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Abiraterone and Increased Survival in Metastatic Prostate Cancer

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ABSTRACT

BACKGROUND

Biosynthesis of extragonadal androgen may contribute to the progression of castration-resistant prostate cancer. We evaluated whether abiraterone acetate, an inhibitor of androgen biosynthesis, prolongs overall survival among patients with metastatic castration-resistant prostate cancer who have received chemotherapy.

METHODS

We randomly assigned, in a 2:1 ratio, 1195 patients who had previously received docetaxel to receive 5 mg of prednisone twice daily with either 1000 mg of abiraterone acetate (797 patients) or placebo (398 patients). The primary end point was overall survival. The secondary end points included time to prostate-specific antigen (PSA) progression (elevation in the PSA level according to prespecified criteria), progression-free survival according to radiologic findings based on prespecified criteria, and the PSA response rate.

RESULTS

After a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate–prednisone group than in the placebo–prednisone group (14.8 months vs. 10.9 months; hazard ratio, 0.65; 95% confidence interval, 0.54 to 0.77; P<0.001). Data were unblinded at the interim analysis, since these results exceeded the preplanned criteria for study termination. All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; P<0.001), progression-free survival (5.6 months vs. 3.6 months; P<0.001), and PSA response rate (29% vs. 6%, P<0.001), favored the treatment group. Mineralocorticoid-related adverse events, including fluid retention, hypertension, and hypokalemia, were more frequently reported in the abiraterone acetate–prednisone group than in the placebo–prednisone group.

CONCLUSIONS

The inhibition of androgen biosynthesis by abiraterone acetate prolonged overall survival among patients with metastatic castration-resistant prostate cancer who previously received chemotherapy. (Funded by Cougar Biotechnology; COU-AA-301 ClinicalTrials.gov number, NCT00638690.)

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For the past 70 years, depleting or blocking the action of androgens has been the standard of care for men with advanced prostate cancer.[1] Androgen deprivation results in a decrease in the concentration of prostate-specific antigen (PSA) as well as tumor regression and relief of symptoms in most patients, but the response to treatment is not durable in patients with advanced cancer, and with time, PSA concentrations increase, indicating reactivated androgen-receptor signaling and a transition to a castration-resistant state that is invariably fatal.[2] Many endocrine therapies have been evaluated in these patients, but none have prolonged survival.[3] Three nonhormonal systemic approaches have been found to prolong survival: docetaxel[4] as first-line and cabazitaxel[5] as second-line cytotoxic chemotherapy, and active cellular immunotherapy with sipuleucel-T.[6]

A unique molecular alteration described in castration-resistant prostate cancer is the up-regulation of androgen biosynthesis enzymes, leading to an increase in intratumoral androgen concentrations, which can exceed the levels measured in the blood.[7-9] Other alterations include overexpression of androgen receptors, and androgen-receptor mutations leading to androgen-receptor binding by additional ligands that would not stimulate the wild-type receptor.[2,10] Abiraterone acetate, a prodrug of abiraterone, is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis by the adrenal glands and testes and within the prostate tumor.[11-14] In phase 1–2 trials, treatment with abiraterone acetate, either as a single agent or in combination with low-dose glucocorticoids such as prednisone, resulted in significant antitumor activity among both patients with progressing castration-resistant prostate cancer who had not received chemotherapy and those who had received chemotherapy.[15-20] The most common adverse events, which were associated with increased mineralocorticoid levels, included hypokalemia, fluid retention, and hypertension; these events were largely abrogated by coadministering low-dose glucocorticoids. We hypothesized that inhibition of androgen biosynthesis with abiraterone acetate and prednisone would improve overall survival among patients with advanced prostate cancer.

