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Clinical Experience of Steroid Switch from Prednisone to Dexamethasone in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Abiraterone Acetate

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Steroid · Switch · Prostate cancer · Abiraterone

Abstract
Objective: To evaluate the therapeutic efficacy of a steroid switch