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Original Articles

KETOCONAZOLE RETAINS ACTIVITY IN ADVANCED PROSTATE CANCER PATIENTS WITH PROGRESSION DESPITE FLUTAMIDE WITHDRAWAL

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ABSTRACT

Purpose: We tested the hypothesis that certain patients with hormone refractory prostate cancer retain hormonal sensitivity even after progression following antiandrogen withdrawal. The efficacy of ketoconazole and hydrocortisone in this patient population was evaluated.

Materials and Methods: A total of 50 consecutive patients with advanced prostate cancer received ketoconazole and hydrocortisone at progression after antiandrogen withdrawal. Prostate specific antigen (PSA) response was defined as greater than a 50% decrease in PSA from baseline that was maintained for at least 8 weeks.

Results: Overall, of 48 evaluable patients 30 (62.5%, 95% confidence interval 47.3 to 76.1%) had greater than a 50% decrease in PSA, while 23 (48%) had greater than an 80% decrease. The median duration of response was 3.5 months but 23 of 48 patients continue to exhibit a response, ranging from 3.25 to 12.75 or more months. The ketoconazole response rate in patients with no response to prior antiandrogen withdrawal was not different from that in patients with such a response (65 versus 40%, $p = 0.35$). Toxicity was mild. Grade 1 or 2 nausea, fatigue, edema, hepatotoxicity and rash occurred in 10.4 (5 of 48), 6.25, 6.25, 4.2 and 4.2% of patients, respectively, and anorexia occurred in 2%.

Conclusions: Failure to respond to antiandrogen withdrawal does not identify patients with truly hormone refractory disease. Ketoconazole retains significant activity in this setting and is extremely well tolerated.

KEY WORDS: prostate-specific antigen, prostatic neoplasms, ketoconazole, flutamide, neoplasm metastasis

Until recently patients with advanced prostate cancer and failure of combined androgen blockade therapy were considered to have hormone refractory disease. A common belief was that secondary hormonal maneuvers, particularly those aimed at adrenal androgen deprivation, while of use in patients treated only with gonadal androgen deprivation, were unlikely to be efficacious for those already on combined androgen blockade.[1,2] However, the unexpected antitumorigenic activity manifested by the withdrawal of antiandrogens[3–6] has prompted a reexamination of the prior belief that other hormonal maneuvers done after combined androgen blockade are not likely to be of use. It is now apparent that tremendous heterogeneity exists in the population with hormone refractory prostate cancer, and that some cases previously labeled as resistant to hormonal therapy may, in fact, retain a certain degree of hormonal sensitivity.[7] To test the hypothesis that certain hormone refractory cases retain hormonal sensitivity even after progression following antiandrogen withdrawal, we treated 50 patients with progressive prostate cancer after combined androgen blockade, and following flutamide withdrawal with ketoconazole and hydrocortisone. To our knowledge this is the first report of the use of ketoconazole in patients previously treated with an antiandrogen and after antiandrogen withdrawal.

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Editor's Note: **This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1478 and 1479.**

PATIENTS AND METHODS

A total of 50 consecutive patients with histologically confirmed metastatic prostate cancer that had become hormone refractory received treatment with ketoconazole and hydrocortisone. To be considered for this therapy patients had to have progressive disease on combined androgen blockade, undergone antiandrogen withdrawal and have progressive disease after antiandrogen withdrawal. Progressive disease was defined by objective evidence of disease progression on any imaging study or at least 2 consecutive prostate specific antigen (PSA) levels at least 2 weeks apart, each of which demonstrated greater than a 50% increase above the nadir level achieved with the most recent hormonal manipulation. In addition to a 50% increase in PSA level, an arbitrary minimum PSA increase of 2 ng./ml. was required to diagnose progressive disease. Prior therapy with aminoglutethimide, ketoconazole or any investigational agent, chemotherapy or immunotherapy was not permitted.

