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ORIGINAL REPORT

Phase II Multicenter Study of Abiraterone Acetate Plus Prednisone Therapy in Patients With Docetaxel-Treated Castration-Resistant Prostate Cancer

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See accompanying editorial on page 1447 and articles on pages 1481 and 1489

ABSTRACT

Purpose
Persistence of ligand-mediated androgen receptor signaling has been documented in castration-resistant prostate cancers (CRPCs). Abiraterone acetate (AA) is a potent and selective inhibitor of CYP17, which is required for androgen biosynthesis in the testes, adrenal glands, and prostate tissue. This trial evaluated the efficacy and safety of AA in combination with prednisone to reduce the symptoms of secondary hyperaldosteronism that can occur with AA monotherapy.

Patients and Methods
Fifty-eight men with progressive metastatic CRPC who experienced treatment failure with docetaxel-based chemotherapy received AA (1,000 mg daily) with prednisone (5 mg twice daily). Twenty-seven (47%) patients had received prior ketoconazole. The primary outcome was ≥ 50% prostate-specific antigen (PSA) decline, with objective response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and changes in Eastern Cooperative Oncology Group (ECOG) performance status (PS) and circulating tumor cell (CTC) numbers. Safety was also evaluated.

Results
A ≥ 50% decline in PSA was confirmed in 22 (36%) patients, including 14 (45%) of 31 ketoconazole-naïve and seven (26%) of 27 ketoconazole-pretreated patients. Partial responses were seen in four (18%) of 22 patients with RECIST-evaluable target lesions. Improved ECOG PS was seen in 28% of patients. Median time to PSA progression was 169 days (95% CI, 82 to 200 days). CTC conversions with treatment from ≥ 5 to < 5 were noted in 10 (34%) of 29 patients. The majority of AA-related adverse events were grade 1 to 2, and no AA-related grade 4 events were seen.

Conclusion
AA plus prednisone was well tolerated, with encouraging antitumor activity in heavily pretreated CRPC patients. The incidence of mineralocorticoid-related toxicities (hypertension or hypokalemia) was reduced by adding low-dose prednisone. The combination of AA plus prednisone is recommended for phase III investigations.

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INTRODUCTION

Prostate cancer progression despite castrate levels of testosterone is associated with a rising prostate-specific antigen (PSA) level and represents a transition to the lethal phenotype of the disease to which most patients eventually succumb. The rise in PSA, an indication that androgen receptor (AR) signaling has been reactivated, is the result of selective and/or adaptive changes in the AR itself that are oncogenic for growth, of which AR overexpression is the most common.[1] Tumor levels of ligand have received less attention. In 1984, Geller et al[2] documented elevated levels of androgens in tissue homogenates of the prostates of men who were progressing on medical or surgical castration. Adrenal androgen synthesis was the postulated source, although a failure to completely suppress intratumoral androgens could not be excluded. The finding of increased intratumoral

androgens was subsequently confirmed in microdissected locally recurrent and castration-resistant primary and metastatic lesions.[3-6] In 2004, Holzbeierlein et al[7] first reported a microarray analysis of newly diagnosed primary and metastatic and separately posthormone-treated primary and progressive castration-resistant prostate cancers (CRPCs) that showed an up to five-fold induction of several enzymes involved in steroid hormone production. The finding, subsequently confirmed by others,[8,9] suggested the possibility of intracrine signaling as an additional mechanism of AR reactivation.

Abiraterone (CB7630, Cougar Biotechnology, Los Angeles, CA) is a novel, selective, irreversible, and potent inhibitor of 17-[alpha]-hydroxylase/17,20-lyase (CYP17) enzymatic activity that has recently been demonstrated to further reduce testosterone levels in the blood to undetectable range (< 1 ng/dL),[10,11] and is suggested to reduce de novo intratumor androgen synthesis.[12] Significant antitumor effects were seen in patients with progressive CRPC who had not received prior chemotherapy, where secondary hormonal therapies are traditionally used.[11,13] Ketoconazole, a weak inhibitor of adrenal steroid synthesis that suppresses many cytochrome P450 enzymes and other enzymes involved in the conversion of cholesterol to pregnenolone, has also shown activity in the same clinical context[14,15] but is associated with significant toxicities.[16-18]

