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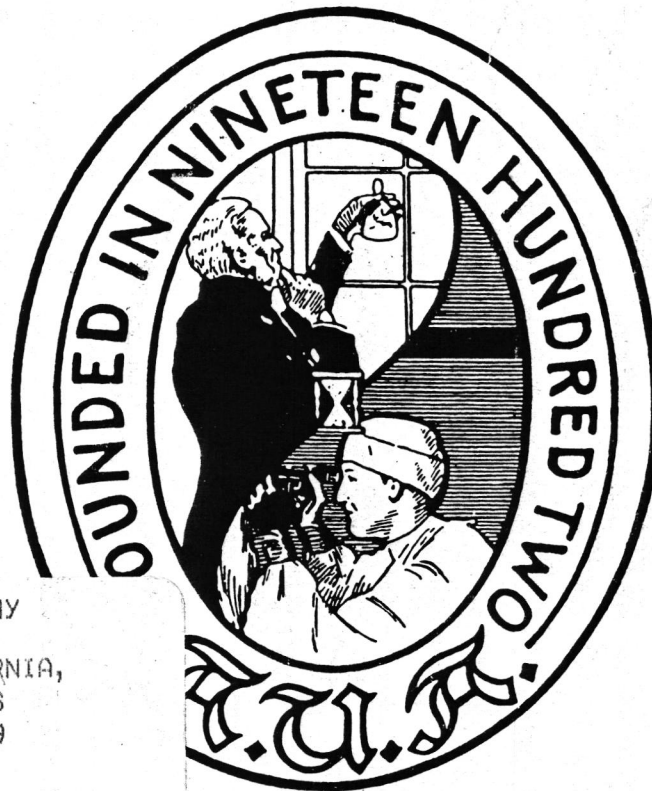
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# HIGH DOSE KETOCONAZOLE FOR THE TREATMENT OF HORMONE REFRACTORY METASTATIC PROSTATE CARCINOMA: 16 CASES AND REVIEW OF THE LITERATURE

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## ABSTRACT

We treated 16 patients who had hormone refractory metastatic prostate cancer with 400 mg. ketoconazole orally every 8 hours. None of the patients had an objective response, although 6 (37.5 per cent) had stable disease (2 of whom had a subjective decrease in bone pain). The median duration of stable disease was 6.8 months (range 2 to 12 months) and side effects were seen in 14 patients. Nausea, vomiting or anorexia was noted in 10 patients, rash and pruritus in 2, transient abnormal liver function tests in 1 and transient pulmonary infiltrates in 1.

Nine prior studies investigating the use of ketoconazole in hormone refractory metastatic prostate cancer were reviewed. Only 1 complete response was reported. A partial response was noted in 14 per cent of the patients. Most of the patients had stable or progressive disease.

High dose ketoconazole as a single agent appears to have limited use in patients who have failed prior systemic therapy. (*J. Urol.*, 142: 89-91, 1989)

Adenocarcinoma of the prostate is androgen dependent in the majority of cases.<sup>1</sup> Most of the circulating androgens in man are secreted by the testes and adrenal glands.<sup>2</sup> Conventional management of advanced prostate cancer has been oriented towards reducing circulating androgens by orchiectomy or estrogen therapy to attempt to induce disease remission. However, although 75 per cent of the patients respond to the aforementioned therapy, disease progression is associated with a 6-month survival of only 50 per cent and median overall survival of 2.5 years.<sup>3,4</sup> In men with hormone refractory disease, cytotoxic chemotherapy has been used with minor success and often is associated with toxicity.<sup>3</sup>

Ketoconazole is an orally administered broad-spectrum antifungal agent that blocks gonadal and adrenal synthesis of androgens,<sup>2</sup> and has a direct antitumor effect on prostatic cancer cells in vitro.<sup>5</sup> Thus, high dose ketoconazole may be of potential value in the treatment of metastatic prostate cancer. Several investigators have reported good initial tumor responses with ketoconazole in patients with untreated advanced prostate cancer, with few treatment-related side effects.<sup>6,7</sup>

The poor response of hormone refractory prostate cancer to alternative systemic therapy and the promising results of the aforementioned pilot studies stimulated us to investigate the activity of ketoconazole in our patients with estrogen or orchiectomy refractory metastatic disease.

## MATERIAL AND METHODS

We studied 16 patients with estrogen or orchiectomy refractory metastatic adenocarcinoma of the prostate. Ten patients had undergone orchiectomy, 4 had received diethylstilbestrol and 2 had received orchiectomy plus diethylstilbestrol. Ketoconazole (400 mg. every 8 hours orally) was given to all patients according to the dosage used in prior studies.<sup>6-16</sup>

Eligibility requirements for this study included histologically proved adenocarcinoma of the prostate with measurable or evaluable disease, life expectancy of at least 3 months, performance status of 2 or better (Eastern Cooperative Oncology Group criteria),<sup>17</sup> no prior treatment with ketoconazole, no hepatic dysfunction (that is total bilirubin less than 2 mg./dl.) and at

least 4 weeks since prior radiotherapy, hormonal therapy or chemotherapy.

The pre-treatment diagnostic evaluation consisted of history and physical examination, complete blood count, liver function tests, total and prostatic acid phosphatase, chest x-ray and bone scan. Subsequent evaluation included history and physical examination, complete blood count and liver function tests every 3 weeks, total and prostatic acid phosphatase and chest x-ray (if a measurable lesion was present) every 6 weeks, and bone scan every 3 months (or earlier if there was increasing bone pain). Serum prostate specific antigen and serum testosterone were not evaluated.