On day 1 of treatment a serum PSA (Tandem-R† assay)

† Hybritech Inc., San Diego, California.

and baseline liver function tests (aspartate aminotransferase, alanine aminotransferase and bilirubin) were obtained. When appropriate, imaging studies were performed before therapy. Treatment consisted of 400 mg. oral ketoconazole every 8 hours, and 20 mg. oral hydrocortisone each morning and 10 mg. orally each evening. Patients were encouraged to take the medications on an empty stomach unless this resulted in nausea or gastrointestinal upset, in which case the ketoconazole was taken at mealtime. Antacids and hydrogen blockers were discouraged but not prohibited, and an effort was made to have patients time the ketoconazole dosage so that it was taken several hours before the next antacid or hydrogen blocker dose. Because of potential adverse drug interactions with ketoconazole, concurrent treatment with astemizole, terfenadine or cisapride was prohibited. PSA, alanine aminotransferase, aspartate aminotransferase and bilirubin were measured once a month. Patients remained on this therapy until there was evidence of progressive disease or toxicity precluded further treatment. When appropriate, imaging studies were repeated. However, since the majority of patients were asymptomatic, in an effort to contain unnecessary costs routine imaging studies were not obtained unless warranted by symptoms or rapid PSA progression. A PSA response to ketoconazole and hydrocortisone therapy was defined as greater than a 50% decrease in PSA from baseline that lasted for at least 8 weeks (a minimum of 2 consecutive determinations at least 4 weeks apart).

The duration of PSA response was measured from the first PSA that decreased to less than 50% of baseline to the first PSA that increased to greater than 50% above the nadir value. Actuarial survival and freedom from PSA progression curves were calculated with the method of Kaplan and Meier. The effect of prior response to antiandrogen withdrawal on the likelihood of response to ketoconazole was analyzed with the log rank test.

RESULTS

Patient characteristics are listed in the table. Median age was 74 years (range 51 to 87) and median serum PSA before initiating therapy was 62 ng./ml. (range 6.7 to 3,190). Of the 50 patients 48 had sufficient followup after initiation of treatment with ketoconazole to be considered evaluable (that is they received 8 weeks of therapy to allow a minimum of 2 PSA measurements at least 4 weeks apart) and they are the basis of this report. Patients who withdrew from treatment before receiving 8 weeks of therapy because of rapid disease progression (1) or early toxicity (3) were not censored and were considered evaluable. Of the 48 evaluable patients 45 had undergone prior androgen deprivation for advanced prostate cancer (positive nodes and/or metastatic disease), while 3 had received hormonal therapy for serological (PSA) progression after definitive local therapy. Prior combined androgen blockade included flutamide in 47 patients and bicalutamide in 1. All 48 patients subsequently underwent antiandrogen withdrawal because of progressive disease. Five of the 48 patients had obtained a prior response to antiandrogen withdrawal, which was somewhat less than our prior experience.[6]

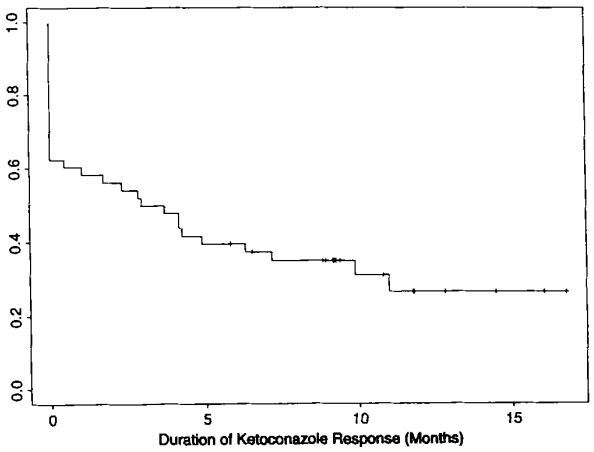
Patient characteristics

No. evaluable pts.	48	
Median (range):		
Age (yrs.)	74	(51–87)
Pretreatment PSA (ng./ml.)	79	(6.7–3,190)
Alkaline phosphatase	131	(59–3,090)
Hemoglobin	12.6	(4.8–15.1)
Creatinine	1.05	(0.6–1.9)
Lactic dehydrogenase	193	(124–506)
No. extent of disease:		
N+M0	11	
M+	34	
PSA only (N0M0)	3	
No. prior therapy:		
Flutamide	47	
Bicalutamide	1	
Prior response to antiandrogen withdrawal	5	

