KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2011.52.11.746

Urological Oncology

Comparison of Ketoconazole and Estramustine for Treating Patients with Castration-Resistant Prostate Cancer

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Purpose: We investigated the efficacy of ketoconazole and estramustine before chemotherapy for treating patients with progressive castration-resistant prostate cancer (CRPC) after anti-androgen withdrawal syndrome.

Materials and Methods: Eighty-four patients who were diagnosed with CRPC and were treated between 2005 and 2009 were included. Thirty-nine patients were treated with 600 mg of ketoconazole and 10 mg of prednisolone per day (group I), and 45 patients were treated with 560 mg of estramustine per day (group II). The prostate-specific antigen (PSA) response, progression-free survival, and side effects were compared.

Results: The median age of the patients, PSA level, and follow-up period were 72 years, 48.5 ng/ml, and 4 months (range, 1 to 29 months), respectively. The overall PSA response rate was 35.7%, and the PSA response rates were 33.3% for group I and 37.8% for group II (p=0.672). The median progression-free survival times were 8 months (95% confidence interval [CI] 5.9-10.1) overall, 5 months (95% CI 1.6-8.3) in group I, and 8 months (95% CI 5.9-10.0) in group II (p=0.282). The most common complications in groups I and II were nausea and vomiting (51.3%) and anemia (77.8%), respectively. Nausea and vomiting and hepatotoxicity were observed more often in group I, and gynecomastia, neutropenia, and anemia were observed more often in group II. The toxicities of each adverse effect were ≤grade 2.

Conclusions: With a resultant PSA decline and mild adverse effects, both ketoconazole and estramustine are worth consideration as treatment options for progressive CRPC patients after primary hormonal therapy.

Key Words: *Estramustine; Ketoconazole; Prostatic neoplasms*

Article History:
received 9 June, 2011
accepted 25 July, 2011

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INTRODUCTION

For patients with progressive castration-resistant prostate cancer (CRPC) despite castration serum testosterone levels following initial androgen-deprivation therapy (ADT) for advanced prostate cancer, the therapeutic options before systemic chemotherapy, such as docetaxel, are anti-androgen withdrawal, replacement of anti-androgens, and secondary hormonal therapy [1].

After anti-androgen withdrawal syndrome in patients with CRPC, drugs for secondary hormonal manipulations include aminoglutethimide, ketoconazole, corticosteroids, and estrogenic compounds. Ketoconazole, a broad-spectrum anti-fungal agent, inhibits steroidogenesis in the testes and adrenal glands, and estramustine exerts not only non-hormonal cytotoxic effects, but also hormonal estrogenic effects. Thus, ketoconazole and estramustine serve as excellent treatment modalities in patients with CRPC [2].

Although several studies have been conducted regarding the therapeutic effects of ketoconazole and estramustine, comparisons of these treatments are limited in the literature. Thus, we investigated the efficacy, progression-free survival, and adverse effects of ketoconazole

and estramustine as a secondary hormonal therapy following anti-androgen withdrawal syndrome in patients with CRPC.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki.

1. Study population

The medical records of 84 patients with CRPC who were treated with ketoconazole and estramustine as a secondary hormonal therapy between 2005 and 2009 were retrospectively reviewed. CRPC was defined as biochemical or radiologic progression after initial ADT, despite castration levels of serum testosterone ($<$50 ng/dl or 1.7 nmol/l). We considered biochemical progression as 3 consecutive increases in the PSA level at least 1 week apart, resulting in 2 increases over the nadir by 50%. Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done to fulfill the criteria for CRPC. Radiologic progression included the appearance of $\geq$2 new lesions on bone scanning or soft tissue (nodal and visceral) lesions with use of the Response Evaluation Criteria in Solid Tumors and with lymph nodes $\geq$2 cm in diameter [3].

2. Data collection

Enrolled subjects were divided into 2 groups according to the drug therapy (group I: n=39, ketoconazole+prednisolone [PD] vs. group II: n=45, estramustine monotherapy). In group I, patients were administered ketoconazole (200 mg orally 3 times daily), unlike the majority of previous high-dose ketoconazole (400 mg) studies, with PD (5 mg twice daily) routinely to counteract the potential adrenal insufficiency induced by ketoconazole. Estramustine was administered orally twice a day for a total dose of 560 mg/day (group II). Patient characteristics, including age and prostate-specific antigen (PSA) level, both at the time of diagnosis and at the time the second drug was started; the Gleason score; clinical stage; prior treatment; PSA response; progression-free survival time; and adverse effects were collected for analyses.

