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Original article

Ketoconazole in Taiwanese castration-resistant prostate cancer patients: Evaluation of response rates, durations, and predictors

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ABSTRACT

Background/purpose: To evaluate the efficacy of ketoconazole in castration-resistant prostate cancer.
Materials and methods: We reviewed the medical records of consecutive patients with pathologically confirmed prostate cancer from May 2006 to December 2008. The inclusion criteria were: (1) receiving 200 or 400 mg ketoconazole three times daily and replacement doses of prednisolone; (2) antiandrogen withdrawal for at least 2 months before ketoconazole treatment; and (3) no prior cytotoxic agents or other CYP17 inhibitors. Treatment consisted of ketoconazole at 200 mg three times daily (Group A) and 400 mg three times daily (Group B). Patients' characteristics, time to prostate-specific antigen (PSA) progression, duration of PSA response, and adverse events were evaluated.
Results: Of the 37 patients in Group A, 14 (37.8%) experienced a PSA response. Of the seven patients in Group B, four (57.1%) experienced a PSA response. Median durations of time to progression in those who experienced a $>$ 50% PSA decline were 7.5 and 11.5 months in Group A and Group B, respectively. Median duration of PSA response was 5.5 and 9.0 months in Group A and Group B, respectively. There was no difference in the PSA response or time to progression between the two groups. Orchiectomy had a borderline unfavorable effect on the PSA response rate ($p = 0.067$).
Conclusion: The present study demonstrated that ketoconazole contributed to the PSA response in patients with castration-resistant prostate cancer. The efficacy and toxicity profiles were comparable to those in previous studies. Orchiectomy had a borderline unfavorable effect on PSA response rate. Further studies are required to confirm the efficacy of ketoconazole therapy in surgically castrated patients.

1. Introduction

Androgen deprivation therapy can achieve a castration status for a period, but prostate cancer eventually progresses to castration resistance. Several mechanisms allow androgen receptor signaling to persist. It is believed that androgen receptors are frequently overexpressed and appear to be activated by castration levels of androgen and adrenal androgens.[1] The adrenal glands secrete ~10% of the circulating androgen in humans. Ketoconazole, a broad-spectrum azole antifungal agent, inhibits cytochrome P-450 and suppresses testicular and adrenal androgen production through inhibiting both adrenocortical 11b-hydroxylase and cholesterol side-chain cleavage.[2] A phase III trial (CALGB 9583) has demonstrated that antiandrogen withdrawal (AAWD) together with high-dose ketoconazole, 400 mg three times daily, and hydrocortisone, 30 mg each morning and 10 mg each evening, was associated with an objective prostate-specific antigen (PSA) response, and 8.6 months median time to PSA progression in 32% of 128 patients with castration-resistant prostate cancer (CRPC).[3] Low-dose ketoconazole, at 200 mg three times daily, with replacement doses of hydrocortisone (20 mg every morning and 10 mg at bedtime), was associated with a PSA response and 30 weeks median duration of PSA response in 46% of 28 patients.[4]

Here, we conducted a retrospective study to share our experience of using ketoconazole in patients with CRPC at National Taiwan University Hospital. The toxicity profiles and predictors of the PSA response were also evaluated.

2. Materials and methods

We retrospectively reviewed the medical records of consecutive patients with CRPC from May 2006 to December 2008. The definition of CRPC was based on European Association of Urology guidelines.[5] The inclusion criteria were: (1) receiving 200 or 400 mg ketoconazole three times daily and replacement doses of

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prednisolone; (2) AAWD for at least 2 months before ketoconazole treatment; and (3) no prior cytotoxic agents or other CYP17 inhibitors.

Patients' characteristics, time to PSA progression, duration of PSA response, and toxicity profiles were evaluated according to guidelines of the Prostate Specific Antigen Working Group and National Cancer Institute Common Toxicity Criteria.[6]

Results were analyzed with commercial statistical software. Age and PSA were compared using the median test. Categorical data were compared using a χ^2 test and Fisher's exact test. For all tests, a two-tailed p value <0.05 was regarded as significant.

3. Results

3.1. Patient characteristics

In total, 44 patients with CRPC were included, with a median age of 73 years (range, 55–88 years). Median serum PSA at diagnosis of prostate cancer was 74.5 ng/mL (range, 4.3–3310 ng/mL). Four patients (9.1%) underwent radical prostatectomy as definitive local therapy at the time of prostate cancer diagnosis, and 10 patients (22.7%) underwent external beam radiotherapy. At the start of ketoconazole therapy, 36 patients (81.8%) had bone metastasis, and the median PSA level was 30.9 ng/mL (range, 5.2–350.2 ng/mL). Thirty-eight patients (86.4%) received luteinizing hormone releasing hormone agonist (LHRHa), and two patients (4.5%) underwent bilateral orchiectomy as androgen deprivation therapy. Four patients (9.1%) received LHRHa and subsequent bilateral orchiectomy. Initial Gleason scores are given in Table 1. The mean duration of hormone therapy before ketoconazole therapy was 32 months (range, 6–208 months). Patient characteristics were categorized into ketoconazole 200 mg three times daily (Group A) and 400 mg three times daily (Group B) and are listed in Table 1. There were no significant differences in patients' characteristics between the groups.

