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ORIGINAL RESEARCH

Impact of paclitaxel on pazopanib pharmacokinetics in patients with ovarian cancers from phase II trial TAPAZ

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Abstract

Background: Combining standard chemotherapy with anti-angiogenic agents could improve efficacy in platinum-resistant recurrent ovarian cancer but is associated with increased toxicity, possibly due to pharmacokinetic (PK) interactions. The objective was to evaluate the impact of paclitaxel on pazopanib PK, and the relationship between toxicity and pazopanib PK in recurrent ovarian cancer patients enrolled in TAPAZ (Paclitaxel/Pazopanib for Platinum Resistant/Refractory Ovarian Cancer) study. **Methods**: TAPAZ randomized phase II trial assessed the efficacy and toxicity of the standard weekly paclitaxel 80 mg/m^2 (P arm) with respect to those of an experimental arm composed of weekly paclitaxel 65 mg/m^2 combined to pazopanib 600–800 mg daily (PP arm) in recurrent ovarian cancer patients. PK sampling was performed during cycle 1 in patients from PP arm. Pazopanib PK data was analysed using non-linear mixed effects modelling. **Results**: The study enrolled 116 patients (n = 79 in PP arm, n = 39 in P arm). Pazopanib PK data were available in 56 patients from PP arm. Co-administration of paclitaxel resulted in a decrease in relative bioavailability of pazopanib (mean decrease: −18.8%, 95% CI (Confidence Interval) = −36.6%; +15.0%), without significant impact on area-under-the-concentration-time curve ($p = 0.50$). During cycle 1, pazopanib dose-limiting toxicity was observed in 23% of patients from PP arm, and was not correlated with pazopanib plasma exposure ($p = 0.26$). **Conclusions**: The present ancillary study of TAPAZ trial showed that paclitaxel does not significantly impact plasma pazopanib exposure. The exacerbated toxicity observed in the combination arm with lower paclitaxel dose could not be explained by increased pazopanib plasma exposure due to a PK drug-drug interaction. **Clnical Trial Registration**: NCT02383251.

Keywords

Ovarian neoplasms; Paclitaxel; Pazopanib; Pharmacokinetics; Pharmacodynamics; Drug-drug interactions

1. Introduction

The prognosis of patients with platinum-resistant recurrent ovarian cancer is poor, with median progression-free survival (PFS) and overall survival (OS) shorter than 6 and 18 months, respectively [1]. The main improvement in the last decade was seen with the combination of the anti-angiogenic monoclonal antibody bevacizumab with the standard chemotherapy regimens (paclitaxel, topotecan or gemcitabine) in AURELIA (A Study of Avastin (Bevacizumab) Added to Chemotherapy in Patients with Platinum-resistant Ovarian Cancer) trial [2]. Indeed, as seen in first-line setting in GOG-0218 (Carboplatin and Paclitaxel with or without Bevacizumab in Treating Patients with Stage III or Stage IV Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube Cancer) and ICON-7 (Carboplatin and Paclitaxel with or without Bevacizumab in Treating Patients with Newly Diagnosed Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cavity Cancer) trial, bevacizumab seems to be more effective in patients with bulky and poorly chemosensitivity diseases [3, 4].

Pazopanib is an oral multitarget tyrosine kinase inhibitor (TKI) of VEGF (vascular endothelial growth factor) receptors 1, 2 and 3, platelet-derived growth factor (PDGF) receptors α and β and proto-oncogene receptor tyrosine kinase (c-KIT). It is currently approved in the treatment of metastatic renal cell carcinoma (RCC) and soft tissue sarcoma (STS) at a fixed dose of 800 mg once daily. Pazopanib exhibited promising anti-angiogenic properties in patients with platinum-resistant ovarian cancers [5]. Therefore, the combination of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 on day 1, 8 and 15 every 4 weeks was assessed in 106 patients with platinum-resistant relapse in a randomized phase II trial [6]. No improvement in PFS or OS was observed. The toxicity profile of the combination was significant, with frequent neutropenia, neuropathy, severe hypertension and two cases of grade 3 bowel perforations [6].

TAPAZ was a multicenter open-label non-comparative randomized phase II trial (NCT02383251), meant to assess the efficacy of a combination regimen with lower doses of pazopanib (600 to 800 mg daily) and reduced dose of paclitaxel (65 mg/m^2) on day 1, 8 and 15 every 4 weeks (as a way of reducing the toxicity profile) compared to the standard weekly paclitaxel (80 mg/m^2) in 116 patients who experienced disease progression while on bevacizumab with a platinum-free interval $\leq$12 months. As previously reported, no benefit in PFS or OS was found [7]. Despite the selection of low treatment doses, the combination therapy was associated with increased toxicity. Discontinuation for toxicity was observed in about 50% of patients treated with combination therapy leading to lower paclitaxel dose-intensity. Finally, the association had negative impact on quality of life.

