LOW DOSE KETOCONAZOLE WITH REPLACEMENT DOSES OF HYDROCORTISONE IN PATIENTS WITH PROGRESSIVE ANDROGEN INDEPENDENT PROSTATE CANCER

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ABSTRACT

Purpose: High-dose (400 mg.) oral ketoconazole 3 times daily with replacement doses of hydrocortisone has become a standard treatment option for patients with advanced prostate cancer which progresses after androgen deprivation. However, toxicity can hinder the ability to deliver treatment and the cost of the regimen can be substantial. Therefore, a prospective phase II study was conducted to assess the efficacy and safety of a regimen of low dose (200 mg.) oral ketoconazole 3 times daily with replacement doses of hydrocortisone in men with androgen independent prostate cancer.

Materials and Methods: The study included 28 patients with progressive prostate cancer despite anorchid levels of testosterone and ongoing testicular androgen suppression. Treatment consisted of low dose ketoconazole and replacement doses of oral hydrocortisone (20 mg. every morning and 10 mg. at bedtime). At the time of disease progression patients were treated with high dose ketoconazole and continued on the same dose of hydrocortisone. Adrenal androgen levels were measured, and baseline and followup levels correlated with clinical outcome.

Results: Overall, 13 (46%) of 28 patients had a prostate specific antigen decrease of more than 50% (95% confidence interval 27.5% to 66.1%). Median duration of prostate specific antigen decrease for all responders was 30+ weeks and 5 patients continue to exhibit a response, ranging from 36+ to 53+ weeks. In general, therapy was well tolerated. There were no grade 4 toxicities. Grade 3 toxicities included hepatotoxicity in 1 patient and depression in 2. The most common toxicities were nausea (29% grades 1 and 2), dry skin (18% grade 1) and fatigue (14% grade 1). Four (14%) patients discontinued low dose ketoconazole due to toxicities. Of the 16 patients who received high dose ketoconazole after disease progression with low dose ketoconazole, 3 were removed from treatment due to toxicity and no patient responded to high dose ketoconazole. There was no difference in the distribution of pretreatment endocrine values between responders and nonresponders, and the magnitude of change in adrenal androgen levels was not associated with response to therapy, although a potential association could easily have been missed due to small sample size.

Conclusions: The regimen of low dose ketoconazole with replacement doses of hydrocortisone is well tolerated and has moderate activity in patients with progressive androgen independent prostate cancer.

KEY WORDS: prostatic neoplasms, ketoconazole, hydrocortisone

It has been reported that in some patients with progressive androgen independent prostate cancer some cells retain some degree of hormonal sensitivity and can be stimulated by adrenal androgens.[1] In this context it is of note that ketoconazole, a systemic antifungal agent, is a clinically useful antagonist of adrenal steroidogenesis. Ketoconazole inhibits cytochrome P-450 and effectively suppresses testicular and adrenal androgen production.[2,3] Interestingly, it may also have direct cytotoxic effects on prostate tumor cells.[4] Originally used as a therapy for advanced prostate cancer before the advent of prostate specific antigen (PSA) as a tumor marker, high dose (400 mg.) oral ketoconazole 3 times daily was reported to produce objective clinical responses in approximately 10% of patients with androgen independent prostate cancer and stable disease in another 35%.[5,6] More recently, we have reported that ketoconazole has moderate activity in patients with androgen independent prostate cancer with durable PSA decrease of greater than 50% observed in 63% of patients who had previously undergone antiandrogen withdrawal[7] and in 55% of those undergoing simultaneous antiandrogen withdrawal.[8] While toxicity is generally mild to moderate, up to 20% of patients experience grades 1 and 2 nausea and emesis,[7,8] requiring dose reduction or cessation of the drug. In addition, 20% of patients will have minor skin toxicity, 10% grade 1 or 2 fatigue and 10% reversible grade 1 or 2 hepatotoxicity.[7,8] Patients with unacceptable toxicity are frequently treated empirically with a dose reduction of oral ketoconazole by half to 200 mg. 3 times daily.

High dose ketoconazole with replacement doses of hydrocortisone has become a commonly used treatment option for patients with disease progression after androgen deprivation due to its efficacy and relative ease of administration.[9] While the mechanism of action of high dose ketoconazole is not fully understood, this dose of ketoconazole has been shown to suppress adrenal androgen production.[5] However, response to treatment with ketoconazole has to date not been shown to correlate with suppression of adrenal androgen levels. LDK

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may be an attractive alternative to high dose ketoconazole. Toxicity with high dose ketoconazole can limit the ability to deliver treatment. Anecdotal evidence suggests that low dose ketoconazole is better tolerated, although this question has not been addressed in a rigorous fashion. In addition, the cost of the high dose regimen is substantial, and a low dose regimen would bring down costs. While clinical responses to low dose ketoconazole have been reported,[10] the low dose has not been systematically studied.

