VOLUME 22 · NUMBER 6 · MARCH 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Antiandrogen Withdrawal Alone or in Combination With Ketoconazole in Androgen-Independent Prostate Cancer Patients: A Phase III Trial (CALGB 9583)

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Submitted June 10, 2003; accepted January 6, 2004.

Supported by grants CA60138 (E.J.S. and B.I.R.), CA47577 (S.H. and E.K.), CA31983 (N.A.D.), CA41287 (W.M.S. and N.J.V.), CA77440 (J.P.), CA11789 (P.G.), and CA03927 (F.M.T.). The research for Cancer and Leukemia Group B Trial 9583 was supported, in part, by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B (Richard L. Schilsky, MD, Chairman). The research was also supported by Janssen Pharmaceutica Products, LP.

Presented in part at the American Society of Clinical Oncology annual meeting, San Francisco, CA, May 12-15, 2001.

The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2206-1025/$20.00

DOI: 10.1200/JCO.2004.06.037

ABSTRACT

Purpose
Antiandrogen withdrawal (AAWD) results in a prostate-specific antigen (PSA) response (decline in PSA level of ≥ 50%) in 15% to 30% of androgen-independent prostate cancer (AiPCa) patients. Thereafter, adrenal androgen ablation with agents such as ketoconazole (K) is commonly utilized. The therapeutic effect of AAWD alone was compared with simultaneous AAWD and K therapy.

Patients and Methods
AiPCa patients were randomized to undergo AAWD alone (n = 132), or together with K (400 mg orally [po] tid) and hydrocortisone (30 mg po each morning, 10 mg po each evening; n = 128). Patients who developed progressive disease after AAWD alone were eligible for deferred treatment with K.

Results
Eleven percent of patients undergoing AAWD alone had a PSA response, compared to 27% of patients who underwent AAWD and simultaneous K ($P = .0002$). Objective responses were observed in 2% of patients treated with AAWD alone compared to 20% in patients treated with AAWD/K ($P = .02$). There was no difference in survival. PSA and objective responses were observed in 32% and 7%, respectively, of patients receiving deferred K, and were more common in patients with prior AAWD response. Treatment with K was well tolerated, and resulted in a decline in adrenal androgen levels, which rose at the time of disease progression.

Conclusion
K has modest activity in AiPCa patients, while AAWD alone has minimal activity. Adrenal androgen levels fall with treatment with K and then climb at the time of progression, suggesting that progressive disease while on K may be due to tachyphylaxis to the adrenolytic properties of K.

J Clin Oncol 22:1025-1033.

INTRODUCTION

Prostate cancer is the most common cancer in men and will account for more than 30,000 deaths in 2003 [1]. The vast majority of deaths are due to the development of metastatic disease unresponsive to androgen deprivation. Androgen deprivation, with gonadal androgen suppression with or without antiandrogen, has been the standard of care in patients with metastatic disease since the 1940s [2] and is being increasingly utilized in patients with less advanced disease [3].

The benefits of adding an antiandrogen such as flutamide or bicalutamide to gonadal androgen suppression at the time of initiating androgen deprivation (early use) are modest at best [4]. The late addition of an antiandrogen after initial failure of androgen deprivation (late use) seems to result in prostate-specific antigen (PSA) declines, and in some cases, objective responses [5]. Thus, at one point or another, most patients with advanced prostate cancer will be treated with an antiandrogen. Despite androgen deprivation, including the use of an antiandrogen, most patients will experience disease progression. For patients with progressive disease, despite androgen deprivation, withdrawal of antiandrogen has been

reported to result in a decline in PSA level of ≥ 50% in 15% to 30% of patients [6-8]. The mechanism of this phenomenon has been attributed to alterations in the androgen signaling cascade, including mutations in the androgen receptor (AR), resulting in the antiandrogen behaving as an activator, not inhibitor, of the AR [9].