METHODS

PATIENTS

Patients were eligible to participate in the study if they had histologically or cytologically confirmed prostate cancer that had previously been treated with docetaxel, disease progression according to the criteria of the Prostate Cancer Working Group[21,22] (for trial entry, patients were considered to have disease progression if they had two consecutive increases in the PSA concentration over a reference value) or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value, and ongoing androgen deprivation, with a serum testosterone level of 50 ng per deciliter or less (≤2.0 nmol per liter).

Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG)[23] performance status score of 2 or less (on a scale from 0 to 5, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work; and 2 indicating that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities) and hematologic and chemical laboratory values that met predefined criteria, including an albumin level of 3.0 g per deciliter or higher.

Patients were excluded if they had abnormal aminotransferase levels (levels of aspartate aminotransferase or alanine aminotransferase that were ≥2.5 times the upper level of the normal range; patients with known liver metastasis who had levels of aspartate aminotransferase or alanine aminotransferase that were ≤5 times the upper level of the normal range were eligible to participate), serious coexisting nonmalignant disease, active or symptomatic viral hepatitis or chronic liver disease, uncontrolled hypertension, a history of pituitary or adrenal dysfunction, clinically significant heart disease, or previous therapy with ketoconazole.

The review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki and the

Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provided written informed consent to participate in the study.

STUDY DESIGN AND TREATMENT

This phase 3, multinational, randomized, double-blind, placebo-controlled study was conducted at 147 sites in 13 countries. Patients were enrolled from May 2008 through July 2009 and were stratified according to baseline ECOG performance status score (0 or 1 vs. 2), level of worst pain over the previous 24 hours on the Brief Pain Inventory–Short Form (BPI-SF) (on a scale of 0 to 10, with 0 to 3 indicating that clinically significant pain is absent vs. 4 to 10 indicating that clinically significant pain is present),[24,25] number of previous chemotherapy regimens (one vs. two), and type of evidence of disease progression (an increase in the PSA concentration only vs. radiographic evidence of progression with or without an increase in the PSA concentration). Patients were then randomly assigned in a 2:1 ratio to receive either abiraterone acetate and prednisone or placebo and prednisone. Blocked randomization was used.

Patients received 1 g of abiraterone acetate (administered as four 250-mg tablets) or four placebo tablets orally once daily at least 1 hour before or 2 hours after a meal, with prednisone at a dose of 5 mg orally twice daily. Each cycle of treatment was 28 days. Treatment could be continued until disease progression was documented on the basis of the PSA concentration, radiographic imaging, and clinical findings. Safety and dosing compliance were evaluated on day 15 of cycle 1 and on day 1 of each subsequent cycle, at the time of treatment discontinuation if applicable, and at the end-of-study visit.

The primary end point was overall survival, defined as the time from randomization to death from any cause. The prespecified secondary end points included the PSA response rate (defined as the proportion of patients with a decrease of ≥50% in the PSA concentration from the pretreatment baseline PSA value, which was confirmed after ≥4 weeks by an additional PSA evaluation). Other secondary end points included time to PSA progression according to prespecified criteria (in patients in whom the PSA level had not decreased, PSA progression was defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 ng per milliliter, which was confirmed by a second value; in patients in whom the PSA had decreased but had not reached response criteria [PSA ≤50%], progressive disease would be considered to have occurred when the PSA level increased 25% over the nadir, provided that the increase was a minimum of 5 ng per milliliter and was confirmed; and if at least a 50% decrease in the PSA level had been achieved, PSA progression would be an increase of 50% above the nadir at a minimum of 5 ng per milliliter), and radiographic evidence of progression-free survival according to prespecified criteria (defined as soft-tissue disease progression according to modified Response Evaluation Criteria in Solid Tumors [RECIST][26] [with a baseline lymph node of ≥2.0 cm considered to be a target lesion] or progression according to bone scans showing two or more new lesions not consistent with tumor flare). A complete response was defined as the disappearance of all target and nontarget lesions, and a partial response as a decrease by at least 30% in the sum of the largest diameter of each target lesion, relative to the corresponding sum at baseline. Stable disease was defined as the absence of shrinkage sufficient for a partial response and the absence of enlargement sufficient for progressive disease, relative to the sum of the largest diameter of each target lesion at baseline, and progressive disease as an increase by at least 20% in the sum of the largest diameter of each target lesion, relative to the smallest corresponding diameter recorded since the start of treatment, or the appearance of one or more new lesions. Definitions of the secondary end points are provided in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY ASSESSMENTS

