Original Study

Phase II Study of Pazopanib and Paclitaxel in Patients With Refractory Urothelial Cancer

Sujata Narayanan,[1] Anthony Lam,[1] Ulka Vaishampayan,[2] Lauren Harshman,[1] Alice Fan,[1] Russell Pachynski,[1] Shermeen Poushnejad,[1] Denise Haas,[1] Shufeng Li,[1] Sandy Srinivas[1]

Abstract

The present phase II study of paclitaxel with an antiangiogenic agent for refractory urothelial cancer resulted in a high objective response rate with limited toxicity.

Introduction: Currently, no standard treatments are available for relapsed or refractory urothelial carcinoma (UC). Paclitaxel has demonstrated efficacy in the treatment of UC when used alone or combined with other cytotoxic therapies. We designed a phase II trial combining paclitaxel with pazopanib, a commonly used antiangiogenic agent with significant antitumor activity in various solid tumors. **Patients and Methods:** We enrolled 32 patients with refractory UC who had demonstrated disease progression after 2 previous chemotherapeutic regimens. The patients received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle and oral pazopanib 800 mg daily. The primary endpoint was the overall response rate (ORR). The secondary endpoints included progression-free survival, overall survival, and a safety assessment of the combination. **Results:** Of the 28 evaluable patients, a complete response was observed in 3 patients and a partial response in 12, with an ORR of 54% (95% confidence interval, 33.9-72.5). The median progression-free and overall survival was 6.2 and 10 months, respectively. The most frequent side effects noted (all grades) were fatigue (63%), diarrhea (44%), and nausea and vomiting (41%). Hematologic toxicities were common and included (all grades) anemia (69%), neutropenia (38%), and thrombocytopenia (47%). Growth factor support was required for 44% of the patients. **Conclusion:** The combination of paclitaxel and pazopanib resulted in a promising ORR of 54% in patients with advanced pretreated UC. This represents a greater response rate and median survival than found with other existing second-line regimens for UC and is worthy of further study.

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Introduction

Recurrent metastatic urothelial cancer (UC) is a challenging disease with few treatment options that improve patient survival. In 2015, cancer statistics estimated approximately 74,000 new cases of UC and 16,000 deaths from UC.[1] Although platinum-based chemotherapy regimens result in high initial response rates ranging from 40% to 70%, they are generally not curative, with a median progression-free survival (PFS) of approximately 8 months and 5-year overall survival (OS) of 15%.[2,3] Thus, most patients with UC will develop a relapse and require additional therapy.

Despite the evaluation of a number of cytotoxic and biologic agents for the treatment of UC in the second-line setting, currently, no standard treatment options are available. Only a few single agents have shown modest response rates in phase II and III trials. Taxanes are frequently implemented after cisplatin-based chemotherapy. In this setting, docetaxel has elicited a response rate of 13.3% and a median survival of 9 months.[4] Weekly paclitaxel attained a response rate of 10%, with a median time to progression of 2.2 months and median OS time of 7.2 months. Nab-paclitaxel achieved a response rate of 27%.[5,6] Combination therapy has demonstrated limited efficacy and increased toxicity.

A. Lam is currently at Skyline Urology, Torrance, CA.

L. Harshman is currently at Dana Farber Cancer Institute and Harvard Medical School, Boston, MA.

R. Pachynski is currently at Washington University School of Medicine, St. Louis, MO.

[1]Stanford Cancer Center, Stanford, CA
[2]Karmanos Cancer Institute, Detroit, MI

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Address for correspondence: Sandy Srinivas, MD, Stanford Cancer Center, 875 Blake Wilbur Drive, Stanford, CA
E-mail contact: sandysri@stanford.edu

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Several preclinical studies have implicated the importance of angiogenesis in the pathogenesis and evolution of UC.[7,8] The activity of pazopanib, an established multitargeted oral tyrosine kinase inhibitor targeting the vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, platelet-derived growth factor receptors α and β, and stem cell factor receptor (c-Kit)[9] was evaluated in a phase II clinical trial of patients with heavily pretreated metastatic UC.[10] In this group, treatment with pazopanib produced an objective response rate (ORR) of 17%.

The combination of pazopanib with weekly paclitaxel in advanced solid tumors has been evaluated in a phase I trial. It was found that a dose of pazopanib at 800 mg once daily could be safely combined with a therapeutic dose of paclitaxel at 80 mg/m^2 administered on days 1, 8, and 15, every 28 days.[11] Of the 26 patients with advanced solid tumors enrolled in that study, 6 (23%) had a partial response (PR) and 15 (58%) had stable disease. The combination of 800 mg pazopanib and 80 mg/m^2 paclitaxel resulted in a 26% greater geometric mean paclitaxel area under the curve, suggesting synergistic activity. Given the encouraging antitumor activity noted by combining these agents, we undertook a phase II study to evaluate the combination of pazopanib with weekly paclitaxel in patients with refractory UC.