The duration of decline in PSA observed with antiandrogen withdrawal (AAWD) is brief, with a median duration of 3.5 to 5.0 months [6-8], after which further therapy is generally required. The mechanism by which prostate cancer patients develop disease progression after AAWD is not understood, but it has been postulated that persistence of a clone of cells with partial or full sensitivity to testosterone might be provided a growth advantage by androgen produced by the adrenal glands. If this were the case, it could be anticipated that adrenal androgen suppression would demonstrate some anticancer activity in this setting. An early report suggested that the addition of aminoglutethimide (an adrenal steroid synthesis inhibitor) at the time of AAWD increased the percentage of patients with a decline in PSA over that which would be expected with antiandrogen alone [10].

Ketoconazole is an azole antifungal agent which exerts its clinical effect through the inhibition of cytochrome P450 14a-demethylase, a catalyst of the conversion of lanosterol to cholesterol. Ketoconazole has been in clinical use as an antifungal agent for more than 20 years. In its initial use as an antifungal agent, it was discovered that a proportion of men who used ketoconazole developed painful gynecomastia, which was later found to be due to the suppression of testicular and adrenal androgen production, and it was postulated that this adverse effect could be useful for prostate cancer therapy. Several trials have evaluated the use of ketoconazole in patients with androgen-independent prostate cancer (AiPCa), though most predated the use of PSA or an understanding of the AAWD syndrome [11-14]. Most recently, the use of ketoconazole after AAWD was reported in a trial of 48 patients, 30 (63%) of whom demonstrated a ≥ 50% decline in PSA response. The decline of ≥ 50% in PSA was comparable in patients who had initially responded to AAWD and in those who had not initially responded to AAWD at 65% *v* 40%, respectively. Toxicity was largely mild in these patients, consisting of grade 1 or 2 nausea, fatigue, edema, hepatoxicity, and rash [15].

It was hypothesized that the simultaneous addition of ketoconazole to AAWD would have additive anticancer activity, simultaneously targeting the stimulating effects of antiandrogen and adrenal androgens. Hence, the principal goals of this study were to prospectively evaluate and compare the effect of AAWD alone on PSA levels, compared with simultaneous AAWD and ketoconazole therapy. In addition, the effect of ketoconazole used in patients whose cancer had progressed after AAWD was also evaluated.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed adenocarcinoma of the prostate with progressive metastatic disease, as defined below, despite anorchid testosterone levels (< 50 ng/mL). Androgen deprivation therapy was required to include at least 4 weeks of ongoing therapy with an antiandrogen (flutamide, bicalutamide, or nilutamide). Ongoing gonadal androgen ablation with a luteinizing hormone-releasing hormone analog or orchiectomy was required. For patients with measurable disease, progression was defined as a greater than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions. For patients with "bone only" disease, a PSA greater than 5 ng/mL, which had risen from baseline on at least two successive occasions at least 4 weeks apart was required. Patients were required to have had metastatic disease demonstrated on imaging at some point during their history, but were not required to have demonstrated metastases on imaging at the time of enrollment. Patients were excluded if they had received prior chemotherapy, immunotherapy, experimental therapy, or prior treatment with ketoconazole, aminoglutethimide, or corticosteroids if they had a Cancer and Leukemia Group B (CALGB) performance status of more than 2, total bilirubin level greater than 1.5× the upper levels of normal (ULN), or serum glutamic-oxaloacetic transaminase level greater than 3× ULN. Because of potential interactions with ketoconazole, no ongoing or concurrent use of terfenadine, astemizole, or cisapride was allowed. All participants signed an institutional review board–approved, protocol-specific, informed consent form in accordance with federal and institutional guidelines.