Given anecdotal evidence suggesting that low dose ketoconazole has reduced toxicity while maintaining efficacy, a prospective phase II study of this regimen in patients with androgen independent prostate cancer was conducted. Replacement doses of oral hydrocortisone (20 mg. every morning, 10 mg. at bedtime) were also administered, since hydrocortisone as a single agent is known to have activity in advanced prostate cancer and we wished to compare the efficacy of low dose with historical high dose ketoconazole data. In addition, there were no compelling data available to suggest whether adrenal insufficiency occurred at this dose of ketoconazole,[11] so that concerns regarding patient safety mandated the use of replacement hydrocortisone.

PATIENTS AND METHODS

Eligible patients had histologically confirmed adenocarcinoma of the prostate with progressive disease, as defined by the Prostate Specific Antigen Working Group Consensus Criteria.[12] All patients had previously undergone antiandrogen withdrawal for a minimum of 8 weeks. Any other hormonal therapies, including any dose of megestrol acetate, finasteride or systemic corticosteroids, had to have been discontinued at least 4 weeks before study enrollment. Required laboratory parameters included total bilirubin and aspartate transaminase less than 2 times the upper limit of normal. All patients had a Karnofsky performance status of 60% or greater and a life expectancy of at least 3 months. Prior therapy with 1 nonchemotherapeutic, nonhormonal investigational agent was permitted, provided it had been discontinued at least 30 days before study enrollment. Exclusion criteria were prior treatment with chemotherapy, aminoglutethimide, ketoconazole or herbal products such as saw palmetto or PC-SPES. Given drug interactions with ketoconazole, the concurrent use of terfenadine, astemizole or cisapride was not allowed. Radiation therapy within 28 days or radiopharmaceutical therapy within 60 days was not permitted.

Eligible patients were evaluated with a history and physical examination at study entry and monthly thereafter. In addition to a complete history and physical examination at each visit, patients were evaluated for adverse events. Formal quality of life or pain assessment was not performed. Complete blood count, PSA, total bilirubin, alkaline phosphatase, aspartate transaminase, creatinine and glucose were measured at baseline and then monthly. An endocrine panel including androstendione, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA) and testosterone was obtained at baseline and after 2 months of treatment. A bone scan and, if clinically indicated, computerized tomography of the abdomen and pelvis were obtained at baseline. If imaging studies were positive at baseline they were repeated every 3 months.

Patients received 200 mg. ketoconazole orally 3 times daily on an empty stomach along with replacement doses of oral hydrocortisone (20 mg. every morning with food and 10 mg. at bedtime with food). At the time progressive disease was documented as defined by the consensus criteria,[12] the dose of ketoconazole was increased to 400 mg. orally 3 times daily and continued until disease progression. 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.

At each visit toxicity was graded according to the National Cancer Institute common toxicity criteria (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. If nausea was reported, the patient was instructed to take ketoconazole with meals. Antiemetics other than corticosteroids were permitted. If grade 2 or 3 nausea persisted despite these measures, the patient was removed from therapy. Patients with other grade 3 or higher toxicity had treatment withheld until toxicity resolved to grade 1 or better. Any patient with grade 4 toxicity or grade 3 toxicity persisting for more than 4 weeks (except as outlined previously) was removed from protocol treatment.

The primary end points of this prospective phase II study were to determine the response proportion and duration of response to low dose ketoconazole and replacement doses of hydrocortisone in patients with progressive prostate cancer despite androgen deprivation. PSA responses were defined according to the consensus criteria.[12] The secondary objectives of this trial were to determine the toxicity profile of this regimen, to assess the use of increasing ketoconazole to high dose in patients with disease progression on low dose and to correlate response to treatment with suppression of adrenal androgen levels.

The study included 28 patients. This sample size was sufficient to detect a response frequency of at least 40% compared to the null hypothesis of 20% with power of approximately 80% (0.79). Descriptive statistics were used to characterize the patient and disease features as well as toxicity. Nonparametric Spearman correlation was calculated to evaluate the association between adrenal androgens. The change in endocrine measurements from before treatment to 2 months after low dose ketoconazole was analyzed using the nonparametric Wilcoxon test for paired data. The distributions of adrenal androgens for responders and nonresponders were compared using the Mann-Whitney test.