In summary, both trials failed to show the benefit of the combination of paclitaxel with the anti-angiogenic TKI pazopanib, in contrast with the outcomes of AURELIA trial. They also suggested that the lack of significant improvement in efficacy could be due to important toxicity which compromised the dose intensity of paclitaxel.

Pharmacokinetic (PK) interactions between pazopanib and paclitaxel might explain the lack of significant improvement in efficacy and/or increased toxicity in the combination arm. It was reported that pazopanib increases area under the concentration-time curve (AUC) of paclitaxel by 26–38% due to inhibition of its elimination via cytochrome P450 (CYP) 3A4 and 2C8 isoenzymes [8]. Moreover, pazopanib is metabolized mainly through CYP3A4, and to a lesser extent by CYP2C8, whilst paclitaxel is a weak inducer of these enzymes [9]. In addition, both paclitaxel and pazopanib exhibit high inter-individual variability in plasma exposure, and previous

studies reported significant relationships between pazopanib exposure and risk of toxicity [10].

According to the above considerations, the objectives of this study were to assess the impact of co-administration of paclitaxel on pazopanib PK using population modelling approach and the relationship between toxicity and pazopanib PK in patients from TAPAZ trial.

2. Materials and methods

2.1 Patients

TAPAZ trial was a multicenter open-label randomized non-comparative phase II trial where patients with recurrent platinum-resistant/refractory ovarian carcinomas were randomized into the experimental arm (PP arm) composed of continuous oral pazopanib 600 mg/day starting 7 days before paclitaxel and then combined to paclitaxel at a 65 mg/m^2 on day 1, 8 and 15 of each 4-week cycle, or a standard arm (P arm) composed of paclitaxel 80 mg/m^2 on day 1, 8 and 15 of each 4-week cycle. Pazopanib was started a week before paclitaxel to enable assessment of a PK drug-drug interaction (*i.e.*, the impact of paclitaxel addition on pazopanib PK). The design of the study is presented in Fig. 1. In the case of satisfactory tolerability with pazopanib in terms of blood pressure, gastro-intestinal adverse events (AE) and mucositis during cycle 1, pazopanib dose could be increased to 800 mg/day on cycle 2 and onwards. The selection of reduced doses of paclitaxel (65 mg/m^2) and pazopanib (600 mg daily) used in TAPAZ trial related to the significant toxicities observed at higher doses in prior studies, such as MITO11 (Weekly Paclitaxel with or without Pazopanib in Platinum Resistant or Refractory Ovarian Cancer) [11]. In MITO11, combining paclitaxel (80 mg/m^2) and pazopanib (800 mg daily) improved progression-free survival (PFS) but led to substantial toxicity, with 54% of patients requiring dose reductions. We assumed that lowering doses could balance efficacy and tolerability, particularly in a population previously treated with bevacizumab. The treatment was given until disease progression or unacceptable toxicity. A radiological evaluation for tumor progression was performed every eight weeks. The occurrence of AEs was evaluated at day 1, 8 and 15 of cycle 1 and 2, and then every three months at day 1 of each cycle. The outcomes of the trial were previously reported [7].

The protocol was approved by the ethic committee Comité de Protection des Personnes and the French health authorities Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). The study was conducted in accordance with the Declaration of Helsinki ethical guidelines. All patients recruited in the study signed an informed written consent.

2.2 Pharmacokinetic data

Determination of pazopanib plasma concentrations was performed during cycle 1 in patients from PP arm at different time points according to two sampling schedules:

• Rich PK sampling on day 7 after pazopanib treatment start (at pre-dose; 1, 2, 4, 6, 8, 12 and 24 hours after dosing) and on day 21 (at pre-dose; 1, 2, 4, 6, 8, 12 and 24 hours after dosing) in a subgroup of patients in the PP arm. Day 7 and 21 of pazopanib treatment corresponded to day 0 and day 14, respectively, of paclitaxel treatment (cycle 1).

• Sparse PK sampling on day 21 after pazopanib treatment start (at pre-dose, 2 and 6 hours after dosing) in all patients in the PP arm.

Blood samples (5 mL) were collected in heparinized tubes. Plasma was separated by centrifugation (4000 rpm, 10 minutes) and stored at −20 °C until analysis. Quantification of pazopanib plasma concentrations was performed using a validated liquid chromatography method coupled with mass spectrometry detection (LC-MS/MS) described in detail in **Supplementary material 1**.

2.3 Pharmacokinetic analysis

Pazopanib concentration-time data were analysed using non-linear mixed effects modeling in NONMEM software version 7.5.0 (ICON Development Solutions, Ellicott City, MD, USA). Processing of the data, statistical analyses and graphical evaluation were performed in R (version 4.1.2) coupled with RStudio (version 1.1.456).

