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Phase I study of the combination of temsirolimus and pazopanib in advanced solid tumors

Thomas J. Semrad, Courtney Eddings, Mrinal P. Dutia, Scott Christensen, and Primo N. Lara Jr.

Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis, Sacramento, California, USA

Abstract

Objectives—Inhibition of either vascular endothelial growth factor receptor (VEGFR) or mammalian target of rapamycin (mTOR) signaling improves outcomes in patients with several advanced solid tumors. We conducted a phase I trial of temsirolimus with pazopanib to investigate the feasibility of simultaneous “vertical inhibition” of VEGFR and mTOR pathways.

Methods—Patients with advanced solid tumors, no prior pazopanib or mTOR inhibitor, good performance status and acceptable end-organ function were eligible. In a typical 3 + 3 escalation design starting at temsirolimus 15 mg by intravenous (IV) infusion weekly and pazopanib 400 mg orally daily, we defined dose-limiting toxicity (DLT) as attributable grade 3 or higher non-hematologic adverse events in the first 28-day cycle and the maximum tolerable dose as the maximum dose level at which less than 2 patients experienced DLT.

Results—At the initial dose level, 2 patients had 4 DLTs (anorexia, fatigue, hyponatremia, hypophosphatemia). After reduction to temsirolimus 10 mg IV weekly and pazopanib 200 mg orally daily, 1 of 3 patients had DLT (fatigue) and the first patient in the subsequent expansion had dose-limiting hypophosphatemia. Attributable grade 3 or higher adverse events in more than one patient included leukopenia, neutropenia, fatigue, and hypophosphatemia. Tumor reduction not meeting RECIST criteria for partial response was the best response in 4 of 7 evaluable patients.

Conclusions—The combination of temsirolimus and pazopanib was not feasible at clinically meaningful doses in this population due to constitutional and electrolyte disturbances.

Keywords

Pazopanib; Temsirolimus; Vertical Pathway Inhibition; Renal Cell Carcinoma; Phase I

Address correspondence to: Thomas J. Semrad M.D., M.A.S., Assistant Professor of Medicine, Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis, 4501 X Street, Suite 3016, Sacramento, CA 95817, USA, Phone: +1-916-734-3771, Fax: +1-916-734-7946, thomas.semrad@ucdmc.ucdavis.edu.

Conflicts of Interest

There is no other conflict of interest disclosure.

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INTRODUCTION

Results of randomized phase III clinical trials led to the recent regulatory approval of several inhibitors of the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways in different tumor types. However, numerous overlapping signaling pathways are involved in tumor proliferation and growth, thereby limiting the efficacy of single-target inhibition. A strategy of multi-target “vertical inhibition” of the overlapping VEGF and mTOR pathways by combination therapy may overcome drug resistance and translate to enhanced efficacy over each single agent alone in renal cell cancer (RCC), pancreatic neuroendocrine tumors, and other malignancies [1, 2]. Indeed, combined VEGF and mTOR pathway inhibition has shown promise in preclinical solid tumor models [3–5].

Temsirolimus (CCI-779) is an intravenous inhibitor of mTOR that is approved by the U.S. Food and Drug Administration for the treatment of advanced RCC based on the results of a large phase III trial of 626 patients with previously untreated, poor-prognosis metastatic RCC [6]. Patients were randomized to temsirolimus alone, interferon alfa alone, or the combination of temsirolimus and interferon alfa. The patients who received temsirolimus alone had prolonged overall (hazard ratio [HR], 0.73; $P=0.008$) and progression-free survival ($P<0.001$) compared to those who received interferon alone. There was no additional benefit to the combination arm. Temsirolimus monotherapy was well tolerated, with fewer serious adverse events compared to interferon ($P=0.02$). These results demonstrate that temsirolimus is active and well-tolerated in advanced RCC and provide the basis for exploration of temsirolimus-based combinations.

Pazopanib is an orally bioavailable tyrosine kinase inhibitor that selectively inhibits VEGF receptor (VEGFR) -1, -2 and -3, as well as c-kit and platelet derived growth factor receptor (PDGF-R) [7]. Pazopanib achieved regulatory approval for advanced RCC based on the results of an international placebo-controlled phase III trial of 435 treatment naïve or cytokine-pretreated patients [8]. Progression-free survival was prolonged from 4.2 to 9.2 months in the pazopanib-treated group (HR, 0.46; $p<0.001$). The toxicity profile was acceptable; grade 3 or higher events included diarrhea, hypertension, asthenia, and transaminitis. Importantly, pazopanib’s toxicity profile appeared to compare favorably to other VEGFR tyrosine kinase inhibitors, making pazopanib an attractive agent to partner with other biologic agents as part of combination therapy.

