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A randomized phase II study of pazopanib in hormone sensitive prostate cancer: a University of Chicago Phase II Consortium/ Department of Defense Prostate Cancer Clinical Trials Consortium study

James E. Ward, MD[1], **Theodore Karrison, PhD**[1], **Gurkamal Chatta, MD**[2], **Maha Hussain, MD**[3], **Daniel Shevrin, MD**[4], **Russell Z. Szmulewitz, MD**[1], **Peter H. O'Donnell, MD**[1], **Walter M. Stadler, MD**[1], and **Edwin M. Posadas, MD**[1,5]

[1]The University of Chicago, Chicago, IL

[2]The University of Pittsburgh, Pittsburgh, PA

[3]The University of Michigan, Ann Arbor, MI

[4]Northshore University Health System, Evanston, IL

[5]Cedars-Sinai Medical Center, Los Angeles, CA

Abstract

Background—Intermittent androgen suppression [1] is an increasingly popular treatment option for hormone sensitive prostate cancer. Based on previous data with anti-angiogenic strategies, we hypothesized that pan-inhibition of the vascular endothelial growth factor receptor (VEGFR) using pazopanib during the IAS off period would result in prolonged time to PSA failure.

Methods—Men with biochemically recurrent prostate cancer whose PSA was < 0.5 ng/mL after 6 months of androgen deprivation therapy (ADT) were randomized to pazopanib 800 mg daily or observation. The planned primary outcome was time to PSA progression >4.0 ng/mL.

Results—Thirty-seven patients were randomized. Of 18 randomized to pazopanib, at the time of study closure, 4 had progressive disease (PD), 1 remained on treatment, and 13 (72%) electively disenrolled, the most common reason being patient request due to grade 1/2 toxicity (8 patients). Two additional patients were removed from treatment due to adverse events. Of 19 patients randomized to observation, at the time of study closure, 4 had PD, 7 remained under protocol defined observation, and 8 (42%) had disenrolled, most commonly due to non-compliance with protocol visits (3 patients). Due to high dropout rates in both arms, the study was halted.

Correspondence: Edwin M. Posadas, MD, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, Office: 310-423-7600, Fax: 310-659-3928, Edwin.Posadas@csmc.edu.

CONFLICT OF INTEREST:

Dr. Posadas has received compensation from GlaxoSmithKline as a member of their speaker's bureau. Drs. Ward, Karrison, Chatta, Hussain, Shevrin, Szmulewitz, O'Donnell and Stadler have nothing to disclose.

Conclusions—IAS is a treatment approach that may facilitate investigation of novel agents in the hormone sensitive state. This trial attempted to investigate the role of antiangiogenic therapy in this setting, but encountered several barriers, including toxicities and patient non-compliance, which can make implementation of such a study difficult. Future investigative efforts in this arena should carefully consider drug toxicity and employ a design that maximizes patient convenience in order to reduce the drop out rate.

Keywords

Prostate cancer; Intermittent Androgen Suppression; Tyrosine Kinase Inhibitors

INTRODUCTION

The importance of androgen deprivation for treatment of prostate cancer has been known since the 1940's [2]. Over the past 70 years, many novel and highly effective treatments have been introduced, however continuous androgen suppression (CAS) currently remains the standard of care for men with hormone sensitive metastatic disease. Intermittent androgen suppression [1] is a concept that advocates alternating periods of treatment with androgen suppression and periods without androgen suppression. The body of literature which supports its use is growing [34567891011121314]. Preliminary results of an ongoing multi-center, randomized controlled phase III trial comparing IAS and CAS in a population of patients with biochemical recurrence following local therapy (NCIC PR7) were recently presented; they demonstrated that IAS was non-inferior to CAS with a mean overall survival (OS) of 8.8 years and 9.1 years respectively (HR=1.02, 95% CI=0.86–1.21; p-value for non-inferiority [HR for IAS vs. CAS > 1.25]=0.009). IAS patients had fewer hot flashes. Quality of life data are not yet evaluable [15].

Several investigators have proposed ways to increase the "off" period of IAS, with the hypothesis that this could improve treatment efficacy, and possibly even decrease long-term ADT toxicities. One class of medications under investigation for this purpose are angiogenesis inhibitors [161718192021]. Elevated plasma and urine VEGF levels have been correlated with shortened survival times in men with hormone refractory disease[22,23] leading to the hypothesis that anti-angiogenesis agents may have a role in prostate cancer treatment. In vivo models using Shionogi mice have shown that castration leads to a regression in the size of androgen-dependent tumors that is coupled with a decrease in VEGF expression [24], however, when tested, anti-angiogenesis agents have not yet demonstrated survival benefits in men with prostate cancer.

