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Comparison of Abiraterone Acetate Versus Ketoconazole in Patients with Metastatic Castration Resistant Prostate Cancer Refractory to Docetaxel

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Abstract

BACKGROUND—Abiraterone, a potent CYP 17 inhibitor, is standard treatment in docetaxel refractory, metastatic castrate resistant prostate cancer (mCRPC). However, in countries where abiraterone has not been approved yet, or for patients who cannot afford it, ketoconazole is used as an alternative CYP 17 inhibitor. Although preclinical data suggests that ketoconazole is a less potent inhibitor of CYP 17, there are limited clinical data comparing both agents. We aimed to compare the clinical effectiveness of abiraterone versus ketoconazole in docetaxel refractory mCRPC.

METHODS—Records from mCRPC patients treated with ketoconazole (international multi-center database, n = 162) were reviewed retrospectively. Twenty-six patients treated post docetaxel were individually matched by clinicopathologic factors to patients treated with abiraterone (national multicenter database, n = 140). We compared the PSA response, biochemical and radiological progression free survival (PFS), and overall survival (OS) between the groups. PFS and OS were determined by Cox regression.

RESULTS—The groups were matched by Gleason score, pre-treatment disease extent, ECOG PS, pre-treatment risk category (Keizman, Oncologist 2012). Furthermore, they were balanced regarding other known confounding risk factors. In the groups of abiraterone versus ketoconazole, PSA response was 46% versus 19% (OR 4.3, $P = 0.04$), median biochemical PFS 7 versus 2 months (HR 1.54, $P = 0.02$), median radiological PFS 8 versus 2.5 months (HR 1.8, $P = 0.043$), median OS 19 versus 11 months (HR 0.53, $P = 0.79$), and treatment interruption d/t severe adverse events 8% (n = 2) versus 31% (n = 8) (OR 0.6, $P = 0.023$).

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CONCLUSIONS—In docetaxel refractory mCRPC, the outcome of abiraterone treatment may be superior to ketoconazole.

Keywords

abiraterone; ketoconazole; metastatic castration resistant and docetaxel refractory prostate cancer; outcome

INTRODUCTION

Prostate cancer is the most common cancer affecting men and the second leading cause of male cancer mortality in the western world [1]. The initial treatment of metastatic prostate cancer consists of androgen deprivation therapy (ADT), usually using a luteinizing hormone-releasing hormone agonist and an antiandrogen [2]. Most patients will respond for 18–48 months, and eventually progress to a castration resistant state [3]. Docetaxel, which was the first agent to be associated with a survival benefit in this setting, is a standard therapy in the castration resistant state [4].

Activation of the androgen receptor is central in the pathogenesis of prostate cancer. In the castration resistant state the AR is exquisitely sensitive to low levels of androgens through its gene amplification, overexpression, activating mutation as well as enhancement of its responses and signaling by stimulation of kinases [5–7]. The source of androgens activating the androgen receptor in the castration resistant state is the adrenal gland where 10–30% of total serum androgens are produced, and intratumoral production of androgens through overexpression of enzymes including the CYP17A1, a key enzyme for de novo steroid and androgen biosynthesis has been emphasized [5–11].

The imidazole antifungal agent ketoconazole, which inhibits several cytochrome *P*450 enzymes including CYP17A1, suppresses adrenal and intratumoral steroidogenesis by inhibiting the conversion of cholesterol to pregnenolone [7–8,12]. It has been used for more than 30 years in the treatment of castration resistant prostate cancer with reported PSA response rate and time to progression of 20–75% and 3–10 months, respectively [6–8,13–17,23,24].

Abiraterone acetate is a more potent and selective CYP 17 inhibitor, including both 17,20-lyase and 17- α -hydroxylase [7,8]. It blocks the synthesis of androgens in the testis, adrenal glands, and prostate, without causing adrenal insufficiency. Early clinical trials in patients with metastatic castration resistant prostate cancer demonstrated that abiraterone acetate is safe and effective [7,18–21]. Subsequently, a prospective randomized trial that demonstrated a survival advantage with the combination of abiraterone plus prednisone over placebo plus prednisone, in men with metastatic castration resistant prostate cancer who had failed docetaxel [22], led to the approval of Abiraterone in the United States and Europe.