Overall, 30 of 48 patients (62.5%, 95% confidence interval 47.3 to 76.1%) obtained a PSA response (greater than 50% decrease in PSA for at least 8 weeks measured at least twice on 2 separate occasions at least 4 weeks apart), while 37 (77%) experienced a decrease of 50% or more for at least 4 weeks in duration and 23 (48%, 95% confidence interval 33.3 to 62.8%) had an 80% or greater decrease for at least 8 weeks. Serum PSA decreased to 0.3 ng./ml. or less in 5 patients (10%) for 3+, 3.5, 4.5+, 7+ and 10+ months, respectively. These patients had pre-ketoconazole PSA values of 22, 47.4, 15, 488 and 6.7 ng./ml., respectively. For all patients the median PSA decrease was 79.5% (range 0 to 99). Median PSA response duration was 3.5 months, although the range was wide (2 to 12+). Median PSA progression-free survival for all patients was 4 months (see figure) and median survival of all patients had not been reached at 6+ months. Routine followup imaging studies, formal quality of life assessment or pain assessment was not done, since most patients were asymptomatic. Of 16 patients (33%) with bone pain attributable to prostate cancer before therapy 8 (50%) experienced improvement in pain with therapy, although this was by patient self-report without use of a formal pain assessment instrument. In the absence of a randomized trial the impact of a placebo effect on improvement in subjective symptoms cannot be determined.

Of the 48 patients 25 remained on therapy 3.25 to 12.75 months after treatment initiation, while 23 discontinued therapy with ketoconazole due to progressive disease (16) and toxicity (7). Two of 5 patients (40%) with a response to prior antiandrogen withdrawal subsequently obtained a PSA response to ketoconazole, compared to 28 of 43 (65%) with no response to prior antiandrogen withdrawal. The proportions of responses were not statistically significant ($p = 0.35$).

Toxicity was moderate. The most common toxicity was gastrointestinal upset and, more specifically, nausea. Grade 1 or 2 nausea occurred in 5 of 48 patients (10.4%). Other toxicities included grade 1 or 2 fatigue, edema, hepatotoxicity and rash in 6.25, 6.25, 4.2 (2 of 48) and 4.2% of the patients, respectively, and anorexia in 2%. One episode of grade 4 congestive heart failure was observed but a causal relationship with ketoconazole therapy could not be determined. The patients who withdrew from treatment because of toxicity



Actuarial Kaplan-Meier plot of probability of freedom from PSA progression after treatment with ketoconazole and hydrocortisone.

had hepatocicity (2), nausea and/or anorexia (3), congestive heart failure (1) and rash with edema (1).

DISCUSSION

We demonstrated a surprisingly high PSA response rate (62.5%) when patients with progressive prostate cancer after combined androgen blockade and antiandrogen withdrawal were subsequently treated with adrenal androgen suppression with ketoconazole and hydrocortisone. Unlike any prior study with ketoconazole to our knowledge, we showed that sensitivity to this agent is retained in patients previously treated with adrenal androgen blockade with an antiandrogen.

Ketoconazole is a substituted imidazole that suppresses testicular and adrenal steroidogenesis by inhibition of the conversion of cholesterol to pregnenolone. Because ketoconazole is a potent inhibitor of all adrenal steroid synthetic pathways, replacement doses of hydrocortisone may be required. The efficacy of corticosteroids in the treatment of advanced prostate cancer has long been appreciated and was recently reviewed.[7] These data indicate that the impact of steroids on PSA response rate, measures of quality of life and, possibly, objective responses must be remembered when considering regimens, such as ketoconazole, that include corticosteroids, even at replacement (physiological) doses. However, it is unlikely that our results with ketoconazole and hydrocortisone can be explained by the effect of steroids alone, since use of corticosteroids as a single agent in patients with progression after antiandrogen withdrawal has been reported to yield a PSA response rate of only 20%.[7] Regardless of the relative contribution of hydrocortisone to our results, we believe that our relatively high response rate is provocative and warrants confirmatory studies.

The efficacy of ketoconazole in patients with advanced prostate cancer has long been appreciated. Overall, objective partial responses have been reported in 16% of patients, with stable disease (National Prostatic Cancer Project criteria) noted in 30%.[1] Our response rate is considerably greater than that previously reported with ketoconazole, although in some earlier studies corticosteroids were not used.[8-11] However, it must be emphasized that many prior reports did not use PSA response criteria, and most contemporary series on any treatment of hormone refractory prostate cancer have noted PSA response rates that were considerably greater than objective response rates. While nearly all of our patients had advanced (nodal or metastatic) disease, only a small percentage were symptomatic, so that routine imaging studies, quality of life assessments and pain assessment were not formally done.