PK model parameters were estimated using first-order conditional estimation method with interaction between η_i and ϵ_i. The structure of the model was based on a previously published population PK (popPK) model for pazopanib [10]. Briefly, the absorption of pazopanib from the gut was described by two first-order processes: fast process followed by a lag time and a slow absorption process. The disposition of pazopanib was described by a two-compartment model. To account for the saturation of pazopanib PK with increasing doses and the decrease in its plasma concentrations in time, the original model included a time- and dose-dependent decrease in relative bioavailability (F_{rel}). During cycle 1 of the TAPAZ study, pazopanib was given at a fixed dose of 600 mg/day with a possibility of a reduction to 400 mg/day. Therefore, the dose range was too narrow to include the dose-dependent F_{rel}. The inter-individual variability (IIV) was assumed to be log-normally distributed. Additive, proportional and combined error models were tested to describe the residual unexplained variability.

The effect of co-administration of paclitaxel on pazopanib PK was assessed in the covariate analysis by adding a categorical covariate on CL/F (Clearance/Biodisponibility) or F_{rel}. This allowed for the estimation of a fractional change of the PK parameter when paclitaxel was co-administered (day 21 of pazopanib treatment) relative to the occasion before start of paclitaxel treatment (day 7 of pazopanib treatment). Additionally, a comparison between empirical Bayes estimates (EBEs) of pazopanib AUC over the dosing interval (0–24 hours) on day 7 (before paclitaxel administration, AUC_{day7}) and on day 21 (AUC_{day21}) was performed using non-parametric Wilcoxon paired test. Only patients treated continuously for 21 days were included in this comparison (*i.e.*, patients with dose reductions or treatment interruptions were excluded). In addition, the following continuous covariates were tested in the base popPK model: age, BW (Body Weight), ALAT (alanine amino transferase), ASAT (amino transferase) and bilirubin on CL/F, Vp/F (Peripheral Volume/Biodisponibility) and F_{rel}. The details of

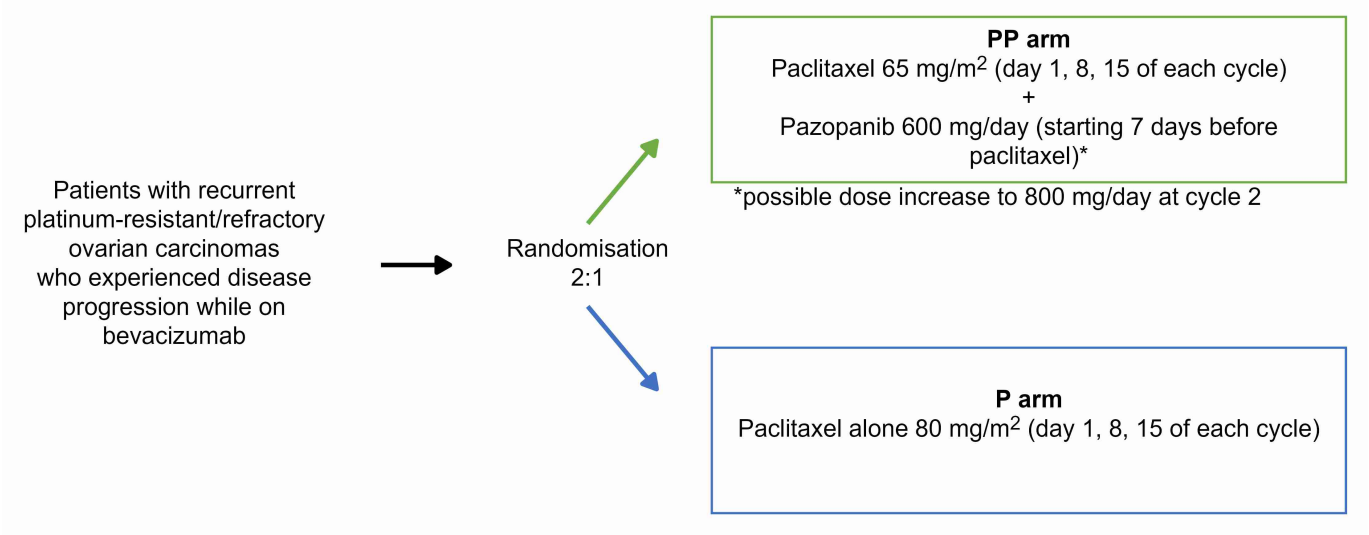

FIGURE 1. Design of the TAPAZ study.

the covariate analysis as well as model validation and evaluation criteria are described in **Supplementary material 2**.