We designed this phase I trial to explore the possibility of combined mTOR and VEGFR pathway inhibition using temsirolimus and pazopanib, to define the toxicities of the combination, and to establish a maximum tolerated dose (MTD) of each agent when used in combination for use in further studies.

METHODS

Patients

Eligible patients were aged 18 years and older with refractory solid tumors and a Zubrod performance status of 0–2. Any number of prior treatments was allowed, as long as

treatment was completed at least two weeks prior to registration and all toxicities had resolved to grade 1 or less. Further inclusion criteria included the ability to give informed consent, the ability to take oral medication, and acceptable end-organ function defined by an absolute neutrophil count $1,500/\text{mm}^3$, platelet count $100,000/\text{mm}^3$, total bilirubin within institutional normal limits, ALT and AST ≤ 2.5 times the upper limit of normal (ULN) or $5 \times \text{ULN}$ for patients with liver involvement, and creatinine ≤ 1.5 times ULN.

Exclusion criteria included any prior treatment with temsirolimus, everolimus, rapamycin or pazopanib and the need for ongoing treatment with warfarin or low molecular-weight heparin. Patients were excluded for significant cardiac comorbidities including New York Heart Association class II or greater congestive heart failure, myocardial infarction within the past 6 months, new onset of angina within the prior 3 months, corrected QT interval of > 480 milliseconds, and systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg despite optimal medical management. Further exclusion criteria included thrombotic or embolic events within the past 6 months, evidence of bleeding diathesis or coagulopathy, fasting cholesterol > 350 mg/dL and fasting triglycerides > 400 mg/dL. Patients with major surgery, open biopsy, or significant traumatic injury within the prior 4 weeks were also excluded, as were patients with non-healing wound, ulcer, or bone fracture or clinically serious active infection. The study protocol was reviewed and approved by the institutional review board of the University of California, Davis. All patients provided written informed consent before treatment.

Study Procedures

Prior to registration, patients underwent a history and physical examination that included assessment of height, weight, performance status, vital signs, and a pregnancy test for all females of child-bearing potential. Although measurable disease was not mandated, radiographic tumor assessment was required within 4 weeks of registration. Tumor measurements were subsequently performed every 8 weeks, and responses were evaluated using RECIST criteria, version 1.0 [9]. History and physical examination were performed by the treating physician weekly during the first 4-week cycle and then once every 4 weeks. An electrocardiogram was performed for assessment of the corrected QT interval each cycle. A blood pressure diary was reviewed at each study visit and toxicity was monitored through the trial using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Treatment Plan

We enrolled patients in a standard $3 + 3$ design. The initial doses were 15 mg of temsirolimus by intravenous (IV) infusion over 30-minutes weekly and 400 mg of pazopanib orally daily. Patients were pre-medicated with diphenhydramine 25–50 mg IV or equivalent approximately 30 minutes prior to temsirolimus infusion. No intra-patient dose escalation was allowed. Dose modification of both temsirolimus and pazopanib for grade 3 or higher toxicity was allowed according to a defined schedule.

Dose limiting toxicity (DLT) was defined as any treatment-related grade 3 or greater non-hematologic toxicity (excluding serum triglycerides up to 1,500 mg/dL which recovered to

grade 1 within 1 week), grade 4 or greater thrombocytopenia, grade 4 or greater febrile neutropenia requiring hospitalization, or treatment delay of > 2 weeks as a result of unresolved toxicity during the first cycle of therapy. To be evaluable for DLT assessment, a patient must have received at least 1 complete cycle of treatment and be observed for at least one week after the fourth dose of temsirolimus or have experienced DLT in the first cycle. All patients enrolled were fully followed for toxicity, but patients who were not evaluable for DLT were replaced.

A preplanned lower dose level (–2) of temsirolimus 10 mg IV weekly and pazopanib 200mg orally daily was available if 2 or more patients experienced DLT at the initial level. If DLT attributable to the study drugs was experienced in exactly 1 of 3 patients, 3 more patients (for a total of 6) were treated at that dose level. Escalation was planned in successive cohorts of 3 to 6 patients and would terminate as soon as two or more patients experienced any DLT attributable to the study drugs at a given dose level other than the initial dose level, or when 6 patients evaluable for DLT assessment were treated at full doses of both temsirolimus and pazopanib.

Treatment was continued in 4-week cycles until unacceptable toxicity, RECIST progression of disease, symptomatic deterioration, the patient withdrew consent, treatment was delayed > 2 weeks due to drug-related toxicity, or > 4 weeks due to any other reason.

