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Phase II trial of bevacizumab and satraplatin in docetaxel-pretreated metastatic castrate-resistant prostate cancer

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Summary

Background: Satraplatin is an oral platinum compound that has demonstrated efficacy and tolerability in prostate cancer. Preclinical synergy between bevacizumab and platinum has been noted.

Methods: Docetaxel-pretreated metastatic castrate-resistant prostate cancer patients with disease progression were eligible. Satraplatin 80 mg/m^2 orally on days 1 to 5, prednisone 5 mg twice daily, and bevacizumab 10 mg/kg on day 1, and 15 mg/kg on day 15 were administered in 35-day cycles.

Results: Thirty one patients were enrolled. Grade 3 or 4 toxicities were pulmonary embolism in 2 patients and thrombocytopenia in 1 patient. 31% of the patients had a $\geq$30% decline in prostate-specific antigen. Median time to progression was 7.0 months (90% confidence interval [CI] 4.7–8.5 mo) and median overall survival was 11.2 months (90% CI 9.1–16.4 mo). Polymorphism in the excision repair cross-complementation-1 (ERCC-1) gene was associated with time to progression (hazard ratio = 1.91). A circulating tumor cell count $\geq$5was moderately prognostic of overall survival (hazard ratio = 1.49) as compared with CTC <5.

Conclusions: The combination was tolerable, and revealed promising efficacy in metastatic castrate-resistant prostate cancer. ERCC1 genotype maybe predictive of clinical benefit with platinum-based therapy in metastatic prostate cancer.

Keywords: Excision repair polymorphism; Prostate cancer; Chemotherapy; Phase II clinical trial

1. Introduction

Docetaxel-based chemotherapy was the first systemic regimen to confer an overall survival benefit in metastatic castrate-resistant prostate cancer (CRPC) [1,2]. About 50% of the patients are unresponsive and all patients eventually progress on docetaxel therapy. Platinum-based therapies have been utilized in this setting. Clinical trials conducted using carboplatin demonstrated a promising efficacy and favorable responses [3,4]. Another platinum agent that has been extensively tested in metastatic CRPC is satraplatin.

Satraplatin is an oral, third-generation platinum compound noted to have preclinical efficacy in platinum-resistant cell lines, and clinical efficacy in metastatic CRPC [5]. Preliminary results of phase I and II trials established the safety of the agent, with the severe toxicities noted being neutropenia, thrombocytopenia, and diarrhea [6,7]. Cisplatin side effects such as nephrotoxicity, neuropathy, and ototoxicity were not observed with satraplatin. The results of a phase II trial of satraplatin and prednisone compared with prednisone alone, revealed that the treatment was well tolerated with a promising prostate-specific antigen (PSA) response rate of 33%, and median progression-free survival (PFS) of 5.2 months in the satraplatin and prednisone arm as compared with a response rate of 9%, and median PFS of 2.5 months, in the prednisone arm [7].

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Median overall survival (OS) estimates were 14.9 months and 11.9 months in the satraplatin and prednisone and the prednisone alone arms, respectively. The Satraplatin and Prednisone Against Refractory Cancer (SPARC) [8] trial evaluated satraplatin plus prednisone vs. placebo plus prednisone as a second-line treatment in 950 patients with metastatic CRPC. The PFS was significantly better ($P < 0.0000003$) in favor of satraplatin [8]. However, the OS analysis revealed no benefit leading to lack of regulatory approval of the agent.

Increased expression of vascular endothelial growth factor (VEGF) contributes to prostate cancer progression, by up-regulating microvessel density, and increasing expressions of VEGF-C and VEGFR-3 with enhanced lymphangiogenesis [9,10]. Bevacizumab is an antiangiogenic, monoclonal antibody that inhibits VEGF and improves the efficiency of the local vasculature, thereby improving chemotherapy penetration and delivery [11–13]. Due to the individual efficacy and tolerability of satraplatin and bevacizumab and the clinical synergy noted between platinum-based chemotherapies and antiangiogenic therapy we conducted a phase II trial of the combination of satraplatin and bevacizumab in pretreated metastatic CRPC.

