Investigational New Drugs (2019) 37:323–330
https://doi.org/10.1007/s10637-018-0692-8

PHASE II STUDIES

Pazopanib with low fat meal (PALM) in advanced renal cell carcinoma

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Received: 7 August 2018 / Accepted: 30 October 2018 / Published online: 5 November 2018

Summary

Background Pazopanib is approved for metastatic renal cell carcinoma (RCC). We assessed the safety and efficacy of pazopanib with a low fat meal (LFM): <400 cal and < 20% fat or 10 g per meal. *Methods* A single arm study of pazopanib with a LFM in 16 adult patients with metastatic RCC with a clear cell component, RECIST 1.1 measurable disease, ECOG PS ≤ 2, and ≤ 3 prior therapies. Pazopanib at 400 mg daily given with LFM for 12 weeks. Incremental dose increases up to 800 mg, or irreversible decreases to 200 mg, allowed every 2 weeks. Primary study endpoint was safety; adverse events (AE) measured per CTCAE version 4.0. Secondary endpoints of RECIST 1.1 response with assessment as 12 weeks; pharmacokinetic (PK) analysis at nine time points, and CYP3A4 polymorphism evaluation. *Results* Pazopanib with a LFM was well tolerated; 13 of 16 subjects completed all 12 weeks. Three patients withdrew due to adverse events (AEs), with five occurrences of grade 3 AEs. *Conclusions* Pazopanib with a LFM has acceptable safety and comparable efficacy to fasting administration. Total median pazopanib dose per subject for the study duration was 63.5% of maximum possible conventional dose. A larger study is warranted. **Clinical Trial Registration Number:** NCT02729194.

Keywords Renal cell carcinoma · Advanced disease · Tyrosine kinase inhibitor therapy · Pazopanib · Fat meal

Introduction

Pazopanib, an oral multi-kinase inhibitor, is approved as first-line therapy for metastatic clear cell renal cell carcinoma (RCC) at 800 mg daily administered in the fasting state [1, 2]. It is known that pazopanib given with either a high- or low-fat meal results in increased AUC and C_{max} by about 2-fold [3]. Abiraterone acetate (AA) is also standardly administered in the fasting state in patients with prostate cancer, but administration with food has been shown to result in reversal of PSA progression [4]. Moreover, low dose AA given with food recently demonstrated non-inferiority when compared with standard dosing [5], with significant attendant cost savings.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10637-018-0692-8) contains supplementary material, which is available to authorized users.

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The retail cost of pazopanib 800 mg daily for 30 days is approximately $12,567.51, and for 12 weeks, would be about $37,702.53. Pazopanib administration at 400 mg daily with a low-fat meal (LFM) could result in notable cost savings of 50%. In the present study we therefore sought to evaluate whether daily pazopanib administration with a standard LFM has an acceptable safety and toxicity profile in patients with metastatic RCC. We hypothesized that daily pazopanib administration at a lower starting dose of 400 mg with a LFM could result in lower drug costs and eliminate the practical considerations of taking the drug in the fasting state. In addition to safety and toxicity assessment, we also sought to generate preliminary data regarding treatment efficacy with this drug administration strategy.

Methods

Patients

Patients included in the study were adults at least 18 years old with unresectable locally advanced or metastatic RCC with a clear cell component, measurable disease per RECIST 1.1 criteria, and ECOG PS of ≤2. Subjects were recruited via routine clinical practice at the University of Michigan Rogel Cancer Center. Informed consent was obtained prior to the initiation of therapy in all patients. No prior pazopanib therapy was allowed. Patients were required to demonstrate adequate baseline organ function with platelets >100,000 mm^3, absolute neutrophil count >1000 mm^3, and AST, ALT and total bilirubin <1.5 x ULN. Patients were allowed 3 prior VEGF or VEGFR targeted therapies, as well as any number of prior cytokine therapies (e.g. high-dose IL-2) or checkpoint inhibitor therapy (e.g. anti-PD1/PDL1, anti-CTLA4) or mTOR inhibitor therapy (e.g. everolimus, temsirolimus). Patients must have been willing to take pazopanib with a low-fat meal per protocol, and were required to discontinue any proton pump inhibitors or strong CYP34A4 inducers or inhibitors. Simvastatin discontinuation was also required given that it is a CYP3A4 substrate along with pazopanib, and the combination could increase the risk of hepatotoxicity [6]. This study was approved by the University of Michigan institutional review board.