Recognizing that PSA levels also rise in patients who are progressing after treatment with cytotoxic agents, we postulated that these tumors might also be sensitive to a potent AR signaling inhibitor. In a separate trial, we showed significant antitumor effects of abiraterone acetate (AA) monotherapy in this patient group, emphasizing further how considering these tumors as hormone-refractory can deny patients effective therapies.[19] The adverse events seen with AA monotherapy were largely those associated with secondary hyperaldosteronism, including hypokalemia, fluid retention, and hypertension that required treatment with the selective aldosterone inhibitor eplerenone or low-dose steroids to suppress the hypothalamic-pituitary-adrenal axis, blunting the feedback rise in adrenocorticotropic hormone to reduce production of adrenal steroids with mineralocorticoid activity.[11,20] Anticipating phase III development, we designed this study to confirm the antitumor activity of AA in patients with CRPC after failure of docetaxel-based chemotherapy using the proposed registration regimen of AA at 1,000 mg daily in combination with prednisone at 5 mg twice daily, and separately, to begin to address the influence on outcome of the number and type of prior hormone treatments, particularly ketoconazole.[21] Importantly, the evaluation of this steroid combination was further supported by our work indicating that low-dose steroids can reverse clinical AA resistance and decrease steroid precursors upstream of CYP17 that can activate AR signaling. Recognizing that PSA changes may not be a reliable indicator of the antitumor effects of an AR signaling–directed therapy and that more informative indicators of clinical benefit represent a critical unmet need for the management of CRPC, we also evaluated pre- and post-therapy circulating tumor cell (CTC) number using an analytically valid assay that is cleared by the US Food and Drug Administration for use as an aid to monitoring treatment and prognosis in patients with breast,[22] colorectal,[23] and prostate cancer.[24]

PATIENTS AND METHODS

Patients

Castrate men (serum testosterone < 50 ng/dL [< 2.0 nmol/L]) with metastatic prostate cancer who had experienced treatment failure with androgen deprivation therapy and docetaxel-based chemotherapy were eligible. Disease progression was defined as documented PSA progression according to Prostate Specific Antigen Working Group 1 criteria[25] and a PSA > 5 ng/mL, or objective progression by Response Evaluation Criteria in Solid Tumors (RECIST) criteria[26] for patients with measurable disease. Patients had to have received prior chemotherapy with docetaxel, and treatment with up to two prior chemotherapy regimens was permitted. Prior treatment with ketoconazole was allowed and was recorded separately. Eligibility criteria also included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2, (Karnofsky PS ≥ 50%), normal serum potassium, and adequate hematologic, hepatic, and renal function. With the exception of luteinizing hormone-releasing hormone agonists, a minimum of 4 weeks must have elapsed from discontinuation of prior prostate cancer therapies and a minimum of 6 weeks for antiandrogen therapy. Patients were excluded if they had brain metastases or spinal cord compression, active autoimmune disease requiring corticosteroid therapy, uncontrolled hypertension, a depressed cardiac ejection fraction or history of cardiac failure (New York Heart Association class III or IV), or a serious concurrent medical illness. The trial protocol was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki, current US

Table 1. Patient Baseline Demographics and Clinical Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	69.5	
Range	44-86	
ECOG performance status		
0	24	41
1	31	53
2	2	3
Unknown	1	2
Gleason score		
Median	7	
Range	5-10	
Baseline PSA, ng/mL		
Median	189.6	
Range	10.1-3,846	
Involved metastatic sites		
Visceral (with or without bone or soft tissue)	13	22
Bone only	11	19
Soft tissue only	8	14
Bone and soft tissue only	26	45
Prior hormonal therapies		
LHRH agonists	57	98
Orchiectomy	3	5
Antiandrogens	53	91
Diethylstilbestrol	8	14
Steroids	21	36
Dexamethasone	5	9
Other	20	34
Ketoconazole	27	47
Prior lines of chemotherapy		
1	44	76
> 1	14	24

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LHRH, luteinizing hormone–releasing hormone.

Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements.

Study Design

After written informed consent was obtained, eligible patients in this multicenter phase II clinical trial received AA at 1,000 mg (four 250-mg tablets daily in the morning after an overnight fast) concurrently with prednisone at 5 mg twice daily. Treatment was administered in 28-day cycles, and up to 12 cycles of therapy were permitted; continuation beyond 12 cycles was allowed on approval by the investigators and sponsor.

Patient Evaluation

Patients were seen and examined at the beginning of every cycle while receiving treatment, and adverse events were recorded using the National Cancer Institute Common Toxicity Criteria, version 3.0. Potential attributions to AA and prednisone were recorded separately. A CBC, chemistry panel, PSA, and androgen levels were evaluated monthly.

Antitumor Outcomes

The primary study objective was determination of the proportion of patients achieving a decline in PSA ≥ 50% according to Prostate Specific Antigen Working Group 1 criteria (PSA response). The maximal and 12-week post-therapy declines in PSA were recorded using waterfall plots. The maximal decline had to be confirmed by a second value obtained ≥ 4 weeks later.[25] Patients who had metastatic disease evident on baseline imaging (computed tomography scan, magnetic resonance imaging, or bone scan) had follow-up studies at 3-month intervals. Measurable disease response rate was reported using the RECIST criteria, while post-treatment changes on radionuclide bone scan were reported as stable or progression per investigator's assessment.

Time to PSA progression was calculated for patients with PSA decline ≥ 50% from baseline at the time the PSA increased to 50% above the nadir and was > 5 ng/mL. For those not meeting the PSA decline criteria, time to PSA progression was the time when PSA increased by 25% from baseline.