Statistical Analysis

Data analysis included descriptive summaries of baseline and demographic information. Toxicities were summarized by frequency and the maximum grade over the course of all cycles of treatment. For patients with measurable disease and at least one follow up assessment, tumor response was analyzed using RECIST criteria.

RESULTS

Patient Characteristics

Dose escalation could not proceed beyond the first dose level due to DLTs. Thus, a total of only 8 patients were ultimately enrolled. Baseline characteristics are summarized in Table 1. The majority of patients had excellent performance status and had received moderate pretreatment (median 2 prior regimens). One patient was treatment-naïve, three patients had previously received prior treatment with a VEGFR tyrosine kinase inhibitor (sunitinib, sorafenib, or ABT-869), and 5 patients had received one to three prior cytotoxic chemotherapy regimens. The most common tumor site was renal cell cancer (38%), although patients with 5 separate tumor types were represented.

Treatment and Adverse Events

We enrolled 4 patients at the initial dose level. One patient was ineligible for DLT assessment due to an unscheduled break in therapy during cycle 1 that was unrelated to treatment. This patient was included in summaries of overall toxicity and treatment response. Amongst eligible patients at the initial dose level, two patients experienced DLTs in the first cycle of treatment including anorexia, fatigue, hyponatremia, and

hypophosphatemia. We subsequently enrolled 3 patients to dose level –2, and observed a DLT (fatigue) in 1 of these 3. After the first patient in the expansion of dose level –2 developed grade 3 hypophosphatemia, we aborted further enrollment onto the study for lack of feasibility at the lowest dose tested. Dose limiting toxicity at each dose level is summarized in Table 2.

A total of 22 complete cycles of the combination were administered. A majority of patients experienced at least one episode of grade 3 or higher toxicity (88%). Common non-hematologic toxicities included fatigue, anorexia, diarrhea, mucositis, nausea, vomiting, electrolyte and cholesterol abnormalities (Table 3). The most common grade 3 or higher toxicities included leucopenia, neutropenia, fatigue, and hypophosphatemia. Electrolyte disturbances were most often asymptomatic and transient although one patient developed mild generalized muscular weakness associated with grade 3 hypophosphatemia that resolved with phosphorus replacement and discontinuation of trial therapy.

Response

Seven patients had at least one follow up imaging study performed to assess for response. The best overall response was stable disease in 4 patients (57%). Tumor shrinkage not meeting criteria for RECIST partial response was observed in each of these 4 patients with stable disease.

DISCUSSION

We observed unacceptably high rates of grade 3 and higher toxicities when temsirolimus and pazopanib were combined at doses far less than the approved dose of each agent as monotherapy. The lowest dose level tested (temsirolimus 10 mg IV weekly and pazopanib 200 mg daily), was 40% and 25% of the clinical dose of each agent respectively. The primary reason for intolerance of this combination was grade 3 and higher constitutional symptoms and electrolyte disturbances.

Our results are consistent with several other trials attempting to simultaneously combine VEGFR tyrosine kinase inhibitors with mTOR inhibitors. The concept of vertical VEGFR and mTOR inhibition was piloted in a phase I trial of the VEGFR tyrosine kinase inhibitor sunitinib and temsirolimus [10]. In that trial, 2 of 3 patients in the first cohort treated with temsirolimus 15 mg IV weekly and sunitinib 25 mg orally once daily for 4 weeks followed by a 2-week rest period experienced DLTs, primarily of the skin and soft tissue. Since substantial toxicity was observed at low starting doses of both agents, the trial was closed for non-feasibility. Phase I studies of the combination of sorafenib and temsirolimus in a several different tumor types have been published or presented at major meetings [11–14]. Although considered feasible in some of these trials, significant mucocutaneous toxicity, constitutional symptoms, and electrolytes disturbances were seen at moderate doses of each agent. Despite its modest toxicity profile as monotherapy, we found that pazopanib is not a better partner for combination with temsirolimus than sunitinib or sorafenib.

Additionally, several trials of the oral mTOR inhibitor everolimus in combination with the VEGFR inhibitors sorafenib and sunitinib have recently been reported [15–18]. In one

study, the combination of full dose sorafenib was tolerable with half doses of everolimus, although DLT was observed in 25% of patients treated at these doses and full dose everolimus with half dose sorafenib was not tolerated [16]. Due to chronic toxicities seen at lower doses over time, no attempt was made to dose both drugs at the full monotherapy doses in this trial. In contrast, Amato et al. found that full doses of everolimus and sorafenib could be given without DLT, at least in their population of predominantly Zubrod 0 performance status patients with RCC [15]. Significant modification of both the dose and schedule of everolimus and sunitinib were required to find a tolerable dose of this combination, and the dose had to be reduced further if patients were to be treated chronically [17].