RESULTS

Patient characteristics. A total of 28 patients with androgen independent prostate cancer was treated and all were on study at least 2 months and were evaluable for toxicity and response. Pretreatment patient characteristics are listed in table 1. Median patient age was 76 years (range 49 to 91). Of the patients 17 had bone only disease, 3 had bone and soft tissue disease, and 8 had PSA elevation as the only manifestation of progressive disease. At the start of therapy median PSA was 48.9 ng./ml. (range, 6.3 to 557.8), alkaline phosphatase 97 units/l. (range, 61 to 489), hemoglobin 13.1 gm./dl.

TABLE 1. *Pretreatment patient characteristics*

Age:	
Median	76
Range	49–91
No. extent of disease:	
PSA only	8
Bone only	17
Bone and soft tissue	3
PSA (ng./ml.):	
Median	48.9
Range	6.3–557.8
Alkaline phosphatase (units per l.):	
Median	97
Range	61–489
Hemoglobin (gm./dl.):	
Median	13.1
Range	10.1–14.3
Performance status:	
Median	0
Range	0–1

(range 10.1 to 14.3) and Eastern Cooperative Oncology Group performance status 0 (range, 0 to 1).

Clinical outcome. Overall, 13 (46%) of 28 patients had a PSA decrease of more than 50% (95% confidence interval 27.5%–66.1%). PSA responses were seen regardless of distribution of disease, although proportionately more PSA decreases were seen in patients with PSA only disease. PSA decreases of greater than 50% were seen in 6 (35%) of 17 patients with bone only disease, 1 (33%) of 3 with bone and soft tissue disease, and 6 (75%) of 8 patients with PSA elevation only. No responses were observed on bone scans or CT. Median duration of PSA decrease for all responders was 30+ weeks and 5 patients continued to exhibit a response ranging from 36+ to 53+ weeks. In 16 patients disease was unresponsive to low dose ketoconazole and the ketoconazole dose was increased to 400 mg. orally 3 times daily. Of these 16 patients 3 were taken off high dose ketoconazole due to toxicity and the remaining 13 did not respond to high dose ketoconazole. However, 2 patients remain on high dose ketoconazole with stable disease at 16+ and 19+ weeks.

Toxicity. Toxicity following low dose ketoconazole for all 28 patients is listed in table 2. In general, therapy was well tolerated. There were no grade 4 toxicities. Grade 3 toxicities included hepatotoxicity in 1 patient and depression in 2. The most common toxicities were grades 1 and 2 nausea (29%), grade 1 dry skin (18%) and grade 1 fatigue (14%). Four patients (14%) discontinued low dose ketoconazole due to persistent grade 2 nausea (1), grade 3 depression (2) and grade 3 hepatotoxicity (1). High dose ketoconazole was discontinued due to persistent grade 2 nausea in 2 patients and grade 2 gastric ulcer with grade 1 gastrointestinal bleeding in 1.

Adrenal androgen levels. Adrenal androgen (androstenedione, DHEA, and DHEAS) levels were measured at baseline and after 2 months of treatment (table 3). The baseline DHEA value significantly correlated with androstenedione ($p = 0.02$) and DHEAS ($p = 0.002$). There was no significant difference in the baseline endocrine values between responders and nonresponders but there was a significant decrease in all 3 parameters after 2 months of therapy. Median change was −0.49 ng./ml. (range −1.98, 0.02) in androstenedione, −1.4 ng./ml. (range −5.2, −0.3) in DHEA and −327.1 ng./ml. (range −1318.9, −23.0) in DHEAS. However, the degree of adrenal androgen suppression was not associated with response nor was the degree of suppression predicted by response to low dose ketoconazole.

DISCUSSION

A PSA response proportion of 46% was demonstrated in this prospective trial of low dose ketoconazole with replacement doses of hydrocortisone. While the use of PSA as an intermediate marker of response and outcome remains controversial, an emerging body of literature supports the use of a greater than 50% decrease in PSA as an intermediate marker of survival[13–16] in patients with androgen independent prostate cancer treated with secondary hormones, cytotoxic agents or suramin. Although it is not appropriate to compare the results for this trial directly with the results of retrospective series using high dose ketoconazole with hydrocortisone replacement, the PSA response proportion observed seemed close to the historic high dose ketoconazole response rate of 50%. Furthermore, increase to high dose ketoconazole failed to "capture" any patients who had progressive disease despite low dose ketoconazole. While this observation clearly does not demonstrate equivalence between low dose ketoconazole and high dose ketoconazole, it suggests that the mechanism of action is unlikely to be significantly different.