Efficacy assessments included the PSA concentration, radiographic imaging, the pain level on the BPI-SF, and analgesic use. Clinical assessments included the patient's medical history, vital-sign measurements, and body weight; a physical examination; review of concomitant therapy and procedures and of adverse events and serious adverse events, including adverse events detected by

means of laboratory tests; blood chemical, hematologic, coagulation, and serum lipid studies; urinalysis; electrocardiography; and measurement of the cardiac ejection fraction. An independent data and safety monitoring committee monitored patient safety at regular intervals.

Other assessments for analyses of exploratory end points included the score on the Functional Assessment of Cancer Therapy–Prostate questionnaire[27]; the score for fatigue, as evaluated by means of the Brief Fatigue Inventory instrument[28]; information on medical resource utilization[29]; and counts of circulating tumor cells.[30]

STUDY OVERSIGHT

This study was designed by both the academic authors and employees of the sponsor, the Ortho Biotech Oncology Research and Development Unit of Cougar Biotechnology. The first draft of the manuscript was written by some of the academic authors and employees of the sponsor; the draft was then completed and approved by the other coauthors. All authors were responsible for writing the manuscript and for the decision to submit the manuscript for publication, and all authors assume responsibility for the completeness and integrity of the data. The blinded database was held at a third-party contract clinical research organization, and queries were issued by both the sponsor and the staff of the clinical research organization. The statistician employed by the independent clinical research organization provided the analysis to the independent data and safety monitoring committee, whose members were invited by the sponsor. After the independent data and safety monitoring committee recommended unblinding of the data, analyses of the data were performed by a statistician employed by the sponsor, and the results were reviewed by the authors.

STATISTICAL ANALYSIS

The planned sample of approximately 1158 patients provided 85% power to detect a hazard ratio of 0.80 for death in the group receiving abiraterone acetate plus prednisone as compared with the group receiving placebo plus prednisone. This sample size was calculated by assuming a median survival of 15 months for the abiraterone acetate group and 12 months for the placebo group, with a two-sided significance level (alpha) of 0.05, an enrollment period of approximately 13 months, and a total study duration of approximately 30 months to observe the required 797 total events. One interim analysis was planned after 534 deaths were observed (67% of 797 total events) in a group-sequential design with the use of the O'Brien–Fleming stopping boundary. Distributions of time-to-event variables and associated 95% confidence intervals were estimated with the use of the Kaplan–Meier product-limit method. The stratified log-rank test was used as the primary analysis for comparison of treatment groups. Statistical inference was evaluated with the use of the chi-square statistic. Analyses of overall survival with the use of the nonstratified log-rank test and Cox proportional-hazards model were also performed as supportive analyses. Subgroup analyses were carried out to assess whether treatment effects were consistent across subgroups.

RESULTS

PATIENTS AND TREATMENT

We randomly assigned 1195 patients to receive abiraterone acetate plus prednisone (797 patients) or placebo plus prednisone (398 patients) (Fig. 1 in the Supplementary Appendix). Baseline demographic and other characteristics were well-balanced between the two treatment groups (Table 1). Most patients (67%) had radiographic evidence of disease progression before study entry. The median duration of treatment was 8 months in the group that received abiraterone acetate plus prednisone (hereinafter referred to as the abiraterone acetate group) and 4 months in the group that received placebo plus prednisone (hereinafter referred to as the placebo group). The median follow-up in the overall study population was 12.8 months.