Study endpoints

In this single-center study, the primary outcome measure was determining safety and feasibility of pazopanib administration with a LFM. To measure safety with this treatment approach, we assessed the frequency and type of toxicities of all grades according to CTCAE version 4.0 criteria. Frequency of dose reductions, duration of treatment, and median total drug dose taken during the duration of the study were also evaluated. An interim safety analysis was also conducted after 8 patients completed 2 cycles of therapy on protocol. Secondary outcome measures included overall response rate (ORR), with objective disease assessment performed at 12 weeks after the start of pazopanib therapy, and imaging response determination by RECIST 1.1 criteria. An additional secondary objective was to explore the pharmacokinetics (PK) of pazopanib administered with a LFM. A sample size of convenience of 16 patients was selected and was felt to be sufficient to assess the feasibility of pazopanib administration with a LFM.

Table 1 Patient demographics and baseline disease characteristics

Parameter	Number (%)
Mean age, years	60
Range	47–75.5
Sex	
Male	12 (75%)
Female	4 (25%)
Race	
White	15 (94%)
Not Reported	1 (6%)
Baseline ECOG performance status	
0	11 (69%)
1	5 (31%)
Histology	
Pure clear cell	11 (69%)
Mixed	5 (31%)
Baseline Disease Site	
Lung	10 (62.5%)
Adrenal	6 (37.5%)
Pancreas	1 (6.25%)
Liver	3 (18.75%)
Bone	1 (6.25%)
Nephrectomy Bed	2 (12.5%)
Retroperitoneal and perisplenic nodule	1 (6.25%)
Heng criteria	
Favorable	3 (18.75%)
Intermediate	13 (81.25%)
Number of prior therapies	
0	12 (75%)
1	3 (18.75%)
3	1 (6.25%)
Prior therapy classification	
Everolimus	1 (6.25%)
High-dose IL-2	3 (18.75%)
Sunitinib	1 (6.25%)
Nivolumab	1 (6.25%)