Table 1
Patient characteristics categorized into Group A (ketoconazole 200 mg three times daily) and Group B (ketoconazole 400 mg three times daily).

	Group A	Group B
Median age, yr (range)	73 (55–88)	76 (59–86)
Median PSA, ng/mL, at diagnosis (range)	92.6 (4.3–3310)	74.5 (13.9–330.5)
Median PSA, ng/mL, at initiation of ketoconazole (range)	29.5 (5.2–350.2)	32.2 (13.8–221.2)
Median duration (mo) between diagnosis of prostate cancer and initiating ketoconazole (range)	30 (6–174)	32 (6–204)
Gleason score, *n*		
4–6	5	2
7	10	1
8–10	19	4
Definitive local therapy, *n*		
Radical prostatectomy	4	0
Radiotherapy	8	2
Castration therapy		
LHRHa	31	7
Orchiectomy	2	0
LHRHa and subsequent orchiectomy	4	0
Metastasis before ketoconazole		
Bone metastasis	20	5
Bone and soft-tissue metastasis	10	1
Soft-tissue metastasis only	2	0

LHRHa = luteinizing hormone releasing hormone agonist.

Table 2
Clinical outcomes in the separate groups.

	Group A	Group B	*p* value
AAWD response	8	1	0.644
≥50% PSA decline, n (%)	14 (37.8%)	4 (57.1%)	0.175
≥75% PSA decline, n (%)	8 (21.6%)	1 (14.3%)	0.585
Among ≥50% PSA decline			
Median time to progression, mo (range)	7.5 (1–87)	11.5 (4–16.5)	1
Median duration of PSA response, mo (range)	5.5 (0.5–86)	9.0 (2–13)	1

Group A, 200 mg ketoconazole three times daily; Group B, 400 mg ketoconazole three times daily; AAWD = antiandrogen withdrawal; PSA = prostate-specific antigen.

3.2. Clinical outcomes

Of the 44 patients, 37 patients received 200 mg ketoconazole three times daily (Group A), and seven patients received 400 mg ketoconazole three times daily (Group B). Eighteen patients experienced a PSA decline of ≥50% after ketoconazole therapy. Of the 37 patients in Group A, 14 (37.8%) had a ≥ 50% PSA decline, and eight (21.6%) had a ≥ 75% PSA decline. Of the seven patients in Group B, four (57.1%) had a ≥ 50% PSA decline, and one (14.3%) had a ≥ 75% PSA decline. There was no significant difference between the two groups. Median time to progression in those who experienced a > 50% PSA decline was 7.5 months and 11.5 months in Group A and Group B, respectively. Median duration of PSA response was 5.5 and 9.0 months in Group A and Group B, respectively. There were no differences in the time to progression or duration of the PSA response between the two groups. Clinical outcomes for the separate groups are listed in Table 2.

Clinical factors of those with a > 50% response and the others were compared. Neither age ($p = 0.417$), initial PSA level ($p = 0.651$), duration between diagnosis of prostate cancer and initiation of ketoconazole ($p = 0.759$), PSA level on initiation of ketoconazole ($p = 0.759$), prior radical prostatectomy ($p = 1.0$), prior radiotherapy ($p = 0.504$), prior LHRHa ($p = 0.634$), prior orchiectomy ($p = 0.067$), metastasis at diagnosis ($p = 0.515$), nor Gleason score ($p = 0.14$) could independently predict PSA response.

4. AAWD response

Nine patients (20.5%) experienced AAWD response before treatment with ketoconazole. There was no significant difference between the two groups.

4.1. Adverse events

Table 3 shows a summary of adverse events during treatment with ketoconazole. Of the 44 patients, 13 (29.5%) experienced adverse events. The most common adverse event was elevation of the liver function. Four patients (9.1%) had grade 1/2, and one patient had grade 3 elevated liver function. The patient

Table 3
Summary of adverse events during treatment with ketoconazole.

Adverse event	Grade 1/2	Grade 3
Fatigue	2	–
Arrhythmia	1	–
Vertigo	1	–
Epigastralgia	2	–
Nausea	1	–
Headache	1	–
Elevation of liver function	4	1

Two patients in Group B experienced adverse events of nausea and vertigo.