Pazopanib is an orally available multi-targeted tyrosine kinase inhibitor with broad activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα, PDGFRβ, and c-kit, among others [25] and is a standard available therapy for advanced renal cell carcinoma [26]. In this randomized phase II study, we tested the hypothesis that pazopanib could prolong the "off" period of IAS.

METHODS

Study Objectives

The primary objective was to determine if pazopanib was able to increase time to PSA progression (TTPP) following 6 months of androgen blockade in patients with stage D0 prostate cancer. Secondary objectives were to describe progression free survival and adverse events related to pazopanib in this population as well as to monitor and compare changes in testosterone in the two treatment arms.

Patients and Eligibility Criteria

Eligible patients had pathologically confirmed prostate cancer, had received definitive local therapy, and had evidence of biochemical recurrence, defined as two consecutive rises in PSA above the nadir following definitive local therapy. Patients with radiologically detectable disease were excluded, which was confirmed with a bone and CT scan if the baseline PSA level was greater than 10 ng/mL. Prior ADT was disallowed. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, normal renal and hepatic function as defined by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE 3.0), as well as a urine protein to creatinine ratio of <1.

Patients were excluded if they had uncontrolled hypertension (> 140/90 mmHg), NYHA class III or IV heart failure, a history of cerebrovascular accident, myocardial infarction, unstable angina, or coronary artery stenting within 6 months of enrollment, or a history of venous thrombosis within 12 weeks of enrollment. Patients who required treatment with strong CYP450 3A4 inhibitors or inducers were not allowed to participate. Other exclusion criteria included inability to take oral medications, and patients with HIV on anti-retroviral therapy.

Study Design

This study employed a multi-center, 2-arm, randomized phase II design. Each center's Institutional Review Board approved the investigational protocol and all subjects provided written informed consent in accordance with the Helsinki Declaration of 1975. The study schema is depicted in Figure 1. Upon verification of eligibility, subjects were enrolled and completed a period of 6 months of androgen blockade with a GnRH agonist without concomitant anti-androgen therapy. At this time, if the subject's PSA was <0.5 ng/mL and total serum testosterone level was <50 ng/mL, he was randomized to treatment with pazopanib 800 mg daily or observation.

The primary endpoint was TTPP which was measured as the time from randomization until the total serum PSA was > 4.0 ng/mL, with non-cancer and non-treatment related deaths censored. The secondary endpoint was PFS, defined as the time from randomization until the time of PSA progression or death from any cause. Subjects were seen monthly with physical examination, history, PSA and testosterone evaluation. Subjects remained on either pazopanib or active surveillance until they met the TTPP criteria withdrew consent, or were removed by the investigator for adverse events or other reasons.

Subjects were monitored for toxicity on a monthly basis and adverse events were classified according to the CTCAE v3.0. All patients measured their blood pressure on a twice-daily basis while on trial and maintained a blood pressure diary. Specific guidelines were provided for management of treatment-associated hypertension, transaminitis, and proteinuria. All subjects were followed for 12 months after disenrollment from the study for toxicity evaluation.

Statistical Analysis

The study was designed to achieve 85% power to detect a difference of 5 vs. 9 months in the median TTPP between the two study treatment groups at the one-sided 0.10 significance level, allowing for a 15% rate of non-cancer deaths. This required a sample size of 94 patients, 47 in each arm. The planned statistical analysis included calculating Kaplan-Meier estimates of the primary endpoint, TTPP, as well as the secondary endpoint of PFS, and comparison of TTPP and PFS between the two treatment arms using the log-rank test.

RESULTS

Patient Data and Treatment Outcomes

Baseline patient characteristics are shown in Table 1. There were no statistically significant differences between the treatment arms in any of the relevant categories at the α=0.05 level. Due to high patient dropout, early closure was recommended by the Data Safety and Monitoring Board as it was no longer possible to validly test the primary hypothesis. At the time that the study was stopped, 37 patients had been randomized, 18 to pazopanib and 19 to observation. We report here the findings from these 37 evaluable patients.