In countries where abiraterone has not been approved yet, or for patients who cannot afford it, ketoconazole is used as an alternative CYP 17 inhibitor. Although preclinical data suggests that ketoconazole is a less potent inhibitor of CYP 17 [7–8], there are limited

clinical data comparing both agents. Thus we aimed to compare the clinical effectiveness of abiraterone versus ketoconazole in mCRPC refractory to docetaxel.

MATERIALS AND METHODS

Patients

We reviewed the records of patients (unselected cohort, international multicenter database, $n=162$) with evidence of metastatic castration resistant prostate cancer who were treated with ketoconazole, and followed by medical oncologists, at four centers across two different countries: the United States (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Baltimore, MD) and Israel (Institute of Oncology, Meir Medical Center, Kfar Saba; Department of Oncology, Asaf Harofe Medical Center, Zerifin; Department of Oncology, Rambam Medical Center, Haifa). Patients treated with ketoconazole after failing docetaxel based chemotherapy were identified and individually matched by clinicopathologic factors to patients treated with abiraterone (unselected cohort, Israeli national multicenter database, $n=140$). Before initiation of ketoconazole or abiraterone treatment, all patients had objective biochemical (PSA) and/or clinical (scans) disease progression on gonadal suppression (orchiectomy or GnRH-agonist). Patient data were retrospectively and personally collected by the investigator D.K. from electronic medical records and paper charts. Outcome data was frozen on June 30, 2013.

Ketoconazole and Abiraterone Treatment

Patients were maintained on gonadal suppression (orchiectomy or GnRH-agonist), staged with a CT scan and bone scan, and treated with ketoconazole 200 or 400 mg three times day orally, with replacement doses of hydrocortisone (30 mg morning and 10 mg night) or abiraterone 1,000 mg once a day, with replacement doses of prednisone 10 mg once a day. Patients were evaluated for adverse events and response to therapy with history, physical examination, and laboratory analysis, including liver function tests and PSA, once a month. Bone scan and CT scan were repeated upon clinical (symptoms) and/or biochemical progression. Treatment was continued until evidence of imaging (scans) progression, or unacceptable adverse events.

Statistical Analysis

Data were analyzed retrospectively. Patients in the groups of ketoconazole and abiraterone therapies were individually matched by the combined Gleason score, pre-treatment disease extent (limited vs. extensive) [23], ECOG performance status, pre-treatment anemia, and pre-treatment risk category (categorized as favorable =0–1 factors, intermediate =2 factors, or poor = 3–4 factors, based on pre-treatment neutrophil to lymphocyte ratio >3 , pre-treatment PSA doubling time <3 months, and prior response to GnRH-agonist <24 months/antiandrogen <6 months) [24].

Pre-treatment PSA doubling time (PSADT) was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement for each patient, using all PSAs >0.1 ng/ml that confirmed progressive castrate resistant prostate cancer by PSA progression [24]. Disease extent was defined as limited if

involving only the axial skeleton and/or lymph nodes, or extensive if involving the appendicular skeleton and/or visceral organs [23].

PSA response was defined as $\geq 50\%$ PSA decline from baseline [24]. Biochemical progression free survival (PFS) was defined as the time from treatment initiation until biochemical progression, as evident by a PSA increase of $\geq 25\%$ and ≥ 2 ng/ml from baseline or nadir (confirmed by a second PSA), as defined by the Prostate Cancer Clinical Trials Working Group criteria [25]. Clinical progression was defined as new findings on physical examination or scans. For the evaluation of measurable disease response and progression, the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 was applied [26]. Bone scan progression (non measurable disease) was defined as two or more new lesions on bone scan [3]. Scans response was assessed by independent radiologists and treating physicians, and personally reviewed by the investigator D.K. Patients who did not progress by June 30, 2013 were censored in progression free survival analysis.

