High-Dose Ketoconazole in Advanced Hormone-Refractory Prostate Cancer: Endocrinologic and Clinical Effects

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High-dose ketoconazole (400 mg orally three times a day) and physiologic replacement doses of glucocorticoids (hydrocortisone, 20 mg 8 AM, 10 mg 4 PM, and 8 PM) were administered to 38 patients with advanced prostatic cancer, refractory to at least initial testicular androgen deprivation. Thirty patients were completely evaluable; six were withdrawn due to possible ketoconazole-related toxicity and were considered drug failures. Two patients were unevaluable due to intercurrent therapy or inability to maintain follow-up. Ketoconazole was generally well tolerated. Mild or moderate nausea and vomiting occurred in 37% of patients, but required dose modification or discontinuation in only three patients; no hepatic damage was seen. Five of 36 patients (14%) responded to ketoconazole as determined by palpable or radiographic tumor mass reduction of 50% or greater and normalization of acid phosphatase or bone scan. Fifty percent of patients entered were stable at 90 days. Plasma androstenedione and dehydroepiandrosterone sulfate (DHEAS) were reduced markedly in almost all patients. Plasma testosterone (T) levels were low and remained unchanged, while gonadotropins were persistently elevated. Mean plasma ketoconazole content was 6.6 μg/mL after 28 days of therapy. While ketoconazole with hydrocortisone does suppress plasma androgens in advanced prostatic cancer patients, this infrequently causes regression of cancer that has progressed despite adequate testicular androgen ablation.

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THE IMPORTANCE of extratesticular androgens in supporting the growth of prostatic carcinoma is uncertain. Labrie et al[1] have presented data suggesting that antagonism of extratesticular androgens and suppression of testicular androgens substantially improves the response and survival of individuals with metastatic prostatic cancer compared with individuals who undergo suppression of testicular androgens only. Preliminary analysis of a randomized trial suggests a small improvement in disease-free survival for patients treated with total androgen deprivation.[2] In men whose prostatic cancer is progressing despite testicular androgen ablation, antagonism of adrenal secretion of "minor" androgens (dehydroepiandrosterone [DHEAS] and androstenedione [A_2]) occasionally appears to be beneficial. Improvement in approximately 20% of these men is seen with adrenalectomy, hypophysectomy, anti-androgens, or drugs that directly antagonize adrenal steroidogenesis.[3-10]

Ketoconazole is a substituted imidazole, originally developed as an antifungal antibiotic. Ketoconazole inhibits ergosterol synthesis in fungi and cholesterol synthesis in mammalian cells.[11] Shortly after its introduction into clinical practice, it was recognized that ketoconazole also suppresses testicular and adrenal steroidogenesis.[12] Disruption of P-450–dependent enzymes, particularly C_{17-20} lyase is the major mechanism for the disruption of androgen synthesis in patients treated with large doses of ketoconazole.[13,14] Soon after the recognition of this effect, efficacy of ketoconazole in advanced prostatic cancer patients was described.[15] Most experience with ketoconazole in prostatic cancer has been in previously untreated patients.[16-18] Because of our interest in the role of adrenal androgen suppression in "endocrine-refractory" prostatic cancer, we conducted this phase II trial of ketoconazole in patients whose cancer had ceased to respond to testicular androgen deprivation. Detailed clinical and endocrinologic monitoring of these patients was performed.

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METHODS

Eligibility

Patients eligible for this trial were required to have symptomatic, progressive, disseminated prostatic cancer, despite primary endocrine management (orchiectomy, 1 mg/d or more of diethylstilbestrol [DES], or gonadotropin hormone-releasing hormone analogues [GnRHa]) and were treated only at the University of Wisconsin. At least one evaluable or measurable parameter of disease was required. Lesions deemed evaluable included soft tissue masses evaluated by radiographic or physical exam or abnormal bone scan. Patients were required to have a WBC of 2,000/μL platelet count of 50,000/μL, creatinine $<$ 3.1 mg/dL and bilirubin, lactic dehydrogenase (LDH), and SGOT less than twice normal. An Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 was required.[19] Patients must not have had major surgery or cytotoxic chemotherapy within 2 weeks, and those with a history of active liver disease, neurologic deficit secondary to spinal cord compression, or a coexisting second primary malignancy were ineligible. There were no restrictions in the extent of prior systemic therapy patients may have received. All patients gave informed consent according to the Department of Health, Education and Welfare (DHEW) and University of Wisconsin guidelines.

Treatment

Ketoconazole, 400 mg, was administered orally every eight hours. All patients received physiologic glucocorticoid replacement therapy with 20 mg of hydrocortisone in the morning, 10 mg at 4 PM, and 10 mg at 8 PM.