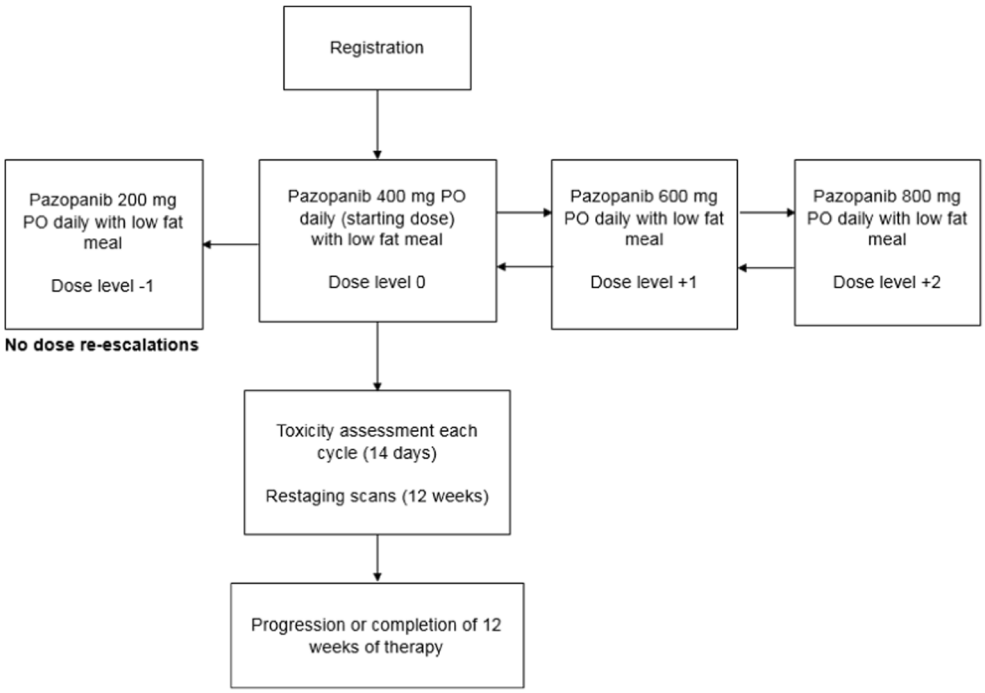

Fig. 1 16 patients were registered for the study, and 15 patients started therapy. The dose modification schema is shown

Study procedures

Study enrollment commenced after all information was confirmed by the Clinical Trials Office Data Manager. Protocol treatment was started within seven days of study registration. Patients were initiated on pazopanib 400 mg once daily with a LFM in 14 day cycles. Consecutive doses were taken 24 h apart (± 4 h). A LFM was designated as containing less than 400 cal and less than 20% fat or 10 g of fat per meal. The sample LFM suggestions provided to the patients are listed in Appendix 1. Patient demographics and baseline disease characteristics are listed in Table 1. As indicated in the CONSORT diagram **(**Fig. 1**)**, we employed a dynamic dosing design in which the pazopanib dose could be increased to 600 mg daily with LFM, and then up to 800 mg daily with LFM for subsequent cycles if the preceding dose level was tolerated as assessed by the treating investigator. The goal of this approach was to ameliorate potential greater toxicities with the fat meal administration. If the 400 mg dose was not tolerated, this could be decreased to 200 mg daily with a LFM; no dose re-escalations were permitted. Toxicities, including the use of anti-hypertensive agents as needed for hypertension, were managed per pazopanib package insert guidelines, which was readily available to the study investigators as part of the clinical trial protocol. Subjects maintained a pill diary and a blood pressure log that was reviewed by the research team at the end of each cycle. Left ventricular ejection fraction (LVEF) was assessed in all study subjects at baseline and again at 12 weeks.

On day 1 of each treatment cycle, subjects underwent physical examination with vital signs, laboratory evaluation with complete blood count with differential, serum chemistries including liver function testing, 12-lead ECG in triplicate, concomitant medication review, and toxicity review. Toxicity review was conducted at the end of each cycle according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3–4 pazopanib-related non-hematologic toxicities necessitated dose reduction by one dose level for the next cycle. Dose adjustments were made according to the organ system showing the greatest degree of toxicity. Pazopanib was held until resolution of toxicity. In the absence of delays due to adverse events, treatment was continued until disease progression, any intercurrent illness preventing further drug administration as deemed by the treating physician, an unacceptable adverse event, voluntary study withdrawal, or completion of 12 weeks of pazopanib with a low-fat meal. Patients were followed for 28 days after removal from treatment or until death, whichever occurred first.

Pharmacokinetic data

Pharmacokinetic data was collected on day 1 of cycle 1. Patients self-administered a dose of pazopanib by mouth with a low-fat meal in the clinic, and the time of drug intake was recorded. Two hours after dose administration, a 6 mL peripheral blood sample was then drawn into an EDTA tube, placed on ice, and centrifuged within 10 min of collection for 10 min at 2000 g, followed by transfer of the plasma layer to secondary non-breakable cryovials for storage at −80 °C. On day 1 of cycle 2, peripheral blood samples were collected in the above described fashion prior to dose administration and at 0.5, 1, 2,