A flowchart outlining the reasons for subject disenrollment is provided in Figure 2A. Seventeen of the 18 patients randomized to the pazopanib arm were off treatment at the time of study closure. Four of the 18 patients (22%) reached the primary endpoint of PSA progression. Thirteen of the 18 patients went off study for other reasons. Two of the 18 (11%) patients were removed for an adverse event, one patient sustained a pulmonary embolism (Grade 4) and one showed recurrent grade 2 hepatotoxicity despite dose adjustment. An additional patient was removed by a study investigator due to non-compliance (undiagnosed pre-existing dementia, unrelated to treatment). Ten patients withdrew consent, including 8 patients (44%) due to drug toxicity (Grade 1–2). Of these 8 patients, 4 withdrew in less than 2 months, another 3 withdrew between 2–6 months, and 1 patient withdrew after 18 months. One patient requested further treatment with ADT and one patient did not provide a reason for withdrawal of consent.

Of the 19 patients who were randomized to the observation arm, 12 (63%) were off treatment at the time of study closure. Four patients out of 19 (21%) met the primary endpoint of PSA progression. Three patients (16%) were removed by the study investigators, including one for non-compliance. Five patients (26%) withdrew consent, including two who requested further treatment with ADT, two who refused study-related visits, and one who transferred care. Including the one patient removed by study investigators due to non-compliance, 5 patients (26%) in this treatment arm left the study

due to issues surrounding the study protocol. All 5 of these patients left or were removed from the study within 5 months of randomization. Patient outcomes are summarized in Figure 2B.

Toxicity Data

All AEs were classified according to CTCAE 3.0. The number and grade of the AEs recorded during the study period are listed in Table 2. All of these were in patients receiving pazopanib. No AEs designated as possibly, probably or definitely related to the treatment were observed in the observation arm. There were a total of 12 grade 3 AEs in 10 patients: 3 patients with HTN, 2 patients each with diarrhea and increased ALT, and 1 patient each with increased AST, anorexia, hypophosphatemia, hyponatremia, and dizziness. There was one grade 4 event, a pulmonary embolism. The most commonly occurring AEs (Table 2) were diarrhea, HTN, increased ALT and increased AST, each with a maximum documented grade of 3 and fatigue, with a maximum grade of 2.

DISCUSSION

IAS is an emerging standard of care for biochemically recurrent prostate cancer and has been proposed as a useful clinical model for developing novel agents in castrate sensitive prostate cancer. Because the re-growth of cancer during the off period is presumably accompanied by angiogenesis [24], angiogenic inhibitors in general and VEGF pathway inhibitors specifically have been hypothesized to be useful in this setting. We undertook a randomized phase 2 trial with the VEGFR tyrosine kinase inhibitor pazopanib to test this hypothesis.

Unfortunately and somewhat unexpectedly, the high dropout rate in both arms of this trial made measurement of the primary outcome at the planned power and significance levels infeasible. The most common reason for dropout in the pazopanib arm was drug-related toxicity (across all grades) accounting for 44% of these patients. The toxicity was predominantly grade 1 or 2 by convention. Compared to published data of pazopanib in advanced renal cell carcinoma, the frequency and severity of toxicities noted in this study were similar and yet the dropout rate was substantially higher, 44.4% vs. < 6% in the pazopanib arm and 26.3% vs. < 3% in the control arm [26]. Studies of other VEGFR inhibitors in patients with castrate resistant prostate cancer have mostly demonstrated similar toxicities without the same issues of patient drop out. One such phase II study of sunitinib in patients with mCRPC in the post-chemotherapy setting did have significant patient dropout (52.8%) [27]. However, an ongoing phase II study as well as a completed phase II study of sunitinib in patients with castrate resistant disease did not report the same difficulties with patient drop out despite a similar toxicity profile [128]. Several phase II studies of sorafenib in patients with castrate resistant disease also did not report high levels of patient drop out [292130]. To our knowledge, however, VEGFR inhibitors have not been studied in the setting of biochemical recurrence, nor has mature data of pazopanib in prostate cancer been presented.

The fact that this trial had higher dropout rates than other studies with pazopanib or other members of this drug class, despite similar toxicity data, suggests a lower tolerance for drug-

related AEs in the setting of IAS. Patients on the off period of IAS suffer fewer adverse effects (hot flashes) [15] and these data suggest it is reasonable to conclude that this population of patients has an expectation for lower treatment related toxicity and thus has a higher likelihood to dropout of clinical studies due to treatment related adverse events. The currently used CTCAE classification system may be appropriate for reporting severity of toxicity and the danger patients experience on treatment. However, dose adjustment guidelines based on these criteria cannot be uniformly applied across tumor models and across the spectra of health states that exist within tumor models. Simply stated, a patient with hormone-sensitive prostate cancer with no symptomatology has presumably less incentive to endure the same level of toxicity or adhere to a prescribed visit schedule as a patient with advanced renal cell carcinoma appropriate for medical intervention. This conclusion is bolstered by the finding in this study that patients in the observation arm also dropped out at a higher than expected rate despite recruitment at centers with expertise and experience in accruing to trials with both novel therapeutic agents and intermittent hormonal therapy. The most common reason for patient dropout, occurring in 26% of the patients in this arm of the study, was due to protocol-related visits and procedures.