2.4 Relationship between pazopanib exposure and dose-limiting toxicity

The association between pazopanib-related toxicity and pazopanib plasma exposure was evaluated in patients in PP arm. Pazopanib dose-limiting toxicity (DLT) was defined as any toxicity leading to pazopanib dose reduction, treatment interruption or discontinuation during cycle 1. The individual PK parameters estimated by the final model were used to obtain mean daily AUC from the first 21 days of treatment ($AUC_{mean,day1-day21}$) for patients who did not present DLT using the following formula Eqn. 1:

$$AUC_{mean,day1-day21} = \frac{\int_0^{day21} C \times dt}{21} \quad (1)$$

Mean daily AUC from the first day of treatment to the day of DLT ($AUC_{mean,day1-dayDLT}$) for patients who presented a DLT was calculated as in Eqn. 2:

$$AUC_{mean,day1-day\ DLT} = \frac{\int_0^{dayDLT} C \times dt}{day\ of\ DLT} \quad (2)$$

The comparison between $AUC_{mean,day1-day21}$ and $AUC_{mean,day1-dayDLT}$ was performed using a non-parametric Wilcoxon test. All statistical tests were two-sided. $p < 0.05$ was considered statistically significant unless otherwise stated.

3. Results

3.1 Patients and data

Between June 2015 and April 2019, 116 patients were enrolled: 79 in PP arm and 37 in P arm. Mean paclitaxel dose in PP arm was 60.9 mg/m^2 (95% CI [59.1–62.7]) and 77.7 mg/m^2 (95% CI [76.0–79.4]) in P arm. Mean pazopanib dose was 534 mg (95% CI [506–562]). The baseline characteristics of the studied population are presented in Table 1. Pazopanib PK sampling was performed in 62 patients from PP arm. After exclusion of 9 concentrations below lower limit of quantification (LLOQ) and concentration-time data from two patients, who had temporary treatment discontinuation during the time of PK sampling, 525 plasma concentrations for 56 patients were included in the analysis. The rich PK sampling was performed in 26 patients, whereas the remaining 30 patients had only sparse PK data. The concomitant intake of PPI (Proton Pump Inhibitors) during cycle 1 was recorded in 7 patients (12.5%).

3.2 Pharmacokinetic analysis

Pazopanib PK data were described by a two-compartment model with two absorption processes, a lag time and a time-dependent decrease in F_{rel}. The estimates of the final model are presented in **Supplementary Table 1**. Fast process accounted for the absorption of 25.7% (RSE (Relative Standard Error) = 22%) of the administered dose (fast absorption rate constant k_{aF} was fixed to the previously reported value of 0.4 h^{-1} [12]) and the remaining fraction was absorbed via a slow process with slow absorption rate constant k_{aS} estimated at 0.124 h^{-1} (RSE = 38%). The study design did not allow for estimation of both the effects of paclitaxel co-administration on pazopanib PK and time-dependent decrease in pazopanib F_{rel}. Thus, the parameters of the time-dependent decrease in F_{rel} were fixed to the values estimated by Yu *et al.* [12]. The model did not include inter-occasion variability.

Inclusion of paclitaxel co-administration as a categorical covariate on F_{rel} resulted in a significant decrease in OFV (Objective Function Value) (ΔOFV = −25 points compared to the base model). This covariate was even more significant on CL/F (ΔOFV = −72 points), but this model was associated with high RSE% and instable estimations of other parameters. The estimated effect of paclitaxel co-administration on F_{rel} was 0.724 (95% CI = 0.700–0.807), and the mean value obtained in non-parametric bootstrap analysis was 0.812 (95% CI =

European Journal of Gynaecological Oncology

TABLE 1. Baseline characteristics of the studied population. Data are presented as median (range) or number (%).

Characteristic	P arm (paclitaxel alone) (n = 37)	PP arm (pazopanib + paclitaxel) (n = 79)	*p*-value
Age (yr)	64 (46–82)	66 (42–85)	0.62
Body weight (kg)	65 (44–102)	63 (42–108)	0.66
Bilirubin (mg/L)	6.3 (2–12.7)	6.0 (2–17.6)	0.46
ASAT (UI/L)	21 (13–61)	21 (10–59)	0.30
ALAT (UI/L)	19 (7–70)	16 (5–98)	0.33
ECOG Performance Status			
0	20 (54.0)	26 (32.9)	0.05
1	16 (43.2)	52 (65.8)	
2	0 (0.0)	1 (1.3)	
Missing	1 (2.8)	0 (0.0)	
FIGO			
IC	1 (2.7)	0 (0.0)	0.92
IIA	0 (0.0)	1 (1.3)	
IIIA/B	2 (5.4)	2 (2.6)	
IIIC	22 (59.5)	53 (67.0)	
IV	12 (32.4)	22 (27.8)	
Missing	0 (0.0)	1 (1.3)	
Histology type			
Clear cells	0 (0.0)	2 (2.5)	0.63
Serous	32 (86.5)	71 (89.9)	
Undifferentiated	2 (5.4)	0 (0.0)	
Others	3 (8.1)	6 (7.6)	

ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics.