Table 2 Treatment-related adverse events

Adverse event	Grade			
	1	2	3	Total
Blood and lymphatic system disorders				
Anemia	1	0	0	1
Lymphopenia	2	0	0	2
Neutropenia	2	0	0	2
Thrombocytopenia	5	0	0	5
White blood cell decreased	5	0	0	5
Total	15	0	0	15
Cardiovascular disorders				
Chest pain – cardiac	0	0	1	1
Sick sinus syndrome	1	0	0	1
Electrocardiogram QT corrected interval prolonged	1	0	0	1
Hypertension	5	4	1	10
Hypotension	0	1	0	1
Total	7	5	2	14
Head, ear, nose and throat disorders				
Blurred vision	1	0	0	1
Middle ear inflammation	1	0	0	1
Dysgeusia	2	1	0	3
Headache	1	0	0	1
Total	5	1	0	6
Endocrine disorders				
Endocrine disorders – Other	1	0	0	1
Hyperthyroidism	2	0	0	2
Hypothyroidism	1	0	0	1
Total	4	0	0	4
Gastrointestinal disorders				
Abdominal pain	1	0	1	2
Constipation	2	0	0	2
Diarrhea	10	0	0	10
Flatulence	1	0	0	1
Gastroesophageal reflux disease	1	0	0	1
Mucositis oral	2	2	0	4
Nausea	6	2	0	8
Oral pain	2	0	0	2
Vomiting	0	1	0	1
Alanine aminotransferase increased	9	1	1	11
Alkaline phosphatase increased	2	0	0	2
Aspartate aminotransferase increased	11	0	1	12
Total bilirubin increased	2	0	0	2
Total	49	6	3	58
Constitutional disorders and administration site conditions				
Fatigue	6	1	0	7
Pain	1	0	0	1
Myalgia	1	0	0	1
Insomnia	1	0	0	1
Wound complication	1	0	0	1
Total	10	1	0	11
Metabolism and nutrition disorders				
Weight loss	1	0	0	1
Anorexia	2	0	0	2
Hyperglycemia	6	2	0	8
Hyperkalemia	5	0	0	5
Hypoglycemia	2	0	0	2
Hyponatremia	1	0	0	1
Total	16	2	0	18
Renal and urinary disorders				
Creatinine increased	3	0	0	3
Chronic kidney disease	1	0	0	1
Total	4	0	0	4
Respiratory, thoracic and mediastinal disorders				
Cough	1	0	0	1
Dyspnea	1	0	0	1
Total	2	0	0	2
Skin and subcutaneous tissue disorders				
Alopecia	1	0	0	1
Hypertrichosis	1	0	0	1
Nail discoloration	1	0	0	1
Palmar-plantar erythrodysesthesia syndrome	1	1	0	2
Pruritus	1	0	0	1
Rash (acneiform)	1	0	0	1
Rash (maculopapular)	2	0	0	2
Skin hypopigmentation	1	0	0	1
Total	9	1	0	10

3 and 4 h after dose administration. On day 1 of cycle 3, peripheral blood samples were collected prior to, and 2 h after dose administration. Plasma pazopanib concentrations were subsequently determined by a published, validated pharmacokinetic assay developed at the Pharmacokinetics Core at the College of Pharmacy at the University of Michigan [7].

Results

Baseline patient characteristics are shown in Table 1. The median age of this patient population was 60 years, and 12 of 16 enrolled patients (75%) were male. Sixty-nine percent of patients had a clear cell RCC histology. All patients had either lung or adrenal metastases (62.5% and 37.5% respectively) in addition to other sites of disease. Notably, 75% of patients had not received any prior therapies prior to initiating pazopanib on this trial.

The primary outcome measure of safety, as assessed by the frequency of grade 3 or higher adverse events, is listed in