Clinical characteristics, PSA response, biochemical and radiological progression free survival, and overall survival were compared between the ketoconazole and abiraterone groups, by chi-square test or Fisher's Exact test for nominal data, and two-sample *t*-test (or Mann–Whitney non-parametric test) for continuous measures, each when appropriate. Progression free survival time and overall survival time were analyzed using Cox proportional hazards regression model for comparison between the two groups.

Furthermore, a univariate analysis (using logistic regression for response rate and Cox regression model for progression free survival) and multivariate analysis (using Cox proportional hazards regression model), of the above mentioned prognostic factors, were done for the entire patient cohort, to determine if the use of abiraterone is independently associated with treatment outcome.

Progression free survival and overall survival times (probability and median) were estimated from Kaplan–Meier curve. Data were analyzed using SPSS-21 software.

Regulatory Considerations

The research was carried out in accordance with the approval by the IRB committee of our institutions.

RESULTS

Study Group

Twenty-six patients with metastatic castration resistant and docetaxel refractory prostate cancer, who were treated by ketoconazole between the years 2006 and 2013, were included in the present study. Sixteen patients were American, and 10 Israeli. Twenty-one patients were treated with ketoconazole 600 mg/day, and five patients with ketoconazole 1,200 mg/day. They were individually matched to patients treated with abiraterone between the years 2011–2013, by the following clinicopathologic factors: combined Gleason score, pre-treatment disease extent (limited vs. extensive) [23], ECOG performance status, pre-treatment anemia, and pre-treatment risk category (categorized as favorable =0–1 factors,

intermediate =2 factors, or poor =3–4 factors, based on pre-treatment neutrophil to lymphocyte ratio >3, pre-treatment PSA doubling time <3 months, and prior response to GnRH-agonist <24 months/antiandrogen <6 months) [24]. Baseline patient characteristics are listed in Table I.

Ketoconazole Versus Abiraterone Treatment

The comparison between the outcome of patients treated with abiraterone versus ketoconazole is shown in Table II. Clinical improvement (in ECOG performance status and/or disease associated symptoms as pain) was reported in 73% (n =19) versus 19% (n =5) (OR 15, $P < 0.0001$). PSA response (50% PSA decline from baseline) was noted in 46% (n =12) versus 19% (n =5) (OR 4.3, $P = 0.04$). Median biochemical progression free survival was 7 versus 2 months (HR 1.54, $P = 0.02$), and median radiological progression free survival 8 versus 2.5 months (HR 1.8, $P = 0.043$) (Fig. 1). Median overall survival was 19 versus 11 months (HR 0.53, $P = 0.79$) (Fig. 2). Treatment interruption d/t severe adverse events occurred in 8% (n =2) versus 31% (n =8) (OR 0.6, $P = 0.023$). In patients treated with abiraterone treatment was interrupted d/t liver dysfunction (n =1), and fluid retention and edema (n =1). In patients treated with ketoconazole treatment was interrupted d/t liver dysfunction (n =2), fluid retention and edema (n =2), nausea/vomiting (n =2), abdominal pain (n =1), and thrombocytopenia (n =1).

Univariate and Multivariate Analysis of the Entire Patient Cohort (n =52)

In a multivariate analysis of clinicopathologic prognostic factors among the entire patient cohort, treatment type (abiraterone vs. ketoconazole; HR 0.5, $P = 0.01$), pre-treatment PSA level (HR 1.1, $P < 0.0001$), and pre-treatment risk category (HR 5.9 and 2.2, $P = 0.001$ and 0.04, for low and intermediate risk vs. high risk, respectively) were associated with radiological progression free survival. Treatment type (abiraterone vs. ketoconazole; HR 0.62, $P = 0.028$), ECOG performance statue (HR 0.2, $P = 0.001$), and pre-treatment risk category (HR 7.6 and 2.4, $P < 0.0001$ and 0.06, for low and intermediate risk vs. high risk, respectively) were associated with overall survival (Table III).

DISCUSSION

The present study suggests that in mCRPC refractory to docetaxel, the outcome of treatment with abiraterone may be superior to ketoconazole. In this retrospective study, patients treated with abiraterone had a significant increase of clinical improvement, PSA response, and biochemical and radiological progression free survival. Patients treated with abiraterone had also a better overall survival (HR 0.53), although not statistically significant at 0.05 significance level (might have been in a larger patient cohort), and less treatment interruption d/t severe adverse events (OR 0.6). Finally, in a multivariate analysis of clinicopathologic prognostic factors among the entire patient cohort, the use of abiraterone was independently associated with radiological progression free survival and overall survival.