We classified the PSA response into the following 4 categories: complete response was a PSA level below the normal baseline (4 ng/dl) for $\geq$4 weeks, partial response was $>$a 50% decrease from baseline, stable disease was a $<$50% decline and a 20% increase from baseline, and progressive disease was a $\geq$20% increase from baseline. Stable and progressive disease were considered as the nonresponse group [3].

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

3. Statistical analysis

Student's t-test, chi-square test, and Fisher's exact test were used to compare the two groups with respect to response rates and adverse effects. Progression-free survival times were calculated and compared by using the Kaplan-Meier method and the log-rank test. A p-value $<$0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics

The baseline median age of the entire study group of 84 patients was 72 years (range, 50 to 90 years), the median PSA level was 48.5 ng/ml (range, 1 to 3,869 ng/ml), and the median follow-up period was 4 months (range, 1 to 29 months). The Gleason score was $\geq$8 in 53 patients (63.1%), the clinical stage was $\geq$T3 in 53 patients (63.1%), and bone metastasis was present in 52 patients (61.9%). Sixty-nine patients (82.1%) previously received LHRH agonist therapy, and 15 patients (17.9%) underwent orchiectomies. The age, PSA level, Gleason score, clinical stage, and prior treatment at the beginning of secondary hormonal therapy were not statistically different (Table 1).

2. Prostate-specific antigen response rate and progression-free survival

Of the entire study group, 30 patients (35.7%) had a PSA response (complete or partial response), and 54 patients (64.3%) had no response (stable or progressive disease). The PSA response rate was higher in the estramustine group than in the ketoconazole group (37.8% vs. 33.3%); however, there was no statistical difference between the groups (p=0.672) (Table 2). Also, the PSA response rates according to Gleason score (p=0.371) and the clinical stage (p=0.839) showed no statistical difference (Tables 3, 4).

The median progression-free survival was 8 months (95% confidence interval [CI] 5.9-10.1) overall; the median progression-free survival was 5 months (95% CI 1.6-8.3) in the ketoconazole group and 8 months (95% CI 5.9-10.0) in the estramustine group. The progression-free survival was not statistically different between the groups (p=0.282) (Fig. 1).

3. Adverse effect of each drug

The most common side effect in the ketoconazole group was nausea and vomiting (51.3%), whereas the most common side effect in the estramustine group was anemia (77.8%). The frequency of anorexia (15 vs. 11, p=0.166) and facial edema (11 vs. 8, p=0.255) was similar in both groups, but nausea and vomiting (20 vs. 11, p=0.011) and hepatotoxicity (9 vs. 2, p=0.012) were more common in the ketoconazole group, and gynecomastia (3 vs. 15, p=0.004), neutropenia (0 vs. 9, p=0.003), and anemia (0 vs. 35, p=0.001) were more common in the estramustine group. All documented side effects were $\leq$grade 2 (Table 5).

DISCUSSION

In this study, there were no significant differences in PSA responses or progression-free survival between the ketoco-

TABLE 1. Patient characteristics

	Median (range) or n (%)			
	Total (n=84)	Group I (n=39)	Group II (n=45)	p-value
Age at diagnosis (yr)	69.5 (49-87)	71.0 (50-87)	69.0 (49-84)	0.866[a]
PSA at diagnosis (ng/ml)	100.3 (5.2-3,080.4)	100.0 (6.0-3,080.4)	106.6 (5.26-1578.0)	0.322[a]
Age at start second drug (yr)	72.0 (50-90)	72.0 (51-89)	71.0 (50-90)	0.512[a]
PSA at start second drug (ng/ml)	48.5 (1-3,869)	60.4 (1-3,869)	44.5 (3-789)	0.390[a]
Gleason score				0.533[b]
4-6	6 (7.1)	4 (10.3)	2 (4.4)	
7	25 (29.8)	10 (25.6)	15 (33.3)	
8-10	53 (63.1)	25 (64.1)	28 (62.2)	
Clinical stage				0.409[b]
T1	0 (0.0)	0 (0.0)	0 (0.0)	
T2	22 (26.2)	13 (33.3)	9 (20.0)	
T3-T4	53 (63.1)	22 (56.4)	31 (68.9)	
Unknown	9 (10.7)	4 (10.3)	5 (11.1)	
Clinical N stage				0.770[b]
N0	36 (42.9)	18 (46.2)	18 (40.0)	
Nx	40 (47.6)	17 (43.6)	23 (51.1)	
Unknown	8 (9.5)	4 (10.3)	4 (8.9)	
Clinical M stage				0.933[b]
M0	26 (31.0)	12 (30.8)	14 (31.1)	
M1	52 (61.9)	24 (61.5)	28 (62.2)	
Mx	1 (1.2)	0 (0.0)	1 (2.2)	
Unknown	5 (6.0)	3 (7.7)	2 (4.4)	
Prior treatments				0.554[c]
LHRH agonist	69 (82.1)	31 (79.5)	38 (84.4)	
Orchiectomy	15 (17.9)	8 (20.5)	7 (15.6)	