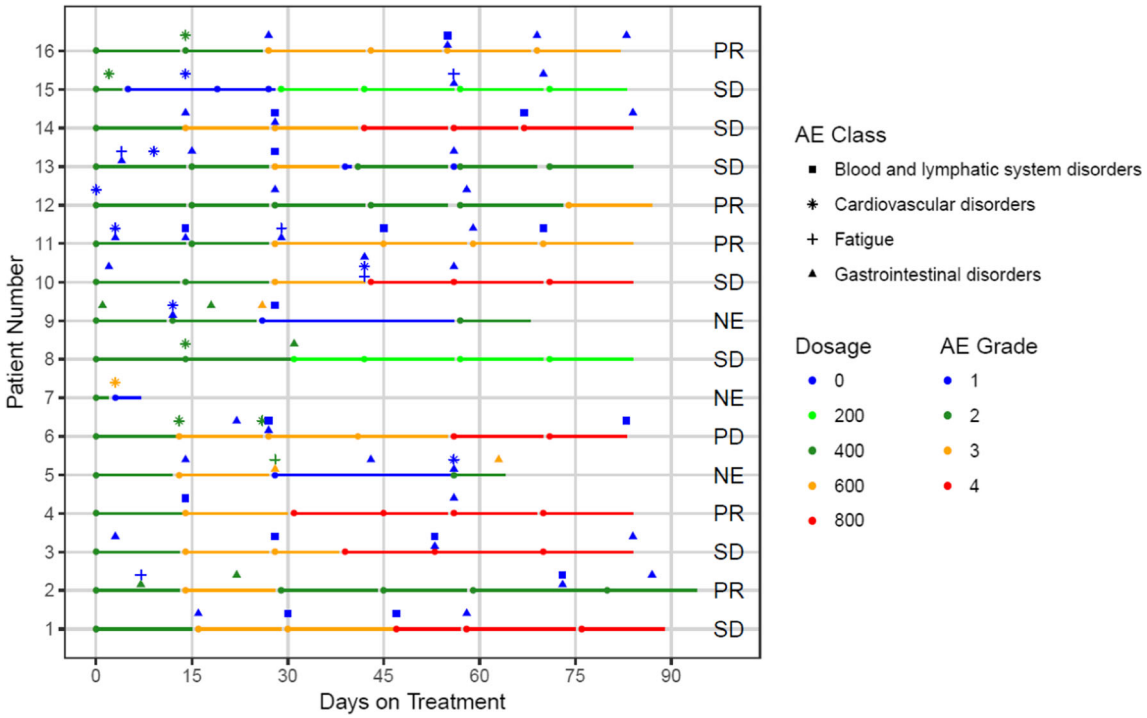

Fig. 2 Patient course on therapy with dose changes, select adverse events occurence and objective response at 12 weeks

Table 2. Three patients discontinued study treatment prematurely due to intolerable adverse events, namely grade 3 hepatotoxicity, ischemic type chest pain, and hypertension respectively. There were no grade 4 or 5 toxicities. Overall, hypertension was managed by the use of anti-hypertensive medications belonging to the angiotensin-converting-enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB) or peripherally acting calcium channel blocker (CCB) classes per standard practice for VEGFR inhibitors. Diarrhea, another common toxicity of pazopanib, was mild in this study, although common, with 10 events of grade 1 diarrhea reported. The remaining adverse events attributable to pazopanib in this study, the majority of which only had one reported occurrence, are listed in Table 2.

Figure 2 highlights the aggregate data for each patient with regard to pazopanib dose, duration at each dose level, timing of associated adverse events, and response to therapy after 12 weeks of treatment.

Generally, the total maximum amount of pazopanib administered at 800 mg daily in the fasting state would be 67,200 mg over 12 weeks, assuming no dose reductions or holds occurred. As shown in Table 3, the median amount of total drug given in our study population was 42,700 mg (range 1200–63,200 mg) for all patients receiving at least one dose of therapy. The median total drug amount administered was 45,000 mg (range 13,000–63,200 mg), or 67% of the theoretical maximum among the 13 patients who completed 12 weeks of therapy on study. Among the 13 patients who completed the study and were evaluable for objective response assessment by RECIST 1.1, partial response (PR) was noted in 5 of 13 patients (31.25%, 95% CI [11–59%]) and stable disease (SD) in 7 of 13 patients (43.75%, 95% CI [20–70%]).

