We investigated the efficacy of ketoconazole, an inhibitor of testicular and adrenal biosynthesis, for treating patients with progression of hormone-refractory prostate cancer. The study comprised 35 patients with progressive disease despite salvage treatment with estramustine with or without vinblastine. Treatment consisted high-doses ketoconazole (400 mg three times daily) and hydrocortisone substitution. Patients were monitored clinically and with serial PSA measurements every 3 months. The principal endpoint of the study was PSA response to applied therapy. Of the 35 patients, 18 (51.4%) showed a decrease in PSA 50% with a median duration of 30 weeks (range 6-60 weeks). A PSA reduction 50% was seen in 15 of 31 patients (48.4%) with established metastasis. Twelve patients (34.2%), all of whom had metastasis, exhibited a PSA decrease 80% with median duration of 9 months (range 3-48 months). The median time to progression was 6.3 months (range 0-27 months) and the median survival time was 12.5 months (range 3-48 months). Twelve (34.3%) reported toxicity related to ketoconazole, whereas no patients required discontinuation of therapy. It is apparent from this study that a reasonable percentage of patients failing salvage chemotherapy (estramustine with or without vinblastine) respond favorably to high-dose ketoconazole and that toxicity is mild. In the absence of studies demonstrating better survival with chemotherapy, we believe that a trial of ketoconazole should be considered when progression of PSA occurs, following initial hormonal androgen deprivation.

Key words: prostate, cancer, ketoconazole.

INTRODUCTION

Cancer of the prostate is now the second leading cause of death from cancer in the United States, exceeded only by lung cancer. Even with localized disease at diagnosis, most patients eventually progress and develop metastasis. Although the majority of these patients initially respond to hormonal ablation, most will ultimately fail and require further therapy. Anti-androgen withdrawal represents one option, with response ranging between 15% and 33%\(^1\,\text{,}\,\text{2,}\,\text{3}\). However, any response tends to be short-lived usually lasting only about 3 months, after which the PSA starts rising again. The pathophysiology of anti-androgen withdrawal response is not completely understood, although androgen receptor gene mutations are a likely explanation. Whatever the mechanism, this heterogeneity of prostate cancer cells in their response to different hormonal maneuvers. This ability to retain hormonal sensitivity has encouraged investigators to evaluate other second-line hormonal manipulations in metastatic prostate cancer.

Ketoconazole, an orally active broad-spectrum antifungal agent, was first reported to have activity against prostate almost 20 years ago\(^4\). It blocks both testicular and androgen biosynthesis by inhibiting cytochrome P450 enzymes involved in steroidogenesis. Within 48 hours of initiation, ketoconazole reduces the concentration of circulating androgens to castrate levels\(^5\). Ketoconazole also had cytotoxic effects against prostate cancer cells in the absence of androgens. In human cell lines of prostate cancer, ketoconazole exerted a cytotoxic effects by inhibiting DNA synthesis\(^6\). In another in vitro study, exposure to ketoconazole, reduced cell viability by 26% of the control\(^7\). Compared to other options for managing hormone-refractory prostate cancer, ketoconazole is an attractive alternative because of its convenience and flexibility of administration. In clinical trials, responses ranging between 31.0% and 62.5%, have been reported using high-doses of ketoconazole (400 mg three times daily)\(^8\,\text{,}\,\text{9}\). Unfortunately, the potential toxicity of ketoconazole remains a major limitation for using this drug. In order to reduce toxicity, one approach is to administer lower doses. However, the main concern with this approach is that therapeutic efficacy may be compromised. Recently published...
study with total daily doses of 900 mg demonstrated satisfied efficacy with mild toxicity. The present study is undertaken to determine the objective and/or PSA response, duration of response, time of disease progression, overall survival and the toxic events, in patients with progressive hormone-refractory prostate cancer following previous chemotherapy (estramusine with or without vinblastine) managed with high-doses of ketoconazole with hydrocortisone substitution.

MATERIAL AND METHODS

We reviewed the medical record of 35 consecutive patients with histologically proved hormone – refractory prostate cancer on progression following initial chemotherapy (estramusine with or without vinblastine) managed with ketoconazole between 2.000 and 2.005.

To be included in this study, patients met the following requirements:
1. progressive metastatic disease on continuous hormonal therapy (orchietomy);
2. without anti-androgens for at least 8 weeks or progression since anti-androgen withdrawal;
3. no more than one previous exposure to cytotoxic agents; (4) PSA 4 ng/ml at entry;
4. creatinine clearance at least 35 ml/min and serum level of hepatic transaminase less than twice the upper limit of normal;
5. no other concurrent therapies were being used. Exclusion criteria for ketoconazole treatment included active peptic disease, second malignancy and uncontrolled lesions within the central nervous system.