The experience of patients in this study provides an important lesson. Given the preliminary results of the National Cancer Institute of Canada PR7 study [15], it is likely that the usage of IAS as a therapeutic strategy for men with castrate sensitive prostate cancer will grow. It follows that future clinical trials will continue to investigate new therapies with the goal of lengthening TTPP, thus allowing for longer periods of time off of ADT during IAS. This study indicates that patients within this population have a low threshold for drug-related toxicity and protocol related visits and procedures. Future trial design within this therapeutic niche should take these results into consideration.

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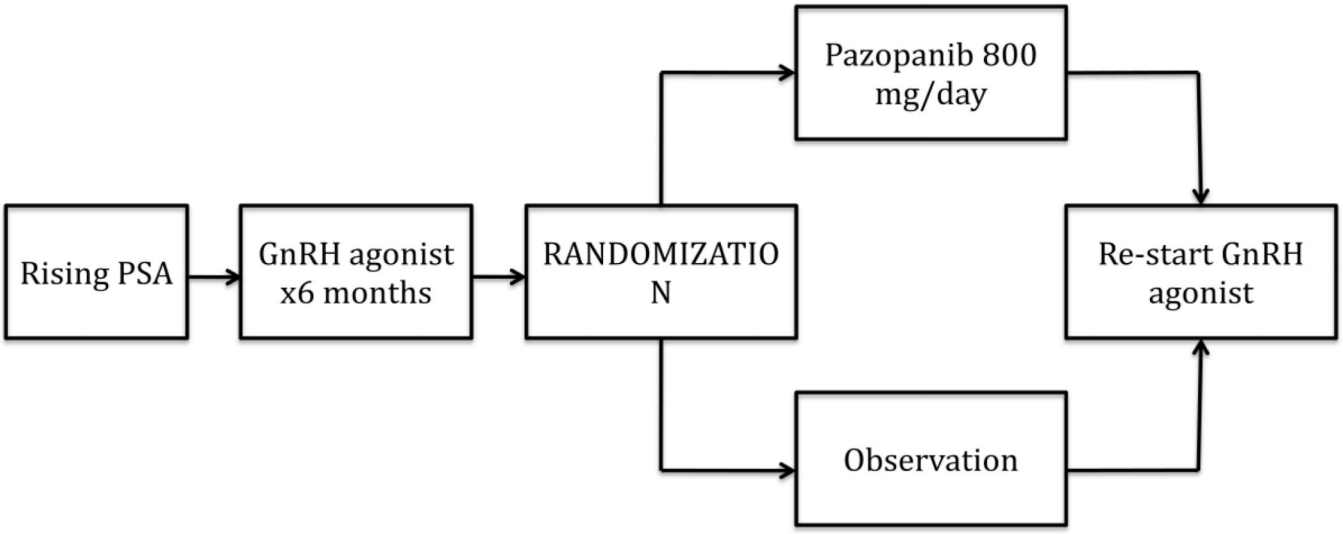
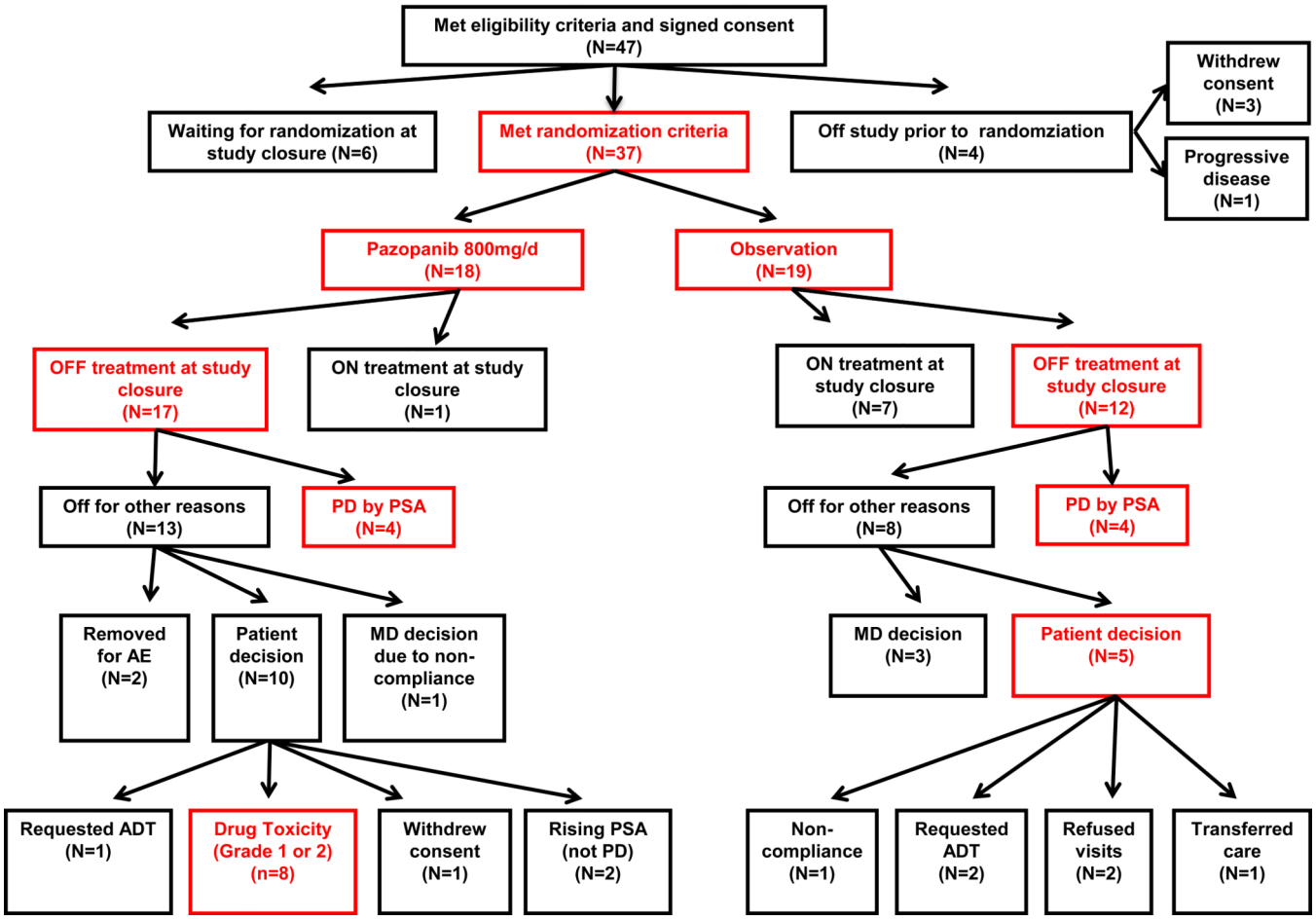