The present study observation is supported by existing preclinical suggesting that abiraterone acetate is a more potent and selective CYP 17 inhibitor than ketoconazole [7–8].

In human microsomes, the concentration of abiraterone required to produce 50% inhibition of CYP17 is approximately 10% that of ketoconazole [27]. The activity of abiraterone acetate is attributed to the reduction of the total androgen pool, with a reduction in levels of both adrenal androgens and testosterone, thereby inhibiting persistent signaling through the androgen receptor [27]. Importantly, unlike ketoconazole, no rise in steroids downstream of CYP17 are observed at disease progression in patients treated with abiraterone, indicating durable irreversible CYP17 inhibition [28]. Furthermore, abiraterone acetate has demonstrated activity in patients previously treated with ketoconazole [27].

Our study has some limitations. First, this is a retrospective study of a widely varied patient population. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Second, the total number of 52 patients analyzed is relatively small. Other clinicopathologic factors that were not found to be significantly associated with outcome in the present study might have been important in a larger patient cohort. Third, since this is a retrospective study, different criteria might have been followed in the different institutions to define progression. Fourth, the pre-treatment pain was worse in the abiraterone group (Table I). This may have biased the clinical improvement noted with abiraterone. Fifth, because the prognostic marker LDH [29] is not routinely measured in our institutions, we could not analyze its association with outcome. Fifth, due to the small number of patients treated with ketoconazole 1,200 mg per day (n =5), we were unable to compare the effect of ketoconazole dose (600 vs. 1,200 mg) on treatment outcome in the present study. However, in a prior study reported by our group [23], the progression free survival was not significantly different between the two doses. Sixth, due to the small number of patients, we were unable to assess the impact of geographic variation (American vs. Israeli) on ketoconazole treatment outcome. Finally, after treatment initiation, bone scan and CT scan were not done regularly. Scans were repeated only upon biochemical or clinical (symptoms) progression.

Despite these limitations, our clinical observation that abiraterone therapy seem to improve patient outcome might contribute to treatment decisions and selection. To the best of our knowledge, there have been no previous clinical studies comparing abiraterone acetate and ketoconazole. Further studies may be warranted to confirm our observation in larger patient cohorts. These may include retrospective subgroup analysis of previously completed large trials of ketoconazole and abiraterone.

CONCLUSIONS

In docetaxel refractory mCRPC, the outcome of abiraterone treatment may be superior to ketoconazole.

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Fig. 1.
Radiological progression free survival stratified by treatment (abirateronevs. ketoconazole).

Fig. 2.
Overall survival stratified by treatment (abiraterone vs. ketoconazole).

TABLE I

Baseline Patient Characteristics

Parameter	Ketoconazole (n =26)	Abiraterone (n =26)	P-value
Age:median (range)	69 (51–83)	71 (55–89)	0.56
Combined Gleason grade			
6	n =1	n =1	1
7	n =6	n =6	
8–10	n =19	n =19	
Prior progression free survival (months) on GnRH-agonist or orchiectomy as primary androgen deprivation for metastatic disease: median (range)	38 (3–120)	20 (2–204)	0.16
Prior progression free survival (months) on docetaxel: median (range)	7 (2–15)	6 (2–18)	0.66
Pre-treatment PSA doubling <3 months	62% (n =16)	65% (n =17)	0.77
Pre-treatment PSA level (ng/ml): median (range)	110 (8–930)	232 (15–1230)	0.21
Disease extent			
Limited (axial skeleton and/or lymph nodes)	8% (n =2)	8% (n =2)	1
Extensive (appendicular skeleton and/or visceral organs)	92% (n =24)	92% (n =24)	
Visceral organs involvement	19% (n =5)	27% (n =7)	0.51
ECOG performance status			
0–1	77% (n =20)	77% (n =20)	1
2	23% (n =6)	23% (n =6)	
Pre-treatment moderate-severe pain	12% (n =3)	42% (n =11)	0.027
Elevated pre-treatment	35% (n =9)	38% (n =10)	0.77
Alkaline phosphatase			
Pre-treatment anemia	92% (n =24)	92% (n =24)	1
Median hemoglobin	11.8	11.3	0.83
Pre-treatment neutrophil to lymphocyte ratio >3	50% (n =13)	54% (n =14)	0.78
Pre-treatment risk category (Ref. [24])			
Favorable	n =9	n =9	1
Intermediate	n =4	n =4	
Poor	n =13	n =13	