EFFICACY

At the time of the preplanned interim analysis, treatment with abiraterone acetate plus prednisone resulted in a 35.4% reduction in the risk of death as compared with placebo plus prednisone (hazard ratio, 0.65; 95% confidence interval [CI], 0.54 to 0.77; P<0.001). A total of 552 patients in the intention-to-treat population died: 333 patients in the abiraterone acetate group (42%) and 219 patients in the placebo group (55%). The median overall survival was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group (Fig. 1A). The effect of abiraterone acetate and prednisone on overall survival was consistent across all subgroups (Fig. 2), and the significance of the treatment effect on overall survival was robust after adjustment for stratification factors in a

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Abiraterone Acetate (N=797)	Placebo (N=398)
Age		
Median (range) — yr	69 (42–95)	69 (39–90)
≥75 yr — no. of patients/total no. (%)	220/797 (28)	111/397 (28)
Disease location — no. of patients/total no. (%)		
Bone	709/797 (89)	357/397 (90)
Node	361/797 (45)	164/397 (41)
Liver	90/797 (11)	30/397 (8)
BPI-SF score for pain†		
No. of patients	792	394
Median score (range)	3.0 (0–10)	3.0 (0–10)
No. of previous cytotoxic chemotherapy regimens — no. of patients/total no. (%)		
1	558/797 (70)	275/398 (69)
2	239/797 (30)	123/398 (31)
ECOG performance status — no. of patients/total no. (%)		
0 or 1	715/797 (90)	353/398 (89)
2	82/797 (10)	45/398 (11)
Prostate-specific antigen		
No. of patients	788	393
Median (range) — ng/ml	128.8 (0.4–9253.0)	137.7 (0.6–10114.0)

* See Table 2 in the Supplementary Appendix for more baseline demographic and clinical characteristics.
† The Brief Pain Inventory–Short Form (BPI-SF) rates pain on a scale of 0 to 10, with 0 to 3 indicating that clinically significant pain is absent and 4 to 10 indicating that clinically significant pain is present. The scores shown are for the worst pain over the previous 24 hours.

multivariate analysis (hazard ratio for death, 0.66; 95% CI, 0.55 to 0.78; P<0.001) (Table 2). These data led the independent data and safety monitoring committee to recommend unblinding of the study data, with patients in the placebo group receiving abiraterone acetate if they met the criteria for crossover treatment specified in protocol amendment 3.0 (see the protocol, available at NEJM.org).

All the secondary end points analyzed provided support for the superiority of abiraterone acetate over placebo (Table 3), including the confirmed PSA response rate (29% vs. 6%, P<0.001), the objective response rate on the basis of RECIST among patients with measurable disease at baseline (14% vs. 3%, P<0.001), time to PSA progression (10.2 months vs. 6.6 months), and median progression-free survival on the basis of radiographic evidence (5.6 vs. 3.6 months). On the basis of the PSA concentration, abiraterone acetate was associated with a 42% reduction in the risk of disease progression (hazard ratio, 0.58; 95% CI, 0.46 to 0.73; P<0.001), and on the basis of radiographic imaging, it was associated with a 33% reduction in the risk of progression (hazard ratio, 0.67; 95% CI, 0.58 to 0.78; P<0.001) (Table 3 and Fig. 1B and 1C).

Evaluations of exploratory end points at the interim analysis also favored abiraterone acetate relative to placebo, including the time to 25% of the patients having a skeletal event (9.9 vs. 4.9 months) and the rate of pain palliation among patients with a baseline pain score of 4 or more and at least one post-baseline pain score (44% vs. 27%, P=0.002). Patients in the abiraterone acetate group had consistently improved pain palliation as compared with those in the placebo group.

SAFETY

The most common adverse event was fatigue, which occurred at a similar frequency in the two treatment groups (Table 4). Other common adverse events in both groups were back pain (30% in the abiraterone acetate group and 33% in the placebo group), nausea (30% and 32%, respectively), consti-

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