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. Glucocorticoids alone may have antitumor effects mediated either by direct interaction with androgen receptors or by feedback inhibition of the hypothalamic-pituitary-adrenal axis. Contemporary studies have tried to control for the beneficial effects of antiandrogen withdrawal in this setting. Kelly et al reported on 30 patients treated with 40 mg. hydrocortisone daily and found that 20% had a decrease of at least 50% in serum PSA maintained for a median of 4 months.[14] Dawson et al treated 34 patients with hormone refractory disease with 30 mg. hydrocortisone daily and found a 29% PSA response proportion.[17] In a recent randomized trial hydrocortisone was evaluated alone or in combination with mitoxantrone in patients with hormone refractory prostate cancer.[18] A greater than 50% decrease in PSA was observed in 22% of patients treated with hydrocortisone alone. Finally, in a large study comparing suramin plus hydrocortisone to placebo plus hydrocortisone in patients with metastatic hormone refractory disease and opioid analgesic requirements 38 (16%) of 230 treated with 40 mg. hydrocortisone daily plus placebo had a greater than 50% reduction in PSA.[19] Taken together, these data suggest that 16% to 29% of patients will have a greater than 50% reduction in PSA when treated with 30 to 40 mg. hydrocortisone daily. The response proportion observed with hydrocortisone plus low dose ketoconazole appears to be considerably higher than that expected with hydrocortisone alone, and supports prior experience that suggested that ketoconazole is an active agent in this group of patients. However, the true benefit of adding ketoconazole to hydrocortisone can only be adequately addressed in a randomized trial.

Baseline levels of androstenedione, DHEA and DHEAS did not differ between responders and nonresponders. While all 3 of these endocrine parameters decreased significantly after 2 months of therapy, the degree of decrease was not predicted by response. Of note, low dose ketoconazole clearly suppresses adrenal steroidogenesis. Therefore, replacement doses of hydrocortisone are recommended, even when ketoconazole is administered at low doses, despite the possibility that it may not be necessary in all patients. While high dose and low dose ketoconazole have been shown to suppress adrenal androgen production,[5,11] no study has shown an association between response to treatment and changes in adrenal androgen levels. While our study was likely too small to detect an association with adequate power, this question is being addressed in a recently completed cancer and leukemic

TABLE 2. *Toxicity to low dose ketoconazole*

Toxicity	No. (%)		
	Grade 1	Grade 2	Grade 3
Nausea	5 (18)	3 (11)	0
Dry skin	5 (18)	0	0
Fatigue	4 (14)	0	0
Bruising	1 (4)	0	0
Liver (aspartate transaminase, alanine transaminase)	0	1 (4)	1 (4)
Stomatitis	0	1 (4)	0
Depression	0	0	2 (7)
Insomnia	0	1 (4)	0

TABLE 3. *Adrenal androgen levels*

	Before Treatment		After 2 Mos.	
	No.	Median Ng./Ml. (range)	No.	Median Ng./Ml. (range)
Androstenedione	27	0.71 (0.33–2.62)	25	0.30 (0.10–0.73)
DHEA	27	2.3 (0.9–6.0)	25	1 (0.5–1.7)
DHEAS*	27	364.8 (50–1,907)	25	50 (9–588.1)

* Two-month values which were reported as less than 50 were coded as 50 for calculations.

group B phase III study of antiandrogen withdrawal alone or with high dose ketoconazole. It is intriguing that preliminary results from this trial revealed that the baseline level of DHEA appeared to be an independent predictor of survival.[20]

Low dose ketoconazole is attractive because of its favorable toxicity profile, ease of use and its reduced cost compared to high dose ketoconazole. All medications are given orally and patients need only monthly laboratory followup. As with high dose ketoconazole, nausea was the most frequent toxicity. However, nausea was generally mild to moderate, and only 1 patient discontinued low dose ketoconazole due to persistent grade 2 nausea. Only 3 patients (11%) experienced grade 3 toxicity (hepatotoxicity in 1 and depression in 2), and no patient experienced grade 4 toxicity. While the relative efficacy and toxicity of low dose compared with high dose ketoconazole can only be assessed in a phase III trial, these data suggest that low dose ketoconazole should be considered as a treatment option in this patient population.

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