Table 3 Drug administration and treatment response measures

Parameter	Value
Total amount of drug administered*	
Median, mg	42,700
Range	1200–63,200
Total dose in 13 subjects who completed 12 weeks of therapy	
Median, mg	45,000
Range	13,000 – 63,200
Maximum pazopanib dose received (mg)	
400	3 (18.75%)
600	6 (37.5%)
800	7 (43.75%)
Off Treatment Reason	
Adverse Event	2
Consent Withdrawn	1
Treatment Complete	13
RECIST Response at 12-week assessment	
Partial Response (PR)	5 (31.25%) 95% CI [11–59%]
Stable Disease (SD)	7 (43.75%) 95% CI [20–70%]
Progressive Disease (PD)	1 (6.25%) 95% CI [0.01–30%]
Discontinued therapy early	3 (18.75%)

*Total mg given for each patient compared to maximum in typical setting (800 mg/day for 12 weeks or 84 days) = 67,200 mg

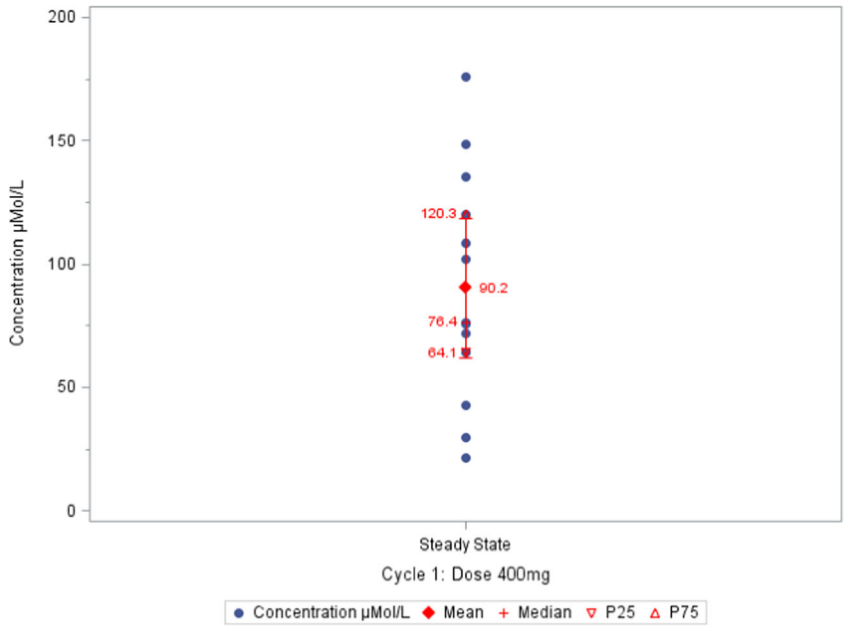

Fig. 3 Steady state pazopanib concentration prior to the start of cycle 2, at which time all patients had received 400 mg with a LFM for one 14-day cycle

One patient had progressive disease (PD) ((6.25%) 95% CI [0.01–30%]).

Average baseline LVEF was 64%, with a range of 53–75%. Three of 13 patients (23%) had a decrease in LVEF of 15% or more from baseline, but no patients had an LVEF of less than 50% at 12 weeks. Urine protein/creatinine ratio (UP/C) was also assessed, with median baseline UP/C 0.07 and a range of 0.02–1.22; there was a 35% change in this parameter throughout the study duration.

For the pharmacokinetic (PK) analysis, we evaluated the steady state pazopanib concentration at the start of cycle 2 at the hour 0 PK time point, which was obtained immediately prior to the observed drug dose administration, at which time all patients had received 1 cycle (two weeks) of therapy at the 400 mg dose level. As shown in Fig. 3, the majority of patients attained a steady state drug level of ≥40 µMo/L, which has been associated with clinical response [8, 9]. Figures 4 and 5 show the patients who remained on a consistent dose of drug, either 400 mg or