Patients and Methods

The present phase II trial was conducted at Stanford Cancer Center (Stanford, CA) and the Karmanos Cancer Institute (Detroit, MI) after institutional review board approval. The eligible patients had histologically confirmed metastatic UC of the bladder, ureter, or renal pelvis, with documented recurrence after a maximum of 2 previous lines of chemotherapy, including previous perioperative chemotherapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 and measureable disease using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[12] Adequate hematologic, renal, and hepatic function were required: absolute neutrophil count $\geq 1.5 \times 10^9$/L, hemoglobin 9 g/dL, platelet count $\geq 100 \times 10^9$/L, prothrombin time or international normalized ratio $\leq 1.2 \times$ upper limit of normal (ULN), total bilirubin $\leq 1.5 \times$ ULN, aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN, serum creatinine $\leq 1.8 \times$ ULN, and urine protein-to-creatinine ratio < 1. Other eligibility criteria included age ≥ 18 years and an ability to provide written informed consent and follow the study-specific procedures. Women of childbearing potential were required to have a negative serum pregnancy test 2 weeks before the first dose and to use adequate contraception during treatment.

The study excluded patients who had received taxane chemotherapy in the previous 12 months and those with evidence of central nervous system or leptomeningeal involvement in the previous 6 months. Patients with any significant cerebrovascular, cardiovascular, or thromboembolic event in the previous 6 months requiring hospitalization or intervention, an increased risk of gastrointestinal bleeding, poorly controlled hypertension, or prolonged QTc interval (> 480 ms), or any evidence of active bleeding or bleeding diathesis were also excluded. The patients were required to have completed radiation, surgery, tumor embolization, chemotherapy, immunotherapy, and/or any biologic or investigational therapy 14 days before the first dose of pazopanib. All patients provided written informed consent before study participation.

Procedures

The baseline assessment of all patients included a detailed history and physical examination, assessment of the ECOG PS, blood counts, coagulation status, electrolytes, renal and hepatic function, cardiac function (electrocardiogram and echocardiogram), computed tomography or positron emission tomography scans (thorax, abdomen, and pelvis), and bone scans (when clinically indicated). The patients received pazopanib at a starting dose of 800 mg daily plus paclitaxel dosed at 80 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle. A detailed physical examination, determination of the ECOG PS, and blood tests were repeated at every cycle. The imaging studies were repeated every 2 cycles to assess the response to therapy using the RECIST, version 1.1, for measureable disease.

The study permitted a dose reduction of pazopanib to 600 mg/d, followed by a paclitaxel dose reduction to 65 mg/m^2 and then to 51 mg/m^2 for grade ≥ 2 neutropenia or thrombocytopenia. Any further reduction in the dose required the withdrawal of the patient from the study.

The treatment was continued until disease progression, as defined by the RECIST, version 1.1, unacceptable side effects from treatment, intercurrent illness, consent withdrawal, or the investigator deemed that the patient's condition was unacceptable for further treatment. The imaging data were also assessed by Virtual Scopics, an independent reviewer for the study. All adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

The primary endpoint of the present study was the ORR of the tumors measured using the RECIST, version 1.1. The secondary endpoints included an assessment of the PFS, OS, and safety and tolerability of the drug combination. The efficacy analysis included evaluable patients, defined as patients who had received ≥ 2 cycles of chemotherapy, and the safety parameters were assessed using the intent-to-treat principle.

The study was designed using Simon's 2-stage design. With an estimated sample size of 32 patients, an interim analysis was planned for the first 9 evaluable patients. If ≥ 1 of the first 9 evaluable patients had a treatment response, the trial would proceed to complete enrollment. Of the 32 evaluable subjects, a response in ≥ 9 patients would reject the null hypothesis that the response rate would be $\leq 15\%$. This design would have 80% power for a true response rate of 35%, with a 5% (α) 1-sided significance level. Kaplan-Meier method was applied to generate survival curves for PFS and OS. All analyses were conducted using the STATA statistical package, version 11.0.[13]

Results

The study enrolled 32 patients from May 2010 to October 2014. The demographic and clinical characteristics of the study patients are listed in Table 1. Of the 32 patients, 41% had received chemotherapy for de novo metastatic disease. Most of the patients (59%) had received perioperative chemotherapy. The median