Treatment

After registration, patients were randomized to AAWD alone or AAWD + ketoconazole by the CALGB Statistical Center. This study was neither blinded nor placebo controlled. A conventional stratified random blocks design was used [16]. That is, within each stratum, patients were assigned to the available two treatments in blocks of treatment assignments so that an equal number of patients was assigned to each of the two treatment arms within each block. Randomization was stratified by four features that could potentially affect the likelihood of response, both to AAWD and/or ketoconazole therapy: (1) prior therapy with flutamide, bicalutamide, or nilutamide; (2) continuous or intermittent treatment; (3) initial or delayed antiandrogen therapy; and (4) imaging studies positive or negative for metastatic disease.

Patient registration, subsequent randomization and data collection were managed by the CALGB Statistical Center. Furthermore, data quality was ensured by careful

review of all data at the CALGB Statistical Center and by the study chairperson. Patients enrolled on the AAWD + ketoconazole arm received ketoconazole 400 mg tid po plus hydrocortisone 40 mg/d po (30 mg each morning and 10 mg every night) continuously until disease progression or unacceptable toxicity, as described below. Patients randomized to the AAWD-alone arm were required to cross over to treatment with ketoconazole on disease progression (see Response and Progression Criteria).

Eligible patients were evaluated with a medical history and physical examination at study entry and monthly thereafter. In addition to a complete medical history and physical examination at each visit, patients were evaluated for adverse events. No formal quality-of-life or pain assessment was undertaken. CBC, PSA, total bilirubin, alkaline phosphatase, asparate transaminase, creatinine, glucose, and lactate dehydrogenase (LDH) were checked at baseline and then monthly. An endocrine panel including androstendione, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), and testosterone was obtained at baseline, at 1 month after starting therapy, at 3 months after starting therapy, and at the time of disease progression. Blood samples were obtained between 8:00 AM and 10:00 AM. Plasma was isolated, frozen, and shipped for analysis at a central laboratory to determine androstendione, DHEAS, DHEA, and testosterone levels. A bone scan and computed tomography scan of the abdomen and pelvis were obtained at baseline. If imaging studies were positive at baseline, they were repeated every 3 months.

Replacement doses of hydrocortisone were continued as long as the patient was receiving ketoconazole. When the patient was no longer receiving ketoconazole, hydrocortisone was tapered by 5 mg every 3 days until completely discontinued. Antacids, H-2 blockers, and proton pump inhibitors were avoided but not explicitly prohibited. This study did not mandate that ketoconazole be taken on an empty stomach or with acidifying procedures. At each visit, toxicity was graded according to the National Cancer Institute common toxicity criteria (CTC, version 2.0) and recorded. In the event of grade 3 or higher hepatotoxicity or symptomatic peptic ulcer or gastritis, patients were removed from protocol treatment. Antiemetics other than corticosteroids were permitted. If grade 2 or 3 nausea persisted despite these measures, the patient was removed from therapy. Patients developing other grade 3 or higher toxicity had treatment held until toxicity resolved to grade 1 or better. Any patient developing grade 4 toxicity or grade 3 toxicity persisting for longer than 4 weeks, except as outlined previously, was removed from protocol treatment.

Response and Progression Criteria

This study was launched before publication of the Response Evaluation Criteria in Solid Tumors criteria or the PSA Consensus Criteria [17], so that a composite end point combining PSA changes with imaging changes was utilized. Therefore, for patients with measurable disease, a partial response was defined as a $\geq$ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions, together with a decline in PSA of $\geq$ 75%, measured at least twice at least 2 weeks apart, whereas a complete response was complete resolution of all visible disease, and normalization of PSA on at least two occasions at least 2 weeks apart. A complete response in patients with bone-only disease was defined as complete normalization of bone scan, again with a normalization of PSA, while a partial response in bone-only patients requires a greater than 75% decline in PSA with no new lesions on bone scan. Additionally, all patients had monitoring of PSA levels, and the percentage of patients with a decline in PSA of $\geq$ 50%, documented on at least two successive occasions, at least 4 weeks apart, was calculated per the PSA Consensus Criteria [17]. An intent-to-treat analysis was utilized. Patients who received less than 2 months of therapy for any reason (including progressive disease, toxicity, or withdrawal of consent) and who therefore did not have two sequential PSA values for response assessment, were nevertheless considered to be nonresponders. Progressive disease was defined by a PSA increase of $\geq$ 50% above nadir, on at least two successive occasions at least 1 month apart, with a minimum rise of 5 ng/mL [17]. Disease progression was also defined by new lesions on bone or computed tomography scan, or for patients with pre-existing measurable disease, a greater than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions. Survival was measured from the time of randomization to the time of death, and time to PSA progression was measured per Consensus Criteria [17].