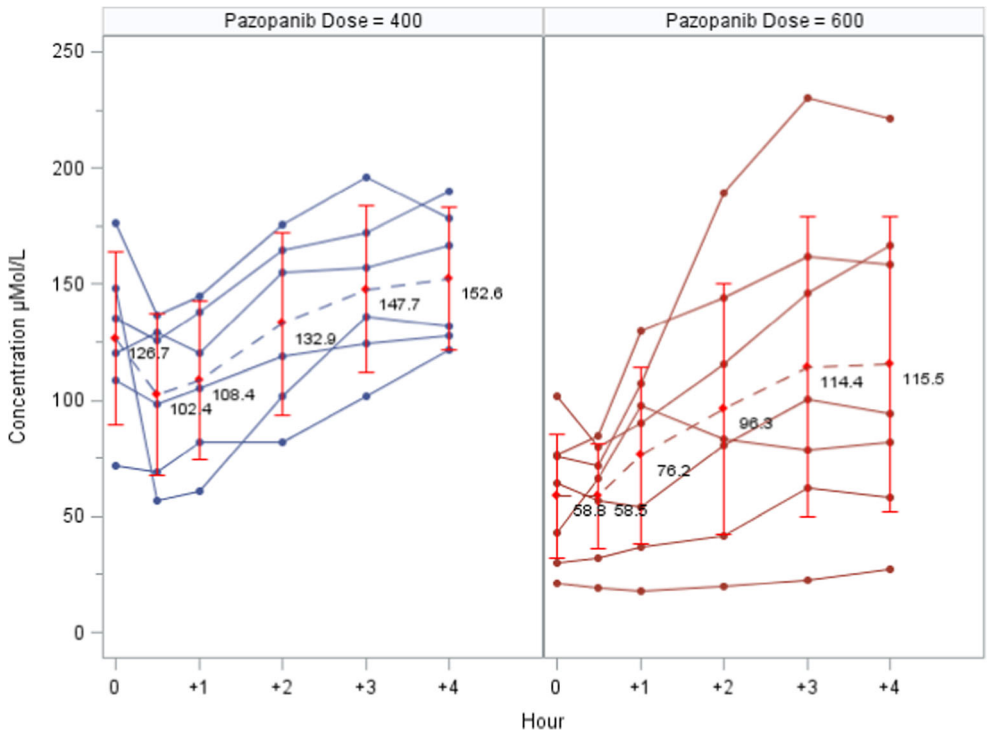

Fig. 4 Drug concentrations in patients who continued at a steady dose level of 400 mg daily or 600 mg daily with LFM throughout cycle 2

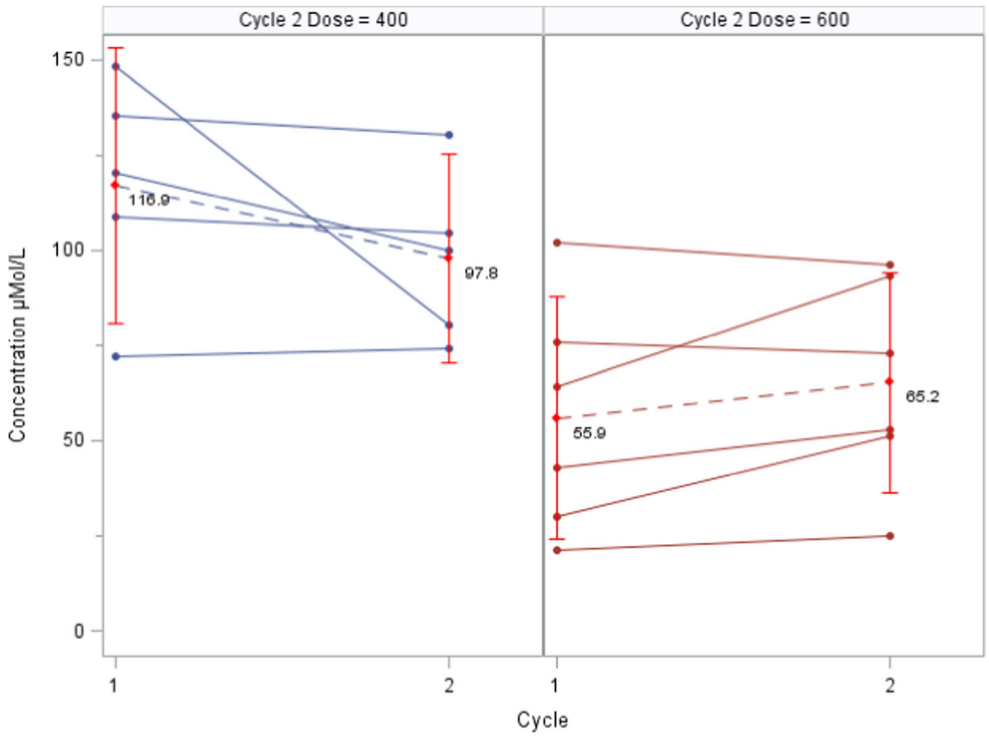

Fig. 5 Changes in mean drug concentration between cycle 1 and 2 for patients who continued on 400 mg and 600 mg with a LFM, respectively