0.634–1.15). In addition, the median pazopanib AUC_{day7} and AUC_{day21} in patients without treatment discontinuations or dose reductions (n = 43) were 949 mg/L·h (range: 261–1943) and 843 mg/L·h (95% CI = 406–1563), respectively. The comparison between pazopanib AUC_{day7} and AUC_{day21} showed no statistical difference between the two occasions suggesting no impact of paclitaxel co-administration on pazopanib PK (Wilcoxon test, $p = 0.50$, Fig. 2). None of the remaining demographic or biological covariates was significantly associated with CL/F, Vp/F or F_{rel}. The final model met the validation criteria as shown by the goodness-of-fit plots (**Supplementary Fig. 1)** and the pcVPC based on 1000 simulations of the final model (Fig. 3). The mean and 95% confidence intervals (95% CI) of the PK parameters obtained by 500 bootstrap analyses were coherent with those estimated with the original dataset (**Supplementary Table 1**).

3.3 Relationship between pazopanib exposure and dose-limiting toxicity

Among 79 patients in PP arm, 18 (23%) presented pazopanib DLT during cycle 1. The median time to DLT onset was 7 days (range: 3–16 days). The relationship between pazopanib PK and DLT was evaluated in patients with available PK data (n = 56). The median pazopanib $AUC_{mean,day1-day21}$ in patients who did not experience DLT was 814 mg/L·h (range: 290–1649 mg/L·h, n = 43), whereas the median $AUC_{mean,day1-dayDLT}$ in patients who experienced DLT was 727 mg/L·h (range: 178–1828 mg/L·h, n = 13). DLT during cycle 1 was not significantly associated with pazopanib exposure (Wilcoxon test, $p = 0.26$, Fig. 4).

4. Discussion

This analysis provides several elements contributing to explain the lack of statistically significant difference in efficacy between patients treated with paclitaxel alone, and those treated with paclitaxel and pazopanib combination, in the TAPAZ trial.

In this study, the pazopanib concentration-time data were analysed using a popPK model already reported by Yu *et al.* [12]. The model successfully described our observed data, and the estimated parameters were consistent with the literature.

When pazopanib PK on day 21 (pazopanib co-administered with paclitaxel) were compared to those on day 7 (pazopanib alone), the only covariate significantly associated with pazopanib PK was the co-administration of paclitaxel, which resulted in a slight decrease in the relative bioavailability F_{rel} by 24.6% (95% CI = 19.3–30.0). However, pazopanib AUC_{day7} and AUC_{day21} were not significantly different (*p*

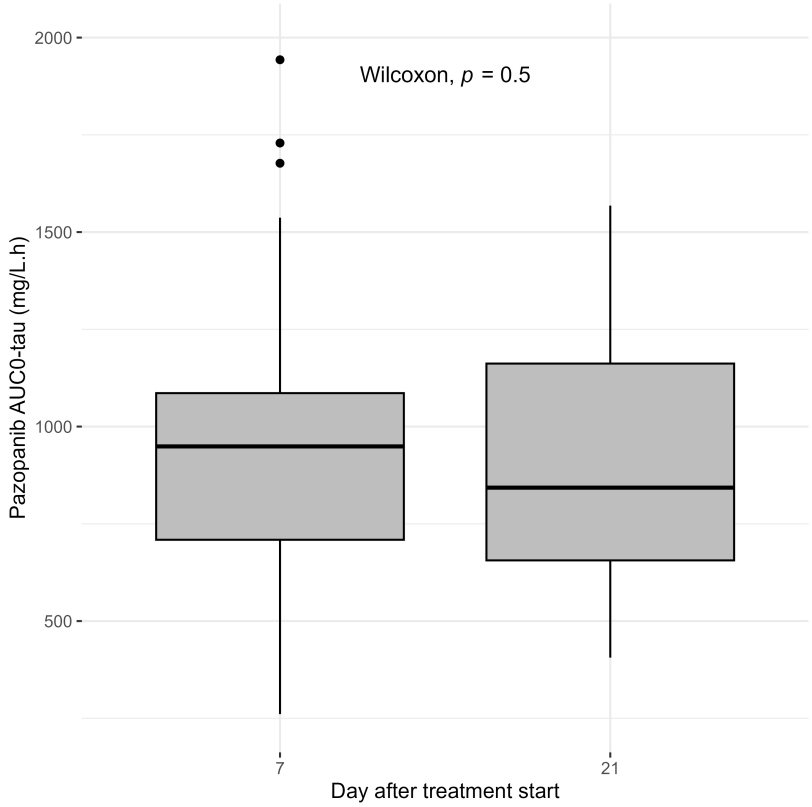

FIGURE 2. Comparison between pazopanib area-under the concentration-time curve (AUC) over the dosing interval at day 7 (before start of paclitaxel treatment) and day 21 (corresponding to day 14 of after paclitaxel treatment start).