Values are presented as median (range) or n (%), Group I: ketoconazole+prednisolone, Group II: estramustine, [a]: Student's t-test, [b]: Fisher's exact test, [c]: Chi-square test

TABLE 2. PSA responses according to treatment

PSA response	No. of patients (%)			
	Total	Group I	Group II	p-value
Response	30 (35.7)	13 (33.3)	17 (37.8)	0.672[e]
Complete response[a]	9 (10.7)	4 (10.3)	5 (11.1)	
Partial response[b]	21 (25.0)	9 (23.1)	12 (26.7)	
Nonresponse	54 (64.3)	26 (66.7)	28 (62.2)	
Stable disease[c]	36 (42.9)	18 (46.2)	18 (40.0)	
Progressive disease[d]	18 (21.4)	8 (20.5)	10 (22.2)	
Total	84 (100)	39 (100)	45 (100)	

Values are presented as number (%), Group I: ketoconazole+prednisolone, Group II: estramustine, PSA: prostate-specific antigen, [a]: PSA level below the normal baseline (4 ng/dl) for ≥4 weeks or more, [b]: ≥50% decrease from baseline, [c]: Between a <50% decline and a 20% increase from baseline, [d]: ≥20% increase from baseline, [e]: Chi-square test

TABLE 3. PSA responses according to Gleason score

PSA response	Gleason score (%)			
	4-6	7	8-10	p-value
Response	3 (50.0)	11 (44.0)	16 (30.2)	0.371[e]
Complete response[a]	2 (33.3)	3 (12.0)	4 (7.6)	
Partial response[b]	1 (16.7)	8 (32.0)	12 (22.6)	
Nonresponse	3 (50.0)	14 (56.0)	37 (69.8)	
Stable disease[c]	2 (33.3)	9 (36.0)	25 (47.2)	
Progressive disease[d]	1 (16.7)	5 (20.0)	12 (22.6)	
Total	6 (100)	25 (100)	53 (100)	

Values are presented as number (%), PSA: prostate-specific antigen, [a]: PSA level below the normal baseline (4 ng/dl) for ≥4 weeks or more, [b]: ≥50% decrease from baseline, [c]: Between a <50% decline and a 20% increase from baseline, [d]: ≥20% increase from baseline, [e]: Chi-square test

nazole and estramustine groups. The results were similar to previous studies for each drug [4-9].

Recently, the term CRPC has been used in comparison with hormone-refractory prostate cancer (HRPC), which refers to prostate cancer that has progressed or recurred after the initial hormonal ablation therapy. Distinguishing CRPC and HRPC is very important because HRPC is resistant to all hormone therapies, whereas CRPC is responsive to secondary hormone therapies such as anti-androgen withdrawal, estrogens, and corticosteroids.

Ketoconazole was originally a broad-spectrum azole anti-fungal agent that inhibits cytochrome p450 enzymes and thus inhibits androgen synthesis from steroid precursors

TABLE 4. PSA responses according to clinical stage

PSA response	Clinical T stage (%)				
	T1	T2	T3-4	Unknown	p-value
Response	0 (0.0)	9 (40.9)	18 (34.0)	3 (33.3)	0.839[e]
Complete response[a]	0 (0.0)	4 (18.2)	5 (9.5)	0 (0.0)	
Partial response[b]	0 (0.0)	5 (22.7)	13 (24.5)	3 (33.3)	
Nonresponse	0 (0.0)	13 (59.1)	35 (66.0)	6 (66.7)	
Stable disease[c]	0 (0.0)	10 (45.5)	21 (39.6)	5 (55.6)	
Progressive disease[d]	0 (0.0)	3 (13.6)	14 (26.4)	1 (11.1)	
Total	0 (0.0)	22 (100)	53 (100)	9 (100)	