Figure 1.
Schema for the randomized, placebo controlled, phase II study.

A



B

	PAZOPANIB	OBSERVATION
Reached study endpoint: PD	22.0% (4/18 pts)	21.0% (4/19 pts)
Off study for other reasons	72.0% (13/18 pts)	42.0% (8/19 pts)
Disenrolled due to drug side effects	44.4% (8/18 pts)	0.0% (0/19 pts)
Disenrolled due to study related visits/rules	16.7% (3/18 pts)	26.3% (5/19 pts)

Figure 2.

A: Flowchart of patient accrual and reasons for study discontinuation

B: Patient outcomes including most common reasons for study discontinuation

Table 1

Baseline patient characteristics

	Observation (n=19)	**Pazopanib (n=18)**
Primary Gleason Score	3.63 (SD 0.50)	3.61 (SD 0.70)
Secondary Gleason Score	3.63 (SD 0.68)	3.61 (SD 0.70)
Stage: ≥T3 ≤T2	66.7% (10/15 pts) 33.3% (5/15 pts)	41.7% (5/12 pts) 58.3% (7/12 pts)
Primary Therapy: Surgery Radiotherapy	94.7% (18/19 pts) 5.3% (1/19 pts)	72.2% (13/18 pts) 27.8% (5/18 pts)
Pre- ADT treatment PSA (ng/mL)	3.29 (SD 2.94)	11.09 (SD 15.03)
% undergoing salvage radiotherapy	78.9 (15/19 pts)	52.9 (9/17 pts)

Table 2

Reported adverse events including most commonly occurring toxicities*

EVENT	Grade 1	Grade 2	Grade 3	Grade 4	TOTAL
No. of events	67	27	12	1	107
Diarrhea	8	3	2	--	13
Fatigue	6	3	--	--	9
HTN	2	2	3	--	7
↑ ALT	3	2	2	--	7
↑ AST	5	1	1	--	7

*All AEs reported here (attribution ≥3, possibly, probably or definitely related to treatement) were documented in the pazopanib arm

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