For patients without measurable disease response was defined as a PSA decrease of at least 50%, sustained for at least 8 weeks, with at least stable symptoms. In addition, patients with conventionally measurable disease were required to show at least 50% reduction in the product of the greatest dimension. Progression was defined by any of the following events:
1. 25% increase in PSA above the nadir level in 3 consecutive measurement that were at least on month apart;
2. new lesions by bone scan or other imaging modality;
3. worsening symptoms attributed to prostate cancer.

The patients were treated with high – dose regime of ketoconazole 400 mg three times daily. All patients received replacement doses of hydrocortisone, 20 mg in the morning and 10 mg at night, to counteract potential adrenal insufficiency induced by ketoconazole. Progression of metastatic disease was demonstrated objectively in all patients prior to starting ketoconazole. PSA level and liver function tests were performed 6 to 8 weeks after initiation of ketoconazole, subsequently every 3 months. At each clinic appointment, patients also underwent a physical examination, and were specifically questioned about side effects. Termination of therapy was undertaken if there was no significant PSA response within 3 months or if side effects were intolerable (G 3-4 hepatotoxicity, symptomatic peptic ulcer or gastritis) and referred to combination cyclophosphamide, vincristine, dexamethason. The principal endpoint of the study was PSA response. When the patients were no longer receiving ketoconazole, hydrocorti-

TABLE 1

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
<td>12.1</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>48.5</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

sone was tapered by 5 mg every 3 days until complete discontinued.

RESULTS

At the time of data collection, 11 patients (31.4%) were still alive. The mean age at last follow-up was 76 years (range 49-81 years), whereas at diagnosis of prostate cancer was 68 years (range 45-86 years). The patients had ECOG performance status 0-1/0 (35%), 1 (65%)/ and life expectancy of at least 3 months. Of 35 patients, 26 (74.3%) had established metastatic disease on bone scintigraphy. Among 9 patients with normal bone scan, 5 had soft tissue metastasis /pelvic lymph nodes (4), lung (1)/. All patients had previously bilateral orchietomy. The distribution of Gleason scores (available for 33 of the 35 patients) and primary treatment are shown in Table 1.

The median interval between diagnosis of prostate cancer and ketoconazole treatment was 3.9 years (range 1-11.3 years). At commencement of therapy, the median PSA value was 98 ng/ml (range 5-3225 ng/ml).

Ten of 20 patients (20%) with painful bone metastasis had subjective improvement. Objective improvement in sense of PSA decline >50% occurred in 18 patients (51.4%). Median time to best response was 8 weeks (range 4-16 weeks) and response duration was 30 weeks (range 6-60 weeks). Five patients (38.5%) continue to exhibit response rate from 38 to 53 weeks. No improvement in bone scan was observed, whereas same response regarding soft tissues metastasis occurred in 3 of 5 patients (60%). For the entire group, median time to progression was 6.3 months (range 0-27 months), median survival time 12.5 months (range 3-48 months), whereas the survival at 2 years was observed in 5 patients (14.3%). PSA decline 50% was found in 15 of 31 patients (48.4%) with established metastasis for mean duration of 6 months (range 3-48 months). Twelve patients (34.2%), all of whom had metastases, exhibited a PSA decrease of 80% with median duration of 9 months (range 3-48 months).Using the 50% PSA response criteria, the median survival time for responders was 22 months compared to 7
months for non-responders (p<0.05). For the PSA 80% response, the median survival time for responders was 30 months versus 9 months for non-responders (p<0.01).

Overall, 12 patients (34.3%) reported toxicity related to ketoconazole. The principle complaints were nausea G1-2 (13.2%), fatigue G1-2 (13.3%), diarrhea G1-2 (1.6%), visual disturbances (2.6%) and abnormal liver function tests (2.6%). None of patients discontinued ketoconazole due to intolerable side effects.

**DISCUSSION**

For patients with hormone-refractory prostate cancer duration of survival is variable, ranging between 7 and 27 months\(^\text{11}\). The optimum management of these patients remains uncertain as no prospective randomized trials have yet to show a survival benefit. Furthermore, no universally accepted algorithm has been developed to manage these patients. Thus second-line hormonal agents, cytotoxic therapies, growth factor inhibitors, antisense oligonucleotides and bisphosphonates all seem reasonable options to discuss with patients since most patients are asymptomatic initially, these therapies should offer the potential for subjective and/or objective responses without significantly compromising quality of life.

Our results indicate that high-doses ketoconazole can induce objective clinical responses in some patients with hormone-refractory prostate cancer. The response rate of 51.4% is similar with that reported in the literature. In one study using high-dose regimens following failure to initial total androgen blockade, 30 of 48 patients (62.5%) demonstrated a PSA reduction >50% with a median duration of 3.5 months\(^\text{8}\). For a PSA reduction >80%, our response rate of 34.2% is also consistent with reported in other studies\(^\text{9}\).