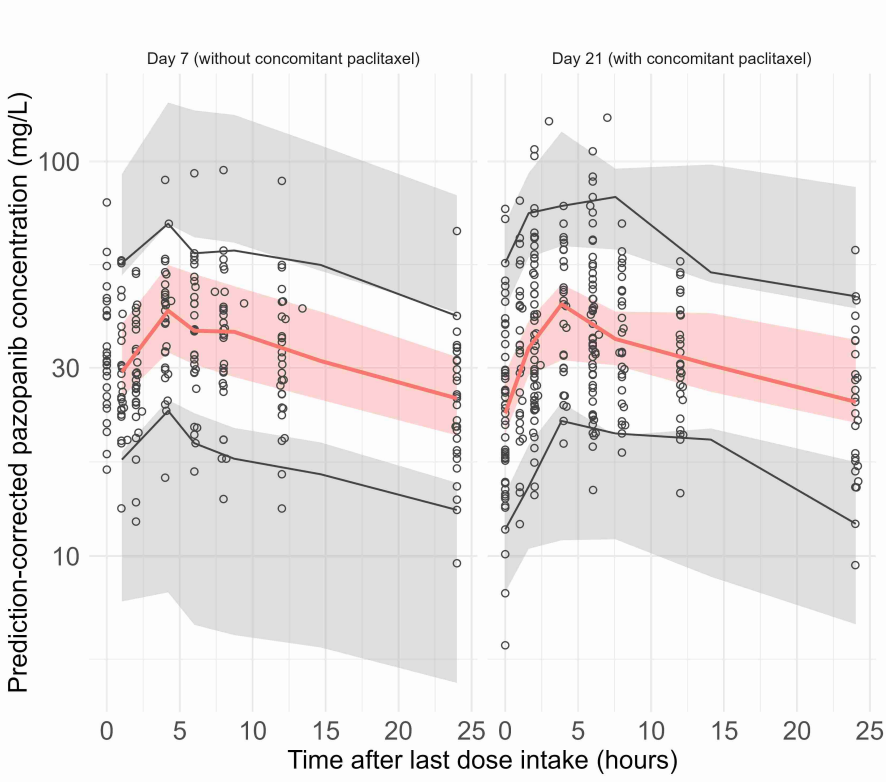

FIGURE 3. Prediction-corrected visual predictive check (pcVPC) for pazopanib final model based on 1000 simulations with the original dataset. The solid lines represent the 5th, 50th and 95th percentiles of the observed concentrations, the shaded areas represent the 95% confidence intervals around the 5th, 50th and 95th percentiles of the simulated concentrations and dots represent the observed concentrations.