Tumor response was evaluated according to National Prostatic Cancer Project criteria.<sup>18</sup>

## RESULTS

Patient characteristics and responses to therapy are noted in table 1. None of the 16 patients had an objective response

TABLE 1. Patient characteristics and results

No. pts. entered	16
Median age (range)	71 (48-84)
Median performance status (range)*	2 (0-2)
Prior treatment:	
Hormonal therapy only:	6
Orchiectomy, 4	
Diethylstilbestrol, 2	
Radiation and hormonal therapy:	9
Orchiectomy, 5	
Diethylstilbestrol, 2	
Orchiectomy plus diethylstilbestrol, 2	
Chemotherapy (cyclophosphamide) plus radiation plus hormonal therapy (orchiectomy)	1
Disease extent:	
Bone only	12
Measurable sites:	4
Lung, 2	
Lymph node, 2	
Response:	
Complete	0
Partial	0
Stable (decreased bone pain)	6 (2)
Progression	10



TABLE 2. Summary of studies on ketoconazole in previously treated patients with metastatic prostate cancer

Reference	Total No. Pts.	Response (No. pts.)				Range of Response Duration (mos.)		
		Complete	Partial	Stable	Subjective Improvement (decrease in bone pain)	Complete	Partial	Stable
Pont <sup>8</sup>	11	0	0	4	5	—	—	—
Vanuytsel and associates <sup>9</sup>	4	0	1*	1	—	—	13	5
Debruyne and associates <sup>10</sup>	39	0	0	23†	21	—	—	—
Johnson and associates <sup>11</sup>	22	0	2	7	13	—	3-6	3-8
Williams and associates <sup>12</sup>	20	1	5‡	2	11	—	—	—
Bredt and associates <sup>13</sup>	15	0	8	—	3	—	1-12	—
Van Cangh and Opsomer <sup>14</sup>	14	0	4†	4	—	—	3-6	3-9
Havlin and associates <sup>15</sup>	15	0	3	6	—	—	3-4	3-4
MacKintosh and associates <sup>16</sup>	12	0	1	10	—	—	—	—
Present study	16	0	0	6*	2	—	—	3-12
Totals (%)	168	1 (0.58)	24 (14.3)	63 (36)	55			

\* National Prostatic Cancer Project criteria used for response.

† European Organization for Research on Treatment of Cancer criteria used for response.

‡ British Prostate Group criteria used for response.

TABLE 3. Side effects in patients treated with ketoconazole

Reference	Total No. Pts.	Gastrointestinal	Skin	Nail Dystrophy	Cardiovascular	Abnormal Liver Function Tests	Fatigue, Lethargy
Pont <sup>8</sup>	11	3	—	—	—	1	2
Vanuytsel and associates <sup>9</sup>	22*	8	9	4	2	3	10
Debruyne and associates <sup>10</sup>	39	14	—	—	—	—	—
Johnson and associates <sup>11</sup>	22	10	—	—	—	—	—
Williams and associates <sup>12</sup>	20	11	—	—	—	3	—
Bredt and associates <sup>13</sup>	15	5	—	—	—	—	—
Van Cangh and Opsomer <sup>14</sup>	14	6	—	—	—	—	—
Havlin and associates <sup>15</sup>	15	5	—	—	—	—	—
MacKintosh and associates <sup>16</sup>	12	7	—	—	—	—	4†
Present study	16	10	2	—	—	1	1
Totals	186	79	11	4	2	8	17

\* Includes treated and untreated patients.

† Two patients had adrenal insufficiency.

although 6 (37.5 per cent) had stable disease, of whom 2 had subjective decrease in bone pain. The serum acid phosphatase was elevated in 12 patients but decreased in only 3 in response to ketoconazole. In the 3 patients in whom a palpable prostatic nodule could be evaluated no response to ketoconazole was noted. The median duration of stable disease was 6.8 months (range 2 to 12 months).

Side effects were seen in 15 patients. Nausea, vomiting and anorexia were noted in 10 patients. One patient had abnormal liver function tests (for example serum glutamic oxaloacetic transaminase of 364 and total bilirubin 6.7) necessitating drug withdrawal 4 days after commencing therapy. These abnormalities resolved after 1 week of treatment. Two patients had pruritus and an erythematous rash that resolved when the drug was temporarily discontinued. When these patients restarted therapy no further skin complications occurred. Severe dyspnea and pulmonary interstitial infiltrates on chest x-ray occurred in 1 patient 4 days after starting treatment. These abnormalities subsided after 14 days off therapy.

#### DISCUSSION

Table 2 compares prior studies with the present series.<sup>8-16</sup> The dose of ketoconazole used in all studies was 400 mg. every 8 hours. In 3 of the studies the dose was reduced to 200 mg. every 8 hours in some patients.<sup>10-12</sup> Only 1 complete response has been reported. Partial responses have been infrequent (14.3 per cent over-all). In those studies in which it was noted the duration of response was short-lived, ranging from 3 to 13 months.<sup>9, 11, 13-15</sup> Most patients have had stable or progressive disease. A subjective improvement in bone pain was noted in some patients despite a lack of objective response. In 4 of the

3). Hepatotoxicity in these studies was rarer and usually resolved quickly after stopping therapy.

In summary, high dose ketoconazole as a single agent appears to have limited use in patients who have failed prior hormonal therapy for advanced prostate cancer. The use of this drug is limited further by its frequent side effects and high cost (approximately \$9 to \$10 daily for 400 mg. 3 times per day).

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