Study Parameters

Patients were evaluated by history, physical examination, serum electrolytes, creatinine, liver function tests, and acid phosphatase before therapy, 2 weeks after beginning therapy, and then at monthly intervals. Chest radiographs were repeated monthly if initially abnormal or every 3 months if initially normal; bone scans and pelvic computerized tomography (CT) scans were done before therapy and every 3 months, if initially abnormal, to assess response.

Endocrinologic Assessment

Plasma testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), DHEAS, A_2, and estradiol (E_2) were measured before therapy and at monthly intervals using standard radioimmunoassay procedures. Ketoconazole plasma levels were also assessed monthly using a described microbiologic assay.[7] Plasma prostate-specific antigen (PSA) was assessed before therapy and monthly by radioimmunoassay (Hybritech). All blood samples were drawn between 8 AM and 10 AM.

Response Criteria

Responses were assessed using the prostate cancer response criteria of the ECOG. Measurable disease: partial response was defined as a 50% or greater reduction in the sum of the products of the perpendicular diameters of measurable tumor masses persisting for more than 1 month in the absence of the appearance of new lesions. Evaluable bone scan response was defined as a return to normal in 50% or more of the abnormal areas noted on pretreatment scan without the appearance of new lesions. Progression was defined as (1) a 25% or greater increase in the product of the perpendicular diameters of measurable tumor masses or, (2) development of new areas of metastatic disease as assessed by plain radiograph, bone scan, CT scan, or physical examination or deterioration by 2 levels in PS.

RESULTS

Thirty-eight patients were entered in this trial. Patient characteristics are listed in Table 1. These patients had good PS and were not heavily pretreated with systemic therapies. Twenty-one of 38 patients had received only a single systemic hormonal therapy for prostate cancer (13, orchiectomy; five, DES; and three $GnRH_a$). While 45% of the patients had received two or more systemic therapies, only three had received cytotoxic chemotherapy (one, carboplatin; one, doxorubicin; and one, estramustine phosphate). Of 38 patients entered, two were declared unevaluable: one due to the initiation of radiation on day 3 of ketoconazole therapy, and the other due to inability to maintain follow-up. Six of the remaining 36 patients (16%) discontinued ketoconazole due to possible or definite drug-related toxicity. Unmanageable nausea and vomiting prompted discontinuation of ketoconazole in three patients (8%). In two of these three patients, nausea and vomiting developed after 1½ and 2 months of therapy, was accompanied by evidence of progressive disease,

Table 1. Characteristics of Patients Treated (N = 38)

Age (yr)	
50-59	5 (13%)
60-69	21 (55%)
70-79	11 (28%)
80-89	1 (2%)
Interval from initial diagnosis of prostate cancer to study entry (yr)	
1 or less	5 (13%)
1-2	8 (21%)
2-5	15 (39%)
5-10	8 (21%)
10 or more	2 (5%)
Prior systemic therapy	
Single hormonal therapy	21
Two or more prior systemic treatments	17
Prior cytotoxic therapy	3
PS	
0	4 (10%)
1	24 (63%)
2	10 (26%)

and did not resolve with discontinuation of ketoconazole; in the third patient, nausea and vomiting began immediately on initiation of ketoconazole, persisted despite dose reduction, and prompted drug discontinuation on day 15 of treatment. The other events leading to termination of therapy were (1) acute myocardial infarction, cardiogenic shock, and death on day 7 in a man with known coronary artery disease; (2) reversible mild renal dysfunction (creatinine 2.3 mg/dL), which resolved with discontinuation of ketoconazole and nonsteroidal antiinflammatory agents; and (3) itchy teeth and hair loss without physical signs of toxicity or other toxic symptoms in this patient. Thirty patients were able to continue therapy without undue toxicity until clear cut response or progression occurred, and are evaluable for response.

Clinical Response to Ketoconazole

Of 30 patients completely evaluable for response, 24 developed progressive disease. The median time to progression was 82 days (range, nine to 347 days). One patient remains stable without objective evidence of response or progression at 455 days. This patient stopped ketoconazole after 300 days, and continues to be stable on no treatment. Eighteen of 36 patients (50%) had either stable disease or had responded 90 days after beginning ketoconazole. Patients stopping therapy due to toxicity were considered treatment failures. In five patients, objective evidence of tumor reduction was seen during ketoconazole therapy. Characteristics of the responding patients are noted in Table 2. The objective response rate following ketoconazole was low: 17% of evaluable patients and 13% of all patients entered. All five responding patients had undergone orchiectomy prior to treatment with ketoconazole. Disease-free interval, age, PS, disease distribution, and initial endocrinologic data were not remarkably different in these five patients compared with nonresponding patients.