Statistical Methods

The primary objective of this trial was to compare the response rates (composite end point, as defined above) of AAWD alone versus AAWD combined with ketoconazole and hydrocortisone. However, secondary objectives were to compare the percent of patients with a posttherapy decline in PSA of $\geq$ 50%, documented on at least two successive occasions, at least 4 weeks apart, per the PSA Consensus Criteria [17]. Secondary objectives were also to evaluate the posttherapy PSA decline in patients who received ketoconazole and hydrocortisone after developing progressive disease despite AAWD. The study also sought to correlate posttherapy decline in PSA of $\geq$ 50% PSA with survival, as well as to evaluate the prognostic value of several pretreatment patient characteristics. Finally, the study evaluated the relationship of pretreatment adrenal androgen levels, and changes in adrenal androgen levels with response to therapy and survival.

With 119 patients per arm, and a one-sided α of .05, the independent two-group binomial test had 80% power to

detect a difference in the percentage of patients with a partial or complete (composite) response from 25% in the AAWD group, to 40% in the AAWD + ketoconazole arm. Allowing for a 5% ineligibility rate, the target sample size was 250 patients.

The study was monitored by the CALGB Data Safety and Monitoring Board. Planned interim analysis used the Lan-DeMets analog of the O'Brien-Fleming sequential boundary to maintain the overall level of significance of .05 [18]. The Lans-DeMets stopping rule was applied to the composite response end point. At the final analysis, the α level was .045. An intent-to-treat approach was used in the analysis. Pearson χ^2 and Fisher's exact test were used to compare the two arms with regard to response rates (composite end point), objective response rates, and 50% decline in PSA [19]. Exact confidence intervals based on the binomial distribution were used to estimate 95% CIs for the response rates. The Kaplan-Meier product-limit method was used to estimate overall survival and PSA progression-free survival by the two arms [20], and the log-rank test was used to compare the two arms on these outcomes (overall survival and PSA progression-free survival). The proportional hazards model was used to assess important factors for predicting survival time adjusting on the stratification factors.

The relationship between overall survival and 50% decline in PSA from baseline was explored. To minimize "lead time bias," landmark analyses were performed at 4, 8, 12, and 16 weeks postrandomization [21]. This method selects a fixed time point after initiation of therapy as a "landmark" and excludes patients who died before reaching the landmark (eg, 8 weeks). Further, the patients alive at the landmark were classified as responders or nonresponders depending on their 50% decline in PSA before the landmark. In these analyses, survival duration was defined as the time between the landmark (eg, 8 weeks) and death. The relationship between survival duration, and PSA decline was examined. For the primary end point, a one-sided $\alpha = .05$ was used to compute the 95% CI and the P value. For the secondary objectives and analyses, tests were performed using a two-sided $\alpha = .05$.