Disappointingly, a survival benefit could not be demonstrated in our study population. This is consistent with other efficacy trials of ketoconazole, and further studies are needed to define its ultimate role of treating this disease. ECOG 1893 is a phase III randomized trial for evaluating second-line hormonal therapy (ketoconazole/hydrocortisone) versus combination chemotherapy (docetaxel/estramustine) on progression free survival in patients with hormone-refractory prostate cancer.

Until such trials are completed, many prostate cancer specialists may feel more comfortable combining ketocconazole with various chemotherapy regimes, given the symbiotic relationship that seems to exist. By combining ketoconazole with doxorubicin, responses ranging between 36% and 55% have been reported\(^\text{9,12,13}\). Furthermore, alternating this regime with estramustine and vinblastine improves therapeutic efficacy further with response reaching 60% to 67%\(^\text{14,15}\). Recently published study compared the efficacy of estramustine, and ketoconazole/hydrocortisone following failure to initial androgen deprivation. PSA decline 50% was observed in 23% and 58% patients, for mean duration of 3 and 7.5 months, respectively. Response rate was higher in patients with LHRH agonist or orchiectomy in comparison to the patients with PSA progression following anti-androgen withdrawal. In estramustine group, 34% patients discontinued therapy due to significant side effects, whereas 9% patients developed deep venous thrombosis. In the ketoconazole group, no WHO G3-4 side effects were observed, none of the patients discontinued treatment.

We acknowledge that concurrent corticosteroid administration may be a significant confounding variable. Indeed use of hydrocortisone alone after anti-androgen withdrawal has been associated with responses ranging between 19% and 22%\(^\text{17-19}\). However, our objective response rate of 51.4% suggests that ketoconazole is responsible for the majority of this activity.

We also acknowledge that our primary end point of PSA response remains controversial and there is still non consensus defining disease progression. It has been demonstrated that PSA responses of 50% correlate with improvement in time to treatment failure and survival\(^\text{20}\).

**CONCLUSION**

The present study demonstrated the reasonable number of patients failing estramustine with or without vinblastine respond favorably to high-doses of ketoconazole with hydrocortisone substitution. PSA decrease >50% appears to represent significant marker of survival in group of patients with androgen refractory but hormone sensitive prostate cancer. PSA response to ketoconazole can be identified within the first 6 to 8 weeks of therapy allowing an early identification of responders and non-responders. Responders will benefit from continuation of therapy with a median survival of about 2 years, and non-responders might be recruited for cytotoxic regimens at and early stage. Our suggestion from the present study is to include combination of ketoconazole with reduced doses of 600 mg and hydrocortisone substitution in patients with progression of PSA following initial androgen deprivation.

**REZIME**

Ispitivana je efikasnost ketokonazola, inhibitora testikularne i androgene biosinteze, kod bolesnika sa progresijom hormono refrakternog karcinoma prostate.

U studiju je uključeno 35 bolesnika sa progresijom bolesti pod hormonohemioterapijom (estramustin fosfata sa ili bez vinblastina). Tretman je podrazumevao visoke doze ketokonazola (400 mg tri puta dnevno) i substituciju hidrokortizonom. Bolesnici su pruženi klinički i odredjivanjem PSA svaka 3 meseca. Glavni cilj rada je bio odredjivanje odgovora PSA na primenjenu terapiju.

Od 35 bolesnika, 18 (51.4%) je imalo smanjenje PSA za 50% za srednje trajanje od 30 nedelja (ranga 6-60 nedelja). Smanjenja PSA za 50% je nadожно kod 15 od 31 bolesnika (48.4%) sa prisutnim metastazama. Dvanaest bolesnika (34.2%), svi sa prisutnim metastazama, imalo je smanjenje PSA za 80% za srednje trajanje od 9 meseci (ranga 3-48 meseci). Srednji vremenski interval za nastanak progresije bolesti je iznosio 6.3 meseca (ranga 0-27 meseci), srednje vreme preživljanja je bilo 12.5 meseci (ranga 3-48 meseci).Dvanaest bolesnika (34.3%) imalo je toksicitet uzrokovan davanjem ketokonazola, ali ni jedan bolesnik nije iziskivao prekid terapije.

Ova studija jasno pokazuje da određeni procenat bolesnika koji ima progresiju kod primene hormonohemi-
oterapije pokazuje zadovoljavajući odgovor na visoke doze ketokonazola i da je toksicitet prihvatljiv. U odsustvu studija koje pokazuju bolje preživljavanje sa hemoterapijom, mišljenja smo da terapija sa ketokonazolom ima svoje mesto kada postoji progresija PSA pod inicijalnom hormonalnom androgenom depresijom.

Ključne reči: prostata, karcinom, ketokonazol.

REFERENCES