Limited data on PSA responsiveness to ketoconazole exist.[12-14] Other than our series, to our knowledge none of these trials has included patients who had been previously treated with an antiandrogen, let alone with antiandrogen withdrawal. Gerber and Chodak observed a PSA decrease (of any magnitude) in 12 of 15 patients (80%), with a median PSA decrease of 49% in those with a response.[12] Trump et al observed objective responses in 5 of 36 patients (14%), with a PSA decrease of greater than 80% in 4.[13] Seven of 21 patients (33%) reported on by Muscato et al had greater than a 90% decrease in PSA.[14]

The mechanism of the antiandrogen withdrawal syndrome is not fully understood but it is hypothesized that a mutation in the hormonal binding domain of the androgen receptor is responsible for the capacity of antiandrogens to act as partial agonists.[15,16] However, in vitro some mutant androgen receptors continue to demonstrate androgen sensitivity as well. We postulated that it is likely that a population of androgen receptors (wild type or mutant) remains in vivo that retain sensitivity to androgenic stimulation, so that suppression of adrenal androgen production in patients who had undergone prior antiandrogen withdrawal might result in a clinical benefit. Indeed, this was the case when our patients were treated with ketoconazole and hydrocortisone.

In addition to ketoconazole, adrenal androgen suppression can be achieved with other agents, including aminoglutethimide and perhaps glucocorticoids. While many previous reports detailed the use of these agents, to our knowledge their use during or after antiandrogen withdrawal has only recently been reported. In the first such study adrenal androgen deprivation consisted of aminoglutethimide and hydrocortisone therapy with a reported 48% PSA response rate,[17] which was considerably greater than that reported for flutamide withdrawal alone.

It is noteworthy that in our series patients with no response initially to the discontinuation of antiandrogen were just as likely to respond to subsequent therapy with ketoconazole as those who had a prior response. This finding suggests that failure to respond to antiandrogen withdrawal does not reliably identify patients with true hormonal resistance, although the small number of patients involved makes it impossible to draw definitive conclusions. In addition, compared to our previous series,[6] a considerably smaller percentage of patients had previously responded to antiandrogen withdrawal (10 versus 15%), raising the possibility of inadvertent patient selection bias. Furthermore, none of our cases was primarily refractory to androgen deprivation. It could be postulated that such patients, while relatively rare, have truly hormonal refractory disease and it is possible that they would be unlikely to respond to ketoconazole.

We are encouraged by the relatively high proportion of our patients who obtained a PSA response and by the duration of PSA decrease that we observed, since a decrease in PSA has been advocated as a surrogate marker for survival in patients with hormone refractory prostate cancer.[18,19] Nonetheless, while it seems clear that greater than a 50% (or in some series 75%) decrease in PSA appears to define patients with improved survival, controversy remains as to the validity of PSA decrease as a surrogate marker of response or survival.[20] In our patients the median survival of responders compared to nonresponders was not statistically different, although our short followup and small number of events (7) compounded with innumerable permutations for subsequent therapies make survival difficult to evaluate. A recently activated multicenter phase III trial addressing the impact of ketoconazole and hydrocortisone after antiandrogen withdrawal may shed further light on the mechanisms of response and define more precisely the efficacy of this regimen.

Ketoconazole is particularly attractive because of its favorable toxicity profile and ease of use. All medications are given orally and patients need only monthly laboratory followup. The most frequent toxicity was nausea, which was generally mild and occurred in 10% of the patients. The remaining toxicities were primarily grades 1 and 2, and in all cases occurred in 6% or fewer patients. For these reasons, while there is no evidence that there is a survival advantage to treatment with ketoconazole, this regimen is nonetheless well suited for patients with progressive prostate cancer (generally by PSA criteria) who are asymptomatic, and unwilling or not eligible to be treated with protocol therapy or more aggressive means. The ease and efficacy (as measured by PSA decreases) of this regimen must be balanced with a lack of survival data and the relatively high cost of ketoconazole.

CONCLUSIONS

During the last 3 to 4 years dramatic changes in the approach to patients with hormone refractory prostate cancer have occurred. It is clear that individuals who have been treated with combined androgen blockade and antiandrogen withdrawal can benefit from additional hormonal maneu-

vers, such as ketoconazole and hydrocortisone, although the impact of these therapies on survival remains unknown. The high PSA response rate observed with ketoconazole and replacement doses of hydrocortisone, coupled with the extremely favorable toxicity profile make this an attractive regimen. Whether a given patient will respond to subsequent hormonal maneuvers cannot be predicted but a reasonable approach is to consider more aggressive therapy for those with apparently primarily hormone refractory disease and those with a rapidly growing tumor burden or progressive symptomatology.

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