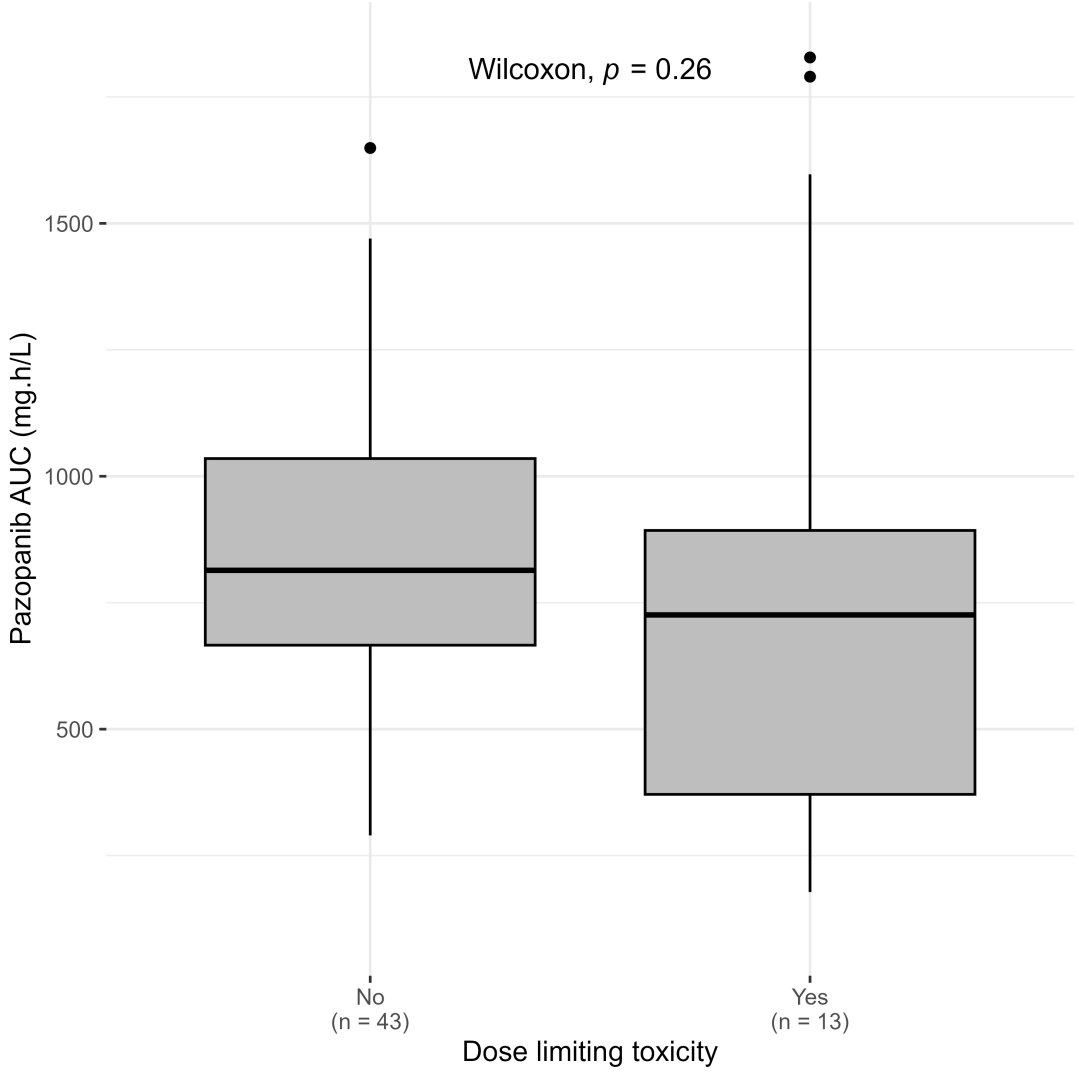

FIGURE 4. Relationship between pazopanib-related dose-limiting toxicity (DLT) and pazopanib area under the concentration-time curve (AUC) in patients included in PP arm for whom pazopanib PK data were available (n = 56). In patients who presented a DLT, $AUC_{mean,day1-dayDLT}$ was calculated as mean AUC from the first day of treatment until the day of DLT, in patients who did not present a DLT, the mean exposure from the first 21 days of treatment was calculated ($AUC_{mean,day1-day21}$).

= 0.50). Therefore, we conclude that paclitaxel did not have a clinically significant impact on pazopanib PK in our study. Our finding is consistent with a phase I study of pazopanib and paclitaxel combination in advanced solid tumor patients, which reported no effect of paclitaxel on pazopanib PK [13].

The concomitant intake of PPI did not have a significant impact on pazopanib PK in our study. In contrast, previous reports suggested that pazopanib plasma concentrations were decreased in patients concomitantly treated with PPI [14, 15]. Another study showed that the use of gastric acid-suppressive agents was associated with a decreased efficacy of pazopanib in sarcoma patients [16]. In our study, only 12.5% of patients were taking PPI during cycle 1, which was probably the reason of insufficient statistical power to estimate the effect of PPI in the covariate analysis.

Pazopanib DLT was observed in 23% of patients at cycle 1. Plasma pazopanib exposure from cycle 1 was not significantly correlated with occurrence of DLT during that cycle in our study. Verheijen *et al*. [17] reported that patients with pazopanib steady-state trough concentration ($C_{min,ss}$) above 51.3 mg/L had increased rate of grade $\geq$3 toxicity, and required a dose reduction to 600 or 400 mg daily. These findings were not confirmed in our study, since patients started treatment at lower dose (600 mg daily) and had concomitant administration of paclitaxel which also contributed to differences in the safety profile.

It was hypothesized that the increased toxicity of the experimental arm could be related to an increased exposure to paclitaxel and/or to pazopanib in the combination arm due to a PK drug-drug interaction. Our outcomes suggest that the exacerbated toxicity observed in the combination arm may not be due to alteration of pazopanib PK by paclitaxel, but rather additive toxicities compromising the dose-intensity of both drugs. In addition, an increase in paclitaxel plasma exposure by pazopanib due to inhibition of its metabolism through CYP3A4 and 2C8 could also contribute to increased toxicity in

the combination arm. Indeed, Tan *et al*. [8] and Kendra *et al*. [13] reported that co-administration of 800 mg pazopanib with paclitaxel resulted in a 26–38% higher geometric mean AUC of paclitaxel compared to administration of paclitaxel alone. Nevertheless, TAPAZ study did not assess the PK of paclitaxel which limits our conclusions. In addition, the low number of patients included in this analysis might have impacted the statistical power of the analyses. Finally, as the study was designed solely to investigate PK interactions, data on the long-term effects of the treatment or patient recovery from side effects were not collected. Consequently, these aspects of tolerability could not be assessed.

The lack of correlation between pazopanib plasma exposure and dose-limiting toxicities raised critical questions about the underlying mechanisms driving the exacerbated toxicity observed in the combination arm. Future studies could explore alternative explanations, such as pharmacodynamic interactions at the molecular or cellular level, off-target effects, or differences in tissue-specific drug accumulation. Additionally, investigations using preclinical models and biomarker-based approaches may provide valuable insights into the mechanistic basis of this toxicity.