Table 1. Baseline Characteristics

	AAWD (n = 132)	AAWD and Ketoconazole (n = 128)	Total (N = 260)
Age, years			
Median	71	72	72
Interquartile range	66-76	64-76	65-76
Race, % white	78	81	79
Sites of disease, %*			
Bone metastases	86	84	84
Measurable disease	31	40	35
Lymph node involvement	28	34	31
Lung metastases	5	6	5
Liver metastases	5	10	6
Lymph node metastases only	5	8	7
Performance status (0 to 1), %	93	93	93
Opioid analgesic use, %	30	28	29
Hemoglobin, g/dL			
Median	12.6	12.6	12.6
Interquartile range	11.7-13.3	11.1-13.6	11.6-13.5
PSA, ng/mL[1]			
Median	58	58	58
Interquartile range	17-162	20-137	20-151
Alkaline phosphatase, U/L			
Median	125	120	124
Interquartile range	91-239	85-225	90-235
LDH U/L			
Median	200	215	210
Interquartile range	171-405	189-409	176-405
Creatinine, mg/dL			
Median	1.0	1.1	1.1
Interquartile range	0.9-1.2	1.0-1.3	0.9-1.3
Prior therapy, %			
Flutamide	35.6	37.5	36.5
Bicalutamide	59.1	58.6	58.9
Nilutamide	5.3	3.9	4.6
Androgen deprivation, %			
Intermittent	12.9	16.4	14.6
Continuous	87.2	83.6	85.4
Initial therapy for advanced disease, %			
CAB	59.9	59.4	59.6
Monotherapy/ later antiandrogen	40.1	40.6	40.4

Abbreviations: AAWD, antiandrogen withdrawal; PSA prostate-specific antigen; LDH, lactate dehydrogenase; CAB, combined androgen blockade.
*Patients may have more than one metastasis.

RESULTS

Patient Characteristics

Two hundred sixty patients were enrolled onto this study. No consistent approach to screening patients for this trial was mandated. One hundred thirty-two were randomized to AAWD alone and 128 were randomized to AAWD and ketoconazole. Patient characteristics, including stratification variables, are summarized in Table 1. With regard to stratification variables, approximately 36% of patients (on both arms) received prior flutamide, 59% had prior bicalutamide, and 4% to 5% had received nilutamide. Approximately 15% of patients had received prior intermittent androgen deprivation, and approximately 60% had received initial combined androgen blockade (luteinizing hormone-releasing hormone analog plus antiandrogen). Imaging studies were positive for metastatic disease in 97% and 94% of patients in the AAWD and AAWD and ketoconazole arms, respectively. The two arms were similar regarding age, sites of disease, requirement for opioid analgesics, and a variety of pretreatment prognostic factors, including performance status, hemoglobin, PSA, alkaline phosphatase, LDH, and creatinine. The median age of patients in both arms was just older than 70 years, and 93%

Table 2. Summary of Clinical Outcome

	AAWD Alone (n = 132)	AAWD and Ketoconazole (n = 128)	*P*
PSA decline ≥ 50%			
No. of patients	15/132	34/128	.002
%	11	27	
95% CI	7% to 17%	20% to 35%	
Objective response rate			
No. of patients	1/41	10/50	.020
%	2%	20%	
95% CI	0.1% to 11%	11% to 32%	
Survival time, months			
Median	16.7	15.3	.936
95% CI	14.3 to 21.5	13.40 to 19.5	
Time to PSA progression in PSA responders, months			
Median	5.9	8.6	.063
95% CI	5.3 to 10.1	5.7 to 20.4	
No. of patients	15	34	

Abbreviations: AAWD, antiandrogen withdrawal; PSA, prostate-specific antigen.

had a performance status of 0 or 1. The median serum PSA levels at study entry was 58 ng/mL. Thirty-one percent of patients in the AAWD arm and 39% of patients in the AAWD and ketoconazole arms had measurable disease. More than 80% in both arms had bone metastases, and approximately one-third had lymph node involvement. Approximately 30% of patients were using opioid analgesics at the time of study entry.