Values are presented as number (%), PSA: prostate-specific antigen, [a]: PSA level below the normal baseline (4 ng/dl) for ≥4 weeks or more, [b]: ≥50% decrease from baseline, [c]: Between a <50% decline and a 20% increase from baseline, [d]: ≥20% increase from baseline, [e]: Chi-square test

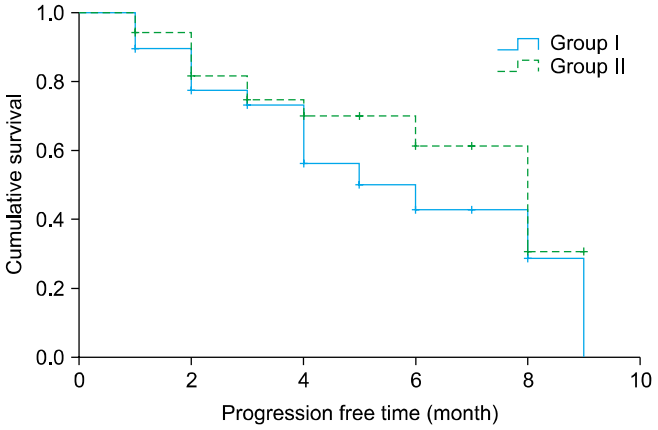

FIG. 1. Progression-free survival curves according to treatment groups were not statistically different by the log-rank test. The median progression-free survival times were 8 months (95% confidence interval [CI] 5.9-10.1) overall, 5 months (95% CI 1.6-8.3) in group I and 8 months (95% CI 5.9-10.0) in group II (p=0.282). Group I: ketoconazole+prednisolone, Group II: estramustine.

TABLE 5. Adverse effects according to treatment

Adverse effects	No. of patients (%)		
	Group I (n=39)	Group II (n=45)	p-value
Nausea/vomiting	20 (51.3)	11 (24.4)	0.011[a]
Anorexia	15 (38.5)	11 (24.4)	0.166[a]
Facial edema	11 (28.2)	8 (17.8)	0.255[a]
Gynecomastia	3 (7.7)	15 (33.3)	0.004[a]
Liver toxicity	9 (23.1)	2 (4.4)	0.012[a]
Neutropenia	0 (0.0)	9 (20.0)	0.003[a]
Anemia	0 (0.0)	35 (77.8)	0.001[a]

Values are presented as number (%), Group I: ketoconazole+prednisolone, Group II: estramustine, [a]: Chi-square test

leading to loss of adrenal steroid synthesis and testosterone synthesis by Leydig cells. Ketoconazole is commonly used with hydrocortisone because of its adrenal-suppressive effect [10]. Choi et al analyzed 11 HRPC cases in which ketoconazole (200 mg 3 times daily) and PD (5 mg 2 or 3 times daily) combination therapy was used and 10 cases in which PD monotherapy was used [4]. In the ketoconazole-PD combination therapy group, the mean PSA reduction was 23%, and the PSA decreased >50% in 27% of the patients. The mean response time was 5.2 months, which was similar to the PD monotherapy group. Wilkinson and Chodak analyzed 38 patients in whom prostate cancer progressed despite combined androgen blockade and then used intermediate-dose ketoconazole (300 mg 3 times daily) and replacement hydrocortisone [5]. Of the 38 patients, 21 (55.3%) had a PSA reduction >50%. The median time-to-progression and the median survival were 5 months and 12 months, respectively. In a prospective, randomized phase III trial, androgen-independent prostate cancer patients were targeted, and the therapeutic effect of anti-androgen withdrawal (AAWD) alone (n=132) was compared with that of simultaneous AAWD and ketoconazole (400 mg 3 times daily) plus hydrocortisone therapy (n=128) [6]. A PSA decline of >50% was observed in 11% of the patients undergoing AAWD. The median time-to-PSA progression was 5.9 months. A PSA decrease of >50% was observed in 27% of patients treated with concurrent AAWD and ketoconazole and in 32% of patients treated with ketoconazole after AAWD. The median time-to-PSA progression was 5.9 months in patients treated with AAWD alone and 8.6 months in patients treated with simultaneous AAWD and ketoconazole. According to Scholz et al, in 78 patients with high-dose ketoconazole (400 mg every 8 hours) and hydrocortisone, the median time-to-PSA progression and median survival time were 6.7 and 42.4 months, respectively [7]. A total of 34 (44 %) men had a decrease in PSA >75%. Their data indicated that a PSA decrease >75% predicted better survival than that in men with a <75% decrease.