Other end points recorded were changes in ECOG PS, and pre-and post-therapy CTC counts (number of cells/7.5 mL of blood) were enumerated separately using the CellTracks system (Veridex, Raritan, NJ), as described previously.[27,28]

Statistical Analysis

The primary end point of the trial was the proportion of patients who achieved a PSA decline of ≥ 50% from baseline that was confirmed by a second value following treatment with AA plus prednisone. The combination would be considered worthy of further study if ≥ 30% of patients met the end point and not worthy of further study if fewer than 15% achieved the end point. With a population of 50 patients, the null hypothesis would be rejected and further study of the combination would be warranted if > 25% of eligible and treated patients had a ≥ 50% decline in PSA (alpha of 6% with 86% power).

RESULTS

Patients

Between June 2007 and November 2007, 58 men with CRPC were enrolled across seven study centers: six in the United States and one in the United Kingdom. Patient demographics and baseline characteristics are listed in Table 1. All were heavily pretreated with a number of hormonal therapies that included a median of four (range, one to eight) prior antiandrogens in 52 (91%) and estrogens in nine (16%), while 27 (47%) had prior ketoconazole. While all had been treated with prior docetaxel, 24% had also received a second chemotherapy regimen. Consistent with the advanced state of the population, only 11 (19%) had disease limited to bone, while 13 (22%) had visceral spread, and 34 patients (59%) had soft tissue disease with or without osseous spread. The median PSA level at baseline was 190 ng/mL (range, 10 to 3,846 ng/mL). The median testosterone level was 4.8 ng/dL (range, below limit of detection [0.05] to 30.5 ng/dL).

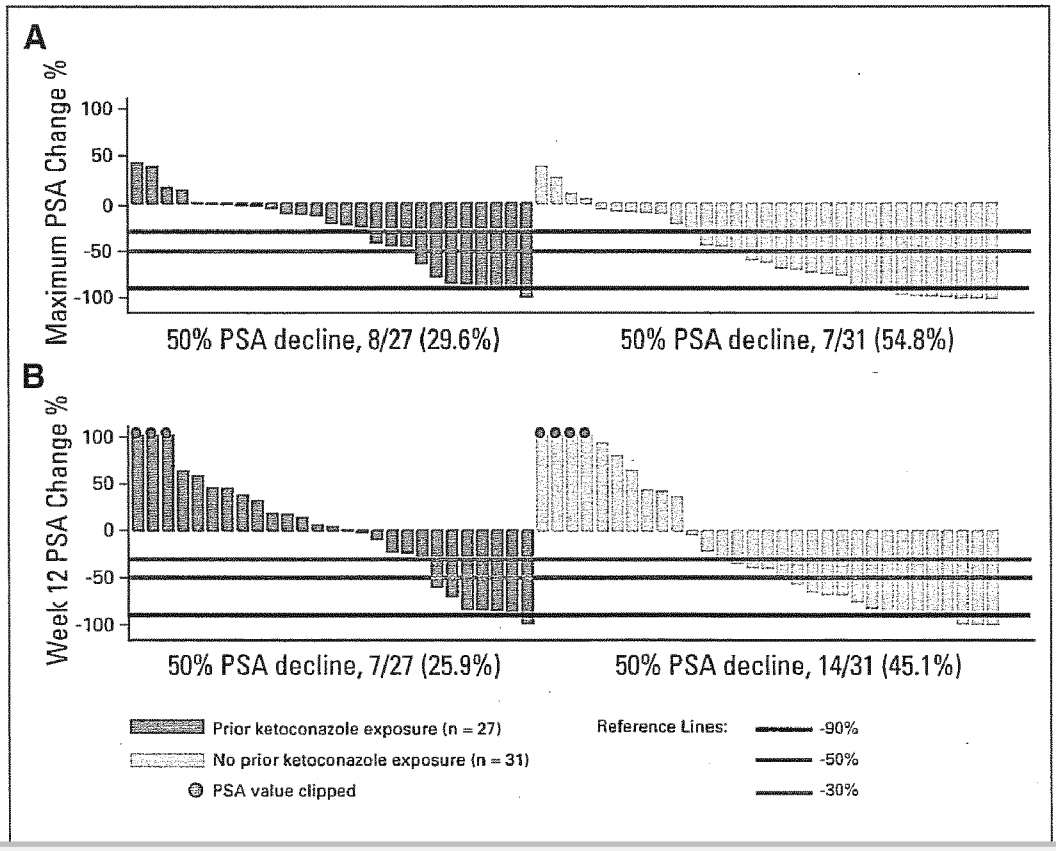

Fig 1. Changes in prostate-specific antigen (PSA) levels with abiraterone acetate plus prednisone. Waterfall plots of (A) maximum PSA change and (B) change at week 12. Patients with prior ketoconazole exposure appear on the left side of the panel in blue and those without prior ketoconazole exposure appear on the right side of the panel in gold.

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