the difference was not statistically significant. In the PALETTE trial, none of all explored factors were found to be significantly associated with OS (23).

The safety profile of pazopanib in our real-life cohort is generally consistent with previous studies (5,6). In the present study, the univariate analysis identified PS and BMI as risk factors of DLT onset. Regarding PK/PD analysis, a higher risk was observed in patients with increased plasma C_{min} over the first 3 months

of treatment (p=0.01). In RCC patients (n=205), Suttle et al. showed an increased frequency of hypertension, diarrhea, hepatic cytolysis, and stomatitis in the fourth quartile PAZ C_{min} (36-85 mg/L) (9). In the present,study, we did not investigate any PK/PD relationship for these specific adverse events because our study was not statistically designed to address this issue. However, we tested the threshold value of 50 mg/L proposed for DLT onset in RCC patients (16,24,25), but it was not statistically significant (data not shown). This threshold is probably less than 50 mg/L in sarcoma patients owing to their higher fragility compared to RCC patients. Further studies are warranted to clearly identify a threshold value of PAZ C_{min} able to predict DLT onset in sarcoma patients.

The poor tolerance profile of several TKI, especially in patients with poor PS, has led to evaluate the use of a lower daily dose at the initiation with a secondary increase according to tolerance. Such strategies have been validated with regorafenib and afatinib (26,27). but need close clinical monitoring that is not always feasible in daily practice. The use of therapeutic drug monitoring (TDM) could be an alternative approach to ensure therapeutic plasma exposure over the whole treatment course. In case of suboptimal exposure, a dose escalation strategy should be conducted whether the safety profile is favourable to it. However, it is noteworthy to underline that daily of PAZ above 800 mg exhibits a saturation of its intestinal absorption (11). Therefore, splitting the dose into 400 mg twice is strongly recommended to enhance the bioavailability in underexposed patients treated with 800 mg/day (21,28).

The major strength of this study is its sample size, which is the largest about pazopanib pharmacokinetics in sarcoma. Moreover, both survival and tolerance data from this "real-life" study are consistent with the literature. However, the present study also presents several drawbacks, including the monocentric design and the numerous treatment interruption within the first three months that could interfere with PK/PD analysis.

In patients treated with oral targeted anticancer drug, TDM has been recognized as a powerful tool to individualize drug dosing, ensure drug concentrations within the therapeutic window and increase treatment success rates (29). Several PK/PD studies showed the relevance and feasibility of TDM in patients treated with angiogenesis inhibitors such as sorafenib or sunitinib (14,15,30–32). The presents study suggests the clinical benefit to practice early TDM in STS patients under pazopanib, as previously proposed in RCC patients (10). Some clinically drug-drug interactions are also relevant indications for TDM in STS patients treated with PAZ. For example, coadministration of proton pump inhibitors is known to decrease by 40% plasma exposure, which results in significantly shortened PFS and OS (33). Thereby, TDM may be helpful for the clinical management of most patients. Overall, early TDM strategy could be helpful to both prevent early treatment failure and DLT onset.

In conclusion, the present study confirms PAZ C_{min}target >27 mg/L in a large cohort of STS patients to optimize efficacy. In today's era of personalized medicine, early TDM could be helpful to optimize response to pazopanib in these patients, as previously reported in RCC patients. In this context, any STS or RCC patient treated with PAZ should have access to TDM.

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