Endocrine Effects of Ketoconazole/Hydrocortisone Therapy

Total plasma T was low at entry in these patients (mean, 24.4 ng/dL; range, 0 to 261 ng/dL). Thirty of 31 patients, in whom pretreatment data were available, had plasma T < 100 ng/dL. Nineteen patients with low plasma T had previously undergone orchiectomy; in 11 patients, low T was associated with hormonal therapy other than orchiectomy. One patient entered this study with a low normal T (261 ng/dL), though purportedly having received 3 mg/d DES within 1 week before study entry. Plasma T was not further diminished in patients during ketoconazole/hydrocortisone therapy. In two nonorchiectomized patients, plasma T in the low normal range (127 ng/dL and 152 ng/dL) was measured during ketoconazole/hydrocortisone therapy. In one of these patients, concomitant ketoconazole plasma concentration was 9.6 μg/dL, while in the second patient, ketoconazole was undetectable in the plasma. In the patient

Table 2. Patients Responding to Ketoconazole

Patient	Tumor Masses	Acid Phosphatase	Bone Scan	PS	TTF (d)
JS	NE	Normalized	Improved	Improved	386
MD	> 50% reduction pelvic* soft tissue masses	Normalized	No change	Stable	181
RB	> 50% reduction* retroperitoneal, retrocrural adenopathy	> 50% Reduction	No change	Stable	248
KG	> 50% reduction* retroperitoneal, pelvic adenopathy	Normal on study	No change	Stable	319
RZ	> 50% reduction* retroperitoneal adenopathy complete regression of palpable inguinal adenopathy; improvement, biopsy-proven pulmonary infiltrate	Normal on study	No change	Improved (resolution of cough)	567

Abbreviations: NE, not evaluable; PS, performance status; TTF, time to treatment failure.
*Criteria met for objective tumor response.

who entered the trial with plasma T of 261 ng/dL, T decreased on ketoconazole/hydrocortisone to < 50 ng/dL on day 28.

Plasma A_2 content varied among patients at entry; it ranged from 6.9 to 202 ng/dL (normal, 80 to 200 ng/dL). In 32 patients, data after initiation of therapy were available; in 28, A_2 was well below the lower limit of normal. In these 28 patients, A_2 was < 30 ng/dL, and in 22 A_2 content was undetectable (Fig 1). In four patients, A_2 levels were not reduced by ketoconazole/hydrocortisone therapy. However, in each of these, ketoconazole was not measurable in plasma samples obtained when A_2 was still detectable.

DHEAS plasma content was variable at the time of study entry (0 to 242 μg/mL) and was less completely reduced by this regimen. In 29 patients, serial data were available and measurable plasma levels of ketoconazole were present (Fig 2). In 17 of these 29, a 50% or greater decrease in plasma DHEAS content occurred with ketoconazole/hydrocortisone therapy.

Among the five patients who responded to therapy, A_2 fell to undetectable levels in all five, and DHEAS was reduced by more than 50% in three of the four patients in whom serial data were available. However, the frequency of these endocrinologic effects are not strikingly different among responders and nonresponders.

Estrogens were low at entry (mean, 7.0 pg/mL; normal, 40 to 115 pg/mL). Total estrogens remained at this low level throughout the study in all patients.

Mean plasma ketoconazole concentration on

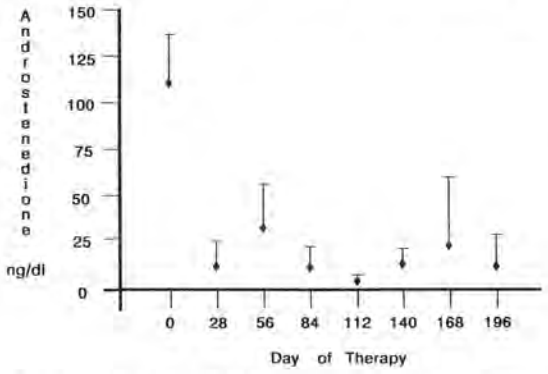

Fig 1. Mean plasma A_2 concentrations before and during therapy with high-dose ketoconazole. Error bars represent upper portion of standard error for each mean value.

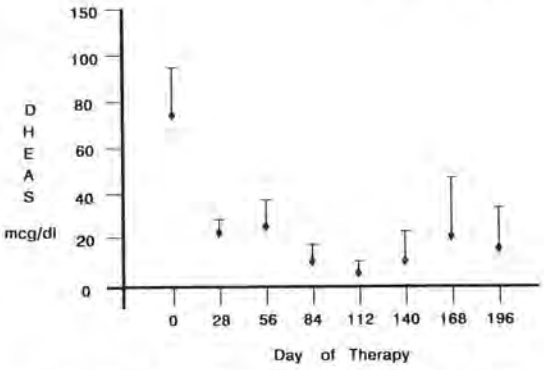

Fig 2. Mean plasma DHEAS concentrations before and during therapy with high-dose ketoconazole. Error bars represent upper portion of standard error for each mean value.

day 28 of therapy was 6 μg/mL (range, 1.33 to 15.5 μg/mL). No significant relationship between response or toxicity and ketoconazole plasma levels was evident. It is of interest that approximately 10% of patients at each monthly interval had plasma ketoconazole concentrations below the lower limit of detection. This indicates that appreciable levels of ketoconazole were not maintained in approximately 10% of patients, either because of rapid drug clearance or poor patient compliance.