In this trial, we intended to collect pharmacokinetic data only in an expanded cohort at the anticipated maximum tolerated dose at the top of the dose escalation schema. Thus, no pharmacokinetic data was collected for the patients treated at the initial dose levels and we cannot determine whether an unfavorable pharmacokinetic interaction occurred between these two agents. However, no pharmacokinetic interactions between mTOR inhibitors and VEGFR tyrosine kinase inhibitors have been observed in the studies in which pharmacokinetic analyses were performed [11–13, 16, 17]. Interestingly, commonly observed grade 3 or higher toxicities include constitutional, mucocutaneous and electrolyte disturbances and are similar across these trials. This suggests that overlapping mTOR inhibitor and VEGFR tyrosine kinase inhibitor toxicities accounts for the inability to combine these classes of agents in most settings.

We included patients with refractory advanced solid tumors with any number of prior therapies, which may have affected tolerance to the study treatment. Indeed, three patients had received treatment with a prior VEGFR tyrosine kinase inhibitor, which had generally been well tolerated. Nonetheless, DLT was observed in the first cycle of treatment even in a patient with treatment-naïve advanced RCC at the lowest tested dose. Finally, this trial was designed to assess concurrent administration of pazopanib and temsirolimus. Future studies could consider alternative strategies such as a single agent run-in or altered schedules, especially given that the concurrent administration of VEGFR and mTOR inhibitors has not proven successful when administered concurrently.

In conclusion, the combination of temsirolimus and pazopanib is not feasible for patients with advanced solid tumors, primarily due to constitutional and electrolyte disturbances. Further research to understand the adverse interaction between VEGFR and mTOR inhibitors is needed. Future studies should also evaluate alternative strategies to mitigate the toxicity seen with these combinations.

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References

1. Sosman JA, Puzanov I, Atkins MB. Opportunities and obstacles to combination targeted therapy in renal cell cancer. *Clin Cancer Res*. 2007; 13:764s–769s. [PubMed: 17255307]
2. Miller RE, Larkin JM. Combination systemic therapy for advanced renal cell carcinoma. *Oncologist*. 2009; 14:1218–1224. [PubMed: 19939892]
3. Molhoek KR, Griesemann H, Shu J, Gershewald JE, Brautigan DL, Slingluff CL Jr. Human melanoma cytotoxicity by combined inhibition of mammalian target of rapamycin and vascular endothelial growth factor/vascular endothelial growth factor receptor-2. *Cancer Res*. 2008; 68:4392–4397. [PubMed: 18519701]
4. Ikezoe T, Yang Y, Nishioka C, Bandobashi K, Nakatani H, Taguchi T, et al. Effect of SU11248 on gastrointestinal stromal tumor-T1 cells: enhancement of growth inhibition via inhibition of 3-kinase/Akt/mammalian target of rapamycin signaling. *Cancer Sci*. 2006; 97:945–951. [PubMed: 16916320]
5. Ikezoe T, Nishioka C, Tasaka T, Yang Y, Komatsu N, Togitani K, et al. The antitumor effects of sunitinib (formerly SU11248) against a variety of human hematologic malignancies: enhancement of growth inhibition via inhibition of mammalian target of rapamycin signaling. *Mol Cancer Ther*. 2006; 5:2522–2530. [PubMed: 17041096]
6. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007; 356:2271–2281. [PubMed: 17538086]
7. Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res*. 2009; 15:4220–4227. [PubMed: 19509175]
8. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010; 28:1061–1068. [PubMed: 20100962]
9. Therasse P, Arbuuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000; 92:205–216. [PubMed: 10655437]
10. Patel PH, Senico PL, Curiel RE, Motzer RJ. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. *Clin Genitourin Cancer*. 2009; 7:24–27. [PubMed: 19213664]
11. Davies MA, Fox PS, Papadopoulos NE, Bedikian AY, Hwu WJ, Lazar AJ, et al. Phase I study of the combination of sorafenib and temsirolimus in patients with metastatic melanoma. *Clin Cancer Res*. 2012; 18:1120–1128. [PubMed: 22223528]
12. Kelley RK, Nimeiri HS, Munster PN, Mulcahy MF, Vergo MT, DeSona A, et al. Phase I trial of temsirolimus (TEM) plus sorafenib (SOR) in advanced hepatocellular carcinoma (HCC) with pharmacokinetic (PK) and biomarker correlates. *J Clin Oncol*. 2012; 30(suppl):abstr 4102.
13. Lee EQ, Kuhn J, Lamborn KR, Abrey L, DeAngelis LM, Lieberman F, et al. Phase I/II study of sorafenib in combination with temsirolimus for recurrent glioblastoma or gliosarcoma: North American Brain Tumor Consortium study 05-02. *Neuro Oncol*. 2012; 14:1511–1518. [PubMed: 23099651]
14. Patnaik A, Ricart A, Cooper J, Papadopoulos K, Beeram M, Mita C, et al. A phase I, pharmacokinetic and pharmacodynamic study of sorafenib (S), a multi-targeted kinase inhibitor in combination with temsirolimus (T), an mTOR inhibitor in patients with advanced solid malignancies. *J Clin Oncol*. 2007; 25(18S):abstr 3512.
15. Amato RJ, Flaherty AL, Stepankiw M. Phase I trial of everolimus plus sorafenib for patients with advanced renal cell cancer. *Clin Genitourin Cancer*. 2012; 10:26–31. [PubMed: 22169794]
16. Harzstark AL, Small EJ, Weinberg VK, Sun J, Ryan CJ, Lin AM, et al. A phase I study of everolimus and sorafenib for metastatic clear cell renal cell carcinoma. *Cancer*. 2011; 117:4194–4200. [PubMed: 21387258]