600 mg, throughout cycle 2. In this graphical representation, only patients who remained on the same dose throughout the cycle were included due to the additional variability introduced by dose changes over the course of a treatment cycle.

Discussion

In this first study of continuous pazopanib administration with a low-fat meal, we demonstrated that pazopanib with a LFM at a starting dose of 400 mg once daily was well tolerated, with an acceptable toxicity profile in 13 of 16 patients enrolled. While our patient sample size was small, we did not identify a marked increase in the frequency or severity of adverse events related to pazopanib administered with a LFM, indicating the safety of this approach.

The therapeutic efficacy in our study seems to be comparable with standard pazopanib administration. At time of disease assessment in the 13 patients who completed 12 weeks on the study, 7 patients were found to have stable disease, and 5 patients demonstrated partial response; only one patient had disease progression while on study.

Figure 3 demonstrates that almost all patients in this cohort achieved a therapeutic drug concentration of ≥40 μMo/L, but with a more than 3-fold difference in intra-patient variability at the same dose level, highlighting the known significant pharmacokinetic variability of this therapy. These results correlated with our PK analysis, with the majority of patients demonstrating steady state plasma pazopanib levels at the start of cycle 2 that are known to correlate with therapeutic drug levels. Nonetheless, this conclusion is limited by the fact that there was intra-patient variability in drug level throughout the course of therapy and during treatment cycles given that drug dose was titrated based on tolerability. This limited our ability to collect steady state PK data during each treatment cycle, and we could therefore not confirm that patients continued to attain therapeutic levels at the end of the treatment period. We acknowledge that attempting simultaneous drug dose escalation in addition to LFM administration added an unnecessary level of complexity to our study. However, Fig. 4 demonstrates that all six patients who continued at a dose of 400 mg daily with a LFM maintained a plasma pazopanib concentration ≥ 40 μMo/L, suggesting ongoing drug concentration in a therapeutic range. Interestingly, however, the six patients who were maintained on 600 mg daily during cycle 2 demonstrated much greater variability in plasma drug concentration, again highlighting the complex pharmacokinetics of this drug [10].

While there have been several studies documenting successful dose titration and optimization of pazopanib using drug levels in the fasting state [11, 12], we would advocate that due to the profound intra-patient variability in plasma pazopanib concentration when administered with a LFM, titration to toxicity and patient tolerability would be a reasonable approach to overcome these differences. In the present study we have demonstrated the safety and feasibility of pazopanib administration with a low fat meal in patients with RCC. Given the increased ease of administration and the overall equivalent therapeutic efficacy that we have demonstrated

in this trial, a larger study of pazopanib administered with a LFM in advanced renal cell carcinoma is warranted.

Acknowledgements We gratefully acknowledge the participation of our patients and their families as well the efforts of the University of Michigan Rogel Cancer Center Dieticians Melissa Shannon-Hagan and Nancy Burke, who counseled patients regarding low-fat meals for this study.

Author contributions M.A.R. and A.S.A. analyzed and interpreted the data and wrote the manuscript. A.S.A, M.M.S. and B.G. R. designed the study and enrolled patients. S.D.N. conducted statistical analysis. R.D. and L.R. collected patient information. J. A. F. and B.W. conducted pharmacokinetic analysis. S.K. provided clinical pharmacy support. C.G. and J.R. conducted pharmacogenomic analysis. D.K. provided nutrition information and counseled patients.

Compliance with ethical standards

Ethical approval Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest The authors declare no potential conflicts of interest.

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