PSA and Acid Phosphatase

Among the five responders, acid phosphatase returned to normal in two, decreased by more than 50% in one, and was always normal in the remaining two patients. PSA decreased by more than 80% in four of five patients; in the fifth, the PSA was slightly increased and did not change during therapy, despite a reduction in retroperitoneal lymph nodes. In the small number of responding patients, PSA seemed to reflect response better than acid phosphatase. Among 30 nonresponders, serial acid phosphatase and PSA data were available in 26. In 12 patients (46%), PSA and acid phosphatase increased by more than 25%, coincident with clinical evidence of progressive disease. In 13 patients, one or both markers either were stable or diminished when clinical progression was evident. In one patient with stable disease, PSA diminished and the acid phosphatase remained normal. Overall, PSA analysis did not appear to substantially change the

judgement regarding response or progression in these patients with advanced prostatic cancer.

Toxicity

The major toxicity of this regimen was nausea and vomiting. Thirty-seven percent of patients experienced at least grade 2 nausea and vomiting; one patient required dose reduction to control nausea and vomiting. In three patients, emesis was uncontrollable and prompted discontinuation of ketoconazole. Hepatic toxicity was not an important problem. Three patients experienced increase in plasma alkaline phosphatase without change in transaminases or bilirubin. In these three patients, progressive bone disease was present. In a fourth patient, hyperbilirubinemia occurred during ketoconazole therapy at a time when progressive hepatic metastases were evident. Dose modification was not required for hepatic toxicity. No other serious or important drug-related toxicity was encountered. A common complaint among patients in this trial was dryness of the skin. No objective findings were noted coincident with this complaint.

DISCUSSION

Treatment of men with prostatic cancer progression despite antagonism of testicular androgens is unsatisfactory. For many years, attempts to further deprive these cancer cells of remaining androgens have been employed. A_2 and DHEAS are the main androgens of adrenal origins. These compounds are weak androgens in their own right and may additionally be converted by a variety of peripheral body tissues to T and dihydrotestosterone.[20,21] Adrenalectomy, hypophysectomy, antiandrogens, progestational agents, and aminoglutethimide have been used to either inhibit secretion of adrenal androgens or to antagonize androgen action on the tumor cells.[3–10] While response rates as high as 40% to 50% have been reported with these measures, clear-cut, objective tumor mass reduction is infrequently seen. No improvement in survival is associated with the use of adrenal androgen antagonists as secondary hormonal therapy. Labrie et al[1] have proposed the use of adrenal and testicular androgen antagonists as part of total androgen deprivation in the initial treatment of advanced prostatic cancer.[1] Preliminary analysis of a randomized trial comparing GnRHa with GnRHa plus antiandrogens suggests a small, but significant, improvement in time to systemic progression for the combined treatment group.[2]

Ketoconazole plus hydrocortisone as employed in our trial consistently reduces adrenal steroid production. Plasma DHEAS and A_2 levels were substantially reduced in all patients in whom detectable ketoconazole levels could be measured. This finding differs from the report of Ahmann et al,[22] who found that the adrenal steroid synthesis inhibitors aminoglutethimide and hydrocortisone were not effective in reducing plasma A_2 levels. In the study of aminoglutethimide, DHEAS level fell in a manner similar to the changes we noted with ketoconazole plus hydrocortisone.

From studies in which hydrocortisone has been used in conjunction with an adrenal antagonist, it is not clear what the relative roles of the antagonist and the glucocorticoid are in reducing plasma androgens. In the present study, a physiologic replacement dose of hydrocortisone was employed. It is unlikely that direct antiproliferative effects or nonspecific constitutional effects of hydrocortisone contributed to the responses that were seen.

If one were to use stable disease at 90 days after initiation of therapy, a response criterion employed in other studies, 50% of patients would be considered responders. Overall, ketoconazole plus hydrocortisone would have to be judged generally ineffective as secondary hormone therapy for most patients with advanced prostatic cancer. However, it is provocative that definite tumor mass reduction was documented in five patients.

It appears that a small subset of previously hormone-treated patients with prostatic cancer may respond to ketoconazole plus hydrocortisone. Responses were limited to patients who had undergone orchiectomy. This regimen was reasonably well tolerated in prostatic cancer patients. The results of this study, the responses seen following aminoglutethimide, and the preliminary data from the leuprolide plus or minus flutamide trial, all suggest a small, but potentially important, role for antagonism of adrenal androgens in individuals with prostate cancer. In addition, Rochlitz et al have recently reported

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