TABLE II

Comparison Between the Outcome of Patients Treated With Abiraterone Versus Ketoconazole

Parameter	Ketoconazole (n =26)	Abiraterone (n =26)	OR, <i>P</i>
Clinical improvement (in ECOG performance status and disease associated symptoms as pain)	19% (n =5)	73% (n =19)	OR 15, <i>P</i> <0.0001
PSA response (< 50% PSA decline from baseline)	19% (n =5)	46% (n =12)	OR 4.3, <i>P</i> =0.04
Biochemical progression free survival (months): median, mean $\pm$ SD (range)	2, 5 $\pm$ 4 (1–24)	7, 8 $\pm$ 5 (1–27)	HR 1.54, <i>P</i> =0.02
Radiological progression free survival (months): median, mean $\pm$ SD (range)	2.5, 5 $\pm$ 3 (1–24)	8, 9 $\pm$ 6 (3–27)	HR 1.8, <i>P</i> =0.043
Overall survival (months): median, mean $\pm$ SD (range)	11, 13 $\pm$ 8 (1–52)	19, 18 $\pm$ 9 (2–31)	HR 0.53, <i>P</i> =0.79
Treatment interruption d/t severe adverse events	31% (n =8)	8% (n =2)	OR 0.6, <i>P</i> =0.023

TABLE III

Univariate and Multivariate Analysis of the Entire Patient Cohort (n =52)

Parameter	Distribution	Univariate analysis (HR, P)		Multivariate analysis (HR, P)	
		rPFS	OS	rPFS	OS
Age: median (range)	71 (51–89)	NS	1.04, 0.04		NS
Combined Gleason grade					
6	4% (n =2)	NS	NS		
7	23% (n =12)				
8–10	73% (n =38)				
Prior progression free survival (months) on docetaxel: median (range)	6.5 (2–18)	0.93, 0.047	0.92, 0.046	NS	NS
Pre-treatment PSA level (ng/ml): median (range)	149 (8–1230)	1.1, <0.0001	1.1, <0.0001	1.1, <0.0001	NS
Disease extent					
Limited (axial skeleton and/or lymph nodes)	8% (n =4)	NS	NS		
Extensive (appendicular Skeleton and/or visceral organs)	92% (n =48)				
ECOG performance status					
0–1	77% (n =40)	NS	4.06, <0.0001		0.2, 0.001
2	23% (n =12)				
Pre-treatment moderate-severe pain	27% (n =14)	NS	NS		
Elevated pre-treatment	37% (n =19)	NS	NS		
Alkaline phosphatase					
Pre-treatment anemia	92% (n =48)	NS	NS		
Median hemoglobin	11.6	NS	NS		
Pre-treatment risk category (Ref. [24])					
Favorable	35% (n =18)	5.01, 0.01 (vs. poor risk)	3.7, 0.007 (vs. poor risk)	5.9, 0.001 (vs. poor risk)	7.6, <0.0001 (vs. poor risk)
Intermediate	15% (n =8)	2.88, 0.04 (vs. poor risk)	1.95, 0.07 (vs. poor risk)	2.2, 0.04 (vs. poor risk)	2.4, 0.06 (vs. poor risk)
Poor	50% (n =26)				
Therapy					
Abiraterone	50% (n =26)	0.57, 0.024 versus ketoconazole	0.048, 0.52 versus ketoconazole	0.5, 0.01 versus ketoconazole	0.62, 0.028 versus ketoconazole
Ketoconazole	50% (n =26)				