This study focused on the short-term effects of the combination therapy involving pazopanib and paclitaxel. Although long-term effects over progression-free survival (PFS) and overall survival (OS), were assessed in Joly *et al.* [18] study. The analysis revealed that pazopanib plasma exposure at Cycle 1, corresponding to AUC cumulated day_1-day_{21}, did not show any benefit in terms of PFS or OS. This highlights that while the combination may affect short-term toxicity and pharmacokinetics, it does not translate into an improved long-term clinical benefit for patients in terms of disease progression or overall survival [18].

5. Conclusions

In conclusion, the present ancillary study of TAPAZ trial did not identify any subpopulations of patients with higher or lower probabilities of toxicity of the pazopanib and paclitaxel combination based on pazopanib PK profiles. Moreover, although a non-significant reduction in the relative bioavailability F_{rel} of pazopanib related to co-administration of paclitaxel was identified, it is unlikely to have significantly impacted the efficacy of the combination based on the results of our PK-PD (Pharmacokinetics/Pharmacodynamics) analyses.

Future development of tyrosine kinase inhibitors for patients with ovarian cancer will require a more comprehensive understanding of the benefit-toxicity balance and the underlying determinants of toxicity. This will necessitate approaches that extend beyond traditional PK/PD studies.

ABBREVIATIONS

PK, pharmacokinetics; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; PDGF, platelet-derived growth factor; RCC, renal cell carcinoma; STS, soft tissue sarcoma; AUC, area under the curve; CYP, cytochrome; AE, adverse events; IIV, inter-individual variability; EBEs, empirical Bayes estimates; DLT, dose-limiting toxicity; LLOQ, lower limit of quantification; RSE, relative standard error; OFV, objective function value; TAPAZ, Paclitaxel/Pazopanib for Platinum Resistant/Refractory Ovarian Cancer; CI, Confidence Interval; AURELIA, A Study of Avastin, Bevacizumab; VEGF, vascular endothelial growth factor; MITO11, Weekly Paclitaxel with or without Pazopanib in Platinum Resistant or Refractory Ovarian Cancer; CL/F, Clearance/Biodisponibility; BW, Body Weight; ALAT, alanine amino transferase; ASAT,amino transferase; Vp/F, Peripheral Volume/Biodisponibility; PPI, Proton Pump Inhibitors; RSE, Relative Standard Error; OFV, Objective Function Value; PK-PD, Pharmacokinetics/Pharmacodynamics.

AVAILABILITY OF DATA AND MATERIALS

Currently no mechanism is in place to allow sharing of individual anonymized participant data. Requests sent to ARCAGY-GINECO (bvotan@arcagy.org) will be considered on a case-by-case basis.

AUTHOR CONTRIBUTIONS

BY, MT, AP—designed the research study, performed the research. AP—analyzed the data. AC, BY, FJL, MF, DB, JL, AF, MC, HB, LBL, FP, AL, DS, JMB, CA, MCKF, DP, MPG, JG, LP, MCG, DB, PEB—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was approved by the ethic committee Comité de Protection des Personnes (2015-03, on 27 January 2015) and the French health authorities Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) (ANX5 140509, on 15 December 2014). The study was conducted in accordance with the Declaration of Helsinki ethical guidelines. All patients recruited in the study signed an informed written consent.

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CONFLICT OF INTEREST

BY Consulting fees: MSD, Astra-Zeneca, GSK-TESARO, BAYER, Roche-Genentech, ECS Progastrine, Novartis,

LEK, Amgen, Clovis Oncology, Merck Serono, BMS, SEAGEN, Myriad. FJL. Consulting fees: AstraZeneca, GSK, Janssen, Ipsen; Honoraria for lectures and scientific boards: AstraZeneca, Clovis, Astellas, BMS, MSD, Bayer, GSK, Ipsen, Janssen; Speaker honoraria: Amgen; Meeting/travel support: Ipsen, GSK; Participation on a data safety monitoring or advisory board: GSK; GINECO guidelines committee. MF Honoraria: AstraZeneca, GSK. AA Consultancy: Amgen, Ipsen, AstraZeneca; Honoraria: AstraZeneca, BMS; Meeting attendance/travel support: BMS, AstraZeneca. AF Honoraria: Clovis Oncology, AstraZeneca, GSK; Meeting attendance/travel: GSK, AstraZeneca, MSD; Leadership: President of SFOG. HV Grants/contracts: Eisai, Novartis, AstraZeneca, Daiichi, Pfizer; Meeting/travel support: Eisai, GSK, MSD, Novartis. CA Grant/contract: GSK; Honoraria: GSK (personal), Clovis Oncology, AstraZeneca (both to institution); Meeting/travel support: Merck (personal fees). PEB. Meeting/travel support: MSD. All other authors declare no conflicts of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1922909910151905280/attachment/Supplementary%20material.docx.

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