Clinical Outcome

Relevant clinical outcomes, including PSA decline, objective response rate, overall survival, and time to PSA progression are summarized in Table 2. Overall, 15 (11%; 95% CI, 7% to 17%) of 132 patients undergoing antiandrogen withdrawal alone experienced a ≥ 50% decline in PSA. By contrast, 34 (27%; 95% CI, 20% to 35%) of 128 patients who underwent AAWD and received simultaneous ketoconazole had a ≥ 50% decline in PSA ($P = .002$). In patients with a ≥ 50% decline in PSA, the subsequent median time to PSA progression was 5.9 months (95% CI, 5.3 to 10.1 months) and 8.6 months (95% CI, 5.7 to 20.4 months) in the AAWD alone and AAWD and ketoconazole arms, respectively (log-rank $P = .063$). Figure 1 demonstrates the overall PSA progression-free survival by treatment arm for those patients who had a 50% decline in PSA. Objective responses in measurable disease were observed in 1 (2%; 95% CI, 0.13% to 11%) of 41 of patients treated with AAWD alone, compared with 10 (20%; 95% CI, 11% to 32%) of 50 in the AAWD and ketoconazole arm ($P = .02$). While no longer currently in use, when the composite end points described were applied, 8 (6%) of 132 of patients treated with AAWD had a response, compared with 22

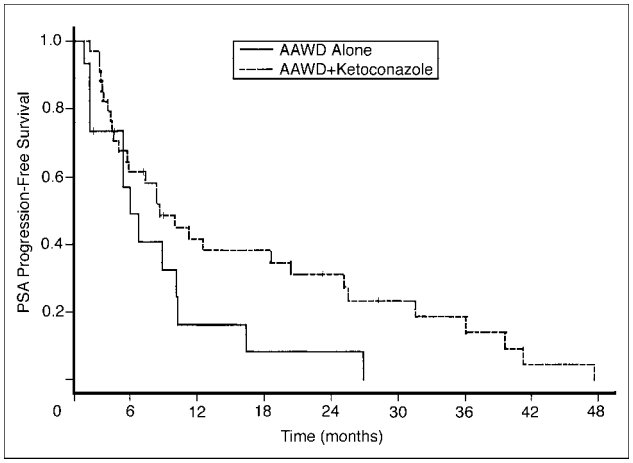

Fig 1. Overall prostate-specific antigen (PSA) progression-free survival by treatment arm in patients with 50% decline in PSA. AAWD, antiandrogen withdrawal.

(17%) of 128 of patients on the AAWD/ketoconazole arm (one-sided $P = .004$).

Eighty-two percent of patients (108 of 132) treated with AAWD alone ultimately received "deferred" ketoconazole/hydrocortisone therapy. Twenty-four patients assigned to initial AAWD alone never received deferred ketoconazole for a variety of reasons, including disease progression and withdrawal of consent. Of the 108 patients receiving deferred ketoconazole, a decline in PSA of ≥ 50% was observed in 35 (32%) of 108 patients. An objective response was seen in 3 (7%) of 41 patients treated with AAWD followed by deferred ketoconazole. Although the study was not designed to compare the aggregate PSA declines and objective responses in patients treated with simultaneous versus sequential AAWD and ketoconazole, there did not seem to be an advantage of either approach over the other. In aggregate, 40 (30%) of 132 patients treated with AAWD followed by ketoconazole had a PSA decline of ≥ 50% compared with 34 (27%) of 128 of patients treated with simultaneous AAWD and ketoconazole. The median survival time was 16.7 months (95% CI, 14.3 to 21.5 months) in the AAWD-alone arm, and 15.3 months (95% CI, 13.4 to 19.5 months) in the group of patients who received simultaneous AAWD and ketoconazole therapy (two-sided $P = .936$; Fig 2).

For those patients receiving sequential AAWD followed by ketoconazole, prior PSA "response" (decline of ≥ 50%) after AAWD seemed to be associated with a higher likelihood of PSA response to subsequent ketoconazole. Overall, 35 patients had a PSA response when treated with deferred ketoconazole. Ten of these PSA responses occurred in the group of 15 patients who had obtained a prior PSA response to AAWD (10 of 15; 67%), whereas an additional 25 patients had a response to deferred ketoconazole from among a group of 117 patients (25 of 117; 21%) who had failed to achieve a PSA response after AAWD.

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