Estramustine, a combination of estradiol phosphate and nornitrogen mustard, shows cytotoxicity by suppressing microtubules. Estramustine has toxicity similar to estro-

gen because the metabolite, estrogen, acts as a hormone that lowers the blood level of testosterone, leading to suppression of testosterone-sensitive tumor growth [11,12]. Han et al compared HRPC patients treated with estramustine monotherapy (n=11), estramustine and etoposide (n=12), or dexamethasone (n=10) combination therapy. The total PSA response rate was 48.5%. In the monotherapy group, etoposide combination therapy group, and dexamethasone combination therapy group, the PSA response rates were 36.4%, 41.7%, and 70.0%, respectively [8]. The overall median time-to-progression was 5 months, whereas in the monotherapy group, etoposide combination therapy group, and dexamethasone combination therapy group, it was 5 months, 5.5 months, and 5 months, respectively. The overall 1 and 2 year survival rates were 63.6% and 27.6%, respectively. Hirano et al conducted a prospective study focusing on the efficacy of estramustine phosphate monotherapy after ADT in 29 HRPC patients; in 7 (24%) patients, the PSA decreased $>50\%$, the median duration of PSA response was 8.0 months, and the cancer-specific survival rates at 1 and 2 years were 72% and 53%, respectively [9]. The cancer-specific survival rate at 2 years was 83% in the PSA responders and 44% in the nonresponders.

In this study, 33.3% of the patients in the ketoconazole group had a PSA response, and the median progression-free survival was 5 months. In the estramustine group, 37.8% of the patients had a PSA response, and the median progression-free survival was 8 months, indicating that there was no statistically significant difference between the two groups. Furthermore, the PSA response and progression-free survival were similar to those reported in previous studies [4-9]. Because the second drugs were started at the time the disease had already progressed to CRPC, it was predictable that there would be no significant differences in the PSA response rates according to Gleason score and the clinical stage categorized at the time of prostate cancer diagnosis.

Small et al reported that 21% of ketoconazole-treated patients experienced grade 3 and 4 toxicities, including neurologic toxicity (4%), malaise or fatigue (3%), and hepatic toxicity [6]. According to Wilkinson et al, ketoconazole-related toxicity occurred in 31.6% of patients, consisting of nausea (13.2%), fatigue (10.6%), diarrhea (2.6%), visual disturbance (2.6%), and abnormal liver function tests (2.6%), and 6 (15.8%) patients discontinued ketoconazole treatment owing to intolerable side effects [5]. Estramustine commonly increases the risk of gastrointestinal problems, gynecomastia, lower extremity edema, and cardiovascular death. Estramustine can also increase the risk of thromboembolism, and in the study by Han et al, thromboembolism occurred in 6.1% of patients treated with estramustine [8]. Hirano et al reported that 15% of patients discontinued estramustine treatment due to severe gastrointestinal symptoms [9]. In this study, the common side effects reported in other studies were present, but the tolerance was relatively good, with $\leq$grade 2 side effects, and no patients discontinued the medication because of serious complications.

This study was not without limitations. First, besides the retrospective nature of the study and the small number of enrolled patients, we did not analyze disease-specific survival. Second, estramustine was a cytotoxic agent rather than a hormonal agent, but we used estramustine for its estrogenic effect. Third, we did not continue ADT because of Korean health insurance issues.

CONCLUSIONS

Both ketoconazole and estramustine showed a PSA decline in CRPC patients before systemic chemotherapy and had mild adverse effects. Thus, either ketoconazole or estramustine can be considered as a treatment option for progressed CRPC patients after primary hormonal therapy. Ketoconazole and estramustine should be used appropriately according to the general conditions of patients and with consideration of the potential side effects of the medications. Also, we suggest that comparing ketoconazole following estramustine and estramustine following ketoconazole would be beneficial to determine optimal secondary hormone therapy in CRPC patients before docetaxel chemotherapy.

Conflicts of Interest

The authors have nothing to disclose.

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