17. Molina AM, Feldman DR, Voss MH, Ginsberg MS, Baum MS, Brocks DR, et al. Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. *Cancer*. 2012; 118:1868–1876. [PubMed: 21898375]
18. Nogova L, Mattonet C, Scheffler M, Bos M, Gardizi M, Papachristou I, et al. SORAVE: Phase I study for the treatment of relapsed solid tumours with the combination of sorafenib and everolimus. *J Clin Oncol*. 2012; 30(suppl):abstr 3044.

Table 1

Patient Demographic and Clinical Characteristics (n = 8)

Characteristic	n (%)
Age, years	
Median (range)	56 (23–74)
Prior Lines of Therapy, n	
Median (range)	2 (0–4)
Zubrod Performance Status	
0	5 (63)
1	3 (38)
Gender	
Female	4 (50)
Male	4 (50)
Race/Ethnicity	
White	7 (87)
Hispanic	1 (13)
Tumor Site	
Renal cell cancer	3 (38)
Soft tissue sarcoma	2 (25)
Adrenal cortical carcinoma	1 (13)
Colorectal Cancer	1 (13)
Head and neck cancer	1 (13)

Table 2

Patient Dosing, Dose Limiting Toxicity and Best Response

Patient	Dose Cohort	Temsirolimus (mg/week)	Pazopanib (mg/day)	Tumor Site	Dose Limiting Toxicity	Best Response
1	1	15	400	Renal Cell	None	SD
2	1	15	400	Renal Cell	Anorexia	SD
3	1	15	400	Head and Neck	Not Evaluable	PD
4	1	15	400	Sarcoma	Fatigue, Hyponatremia, Hypophosphatemia	PD
5	-2	10	200	Colorectal	Fatigue	Not Evaluable
6	-2	10	200	Sarcoma	None	SD
7	-2	10	200	Adrenal	None	SD
8	-2	10	200	Renal Cell	Hypophosphatemia	PD

SD, Stable Disease; PD, Progressive Disease

Table 3Treatment-Related Adverse Events¹

Adverse Event	Any Grade		Grade 3–4	
	N	%	N	%
Any	8	100	7	88
Blood/Bone Marrow				
Hemoglobin	4	50	0	0
Leukopenia	4	50	2	25
Lymphopenia	3	38	0	0
Neutropenia	2	25	2	25
Cardiac				
Hypertension	2	25	0	0
Constitutional				
Fatigue	5	63	2	25
Dermatologic/Skin				
Rash	2	25	0	0
Gastrointestinal				
Anorexia	3	38	1	13
Diarrhea	3	38	0	0
Mucositis	3	38	1	13
Nausea	5	63	0	0
Vomiting	4	50	0	0
Metabolic/Laboratory				
Hypoalbuminemia	3	38	0	0
Alkaline phosphatase	5	63	1	13
ALT	3	38	0	0
AST	3	38	0	0
Hypercholesterolemia	4	50	0	0
Hyperglycemia	1	13	1	13
Hypertriglyceridemia	4	50	0	0
Hypokalemia	1	13	1	13
Hyponatremia	3	38	1	13
Hypophosphatemia	5	63	2	25
Proteinuria	1	13	1	13
Pain				
Abdomen	2	25	0	0
Musculoskeletal	2	25	1	13
Other	2	25	0	0

¹Toxicity of any grade occurring in > 1 patient, and all grade 3 or higher toxicities are included.