2. Patients and Methods

The protocol and the informed consent form were approved and reviewed annually by the Wayne State University Institutional Review Board. Eligibility criteria included histologically confirmed prostate adenocarcinoma with radiologically evident metastases and testosterone ≤ 50 ng/ml. Objective evidence of progression was required. Prior docetaxel-based chemotherapy was required but not more than 1 prior chemotherapy (unless given in combination with docetaxel) for metastatic disease was allowed. Concomitant bisphosphonate therapy was allowed. Prestudy imaging for disease assessment was performed within 28 days of treatment. Antiandrogen withdrawal was required for 4 weeks prior to treatment with flutamide and for 6 weeks prior to treatment with bicalutamide or nilutamide. Radiation therapy had to be completed atleast 28 days prior to enrollment. Performance status of 0 to 2 by Zubrod criteria, life expectancy of atleast 12 weeks, and normal renal, liver, and bone marrow function were required. Patients on anticoagulants were allowed if treated adequately and if no ongoing acute thromboembolic activity was noted. Atleast 28 days had to have elapsed from a major surgical procedure, open biopsy, or significant traumatic injury. Patients with severe congestive heart failure, arrhythmias, or a myocardial infarction within 3 months of registration, were excluded. Patients with urinary protein and creatinine ratio >1, or 24-hour urine protein greater than or equal to 1 g/dl were ineligible. All patients were required to provide a written informed consent.

2.1. Treatment plan

Bevacizumab treatment was administered at 10 mg/kg intravenously on day 1, and 15 mg/kg on day 15, of each 35-day cycle. Premedications were allowed at the treating physician's discretion. Satraplatin 80 mg/m^2 was taken orally with fasting for 1 hour prior, and 2 hours after dosing. Prednisone 5 mg twice daily was taken with meal.

Dose adjustments were made for severe hematologic and nonhematologic toxicities. Treatment was discontinued if there was evidence of disease progression, unacceptable or severe grade 3 or 4 toxicity, or delay in treatment by 4 weeks or more.

2.2. Correlative tests

2.2.1. ERCC1

Approximately 10 ml of blood was drawn using a 10 ml ethylenediaminetetraacetic acid tube for DNA extraction. Genomic DNA was extracted from the serum or the white blood cells present in the buffy coat layers of the whole blood of patients according to the manufacturer's instructions using the UltraSens Virus Kit (Qiagen, CA). Polymerase chain reaction (PCR) was done using the Platinum Taq PCR Kit (Invitrogen, CA) with gene-specific primers. PCR was carried out by denaturation at 94°C for 5 minutes followed by denaturation at 94°C for 30 seconds, annealing at optimal temperature for each pair of primers for 30 seconds, and synthesis for 30 seconds at 72°C for 40 cycles; the final extension was carried out at 72°C for 7 minutes. Direct nucleotide sequencing PCR was conducted using the Big Dye Terminator Cycle Sequencing Ready Reaction kit V3.1 (Applied Biosystems, CA) and an ABI Prism 3130 Genetic Analyzer using the manufacturer's instructions. Immunohistochemical phenotyping of normal peripheral blood leukocytes (PBLs) was done to check for polymorphisms of the (ERCC1) enzyme [14].

2.2.2. Circulating tumor cell (CTC) counts

A single sample of approximately 22.5 ml (three 7.5 ml tubes) of blood was collected from the patients who consented and were treated on the study. Blood collection kits and instructions were provided by CARIS Labs and were performed by CARIS/Veridex (Caris Diagnostics, Irving, TX). Samples were only collected posttherapy, and not at baseline due to funding delays.

2.2.3. Evaluation

Toxicity was categorized according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). All patients who were starting the therapy were considered to be toxicity evaluable. Patients completing a minimum of 1 cycle of therapy followed by assessment were considered to be response evaluable. Imaging studies for tumor assessment were conducted at baseline and every 2 cycles. RECIST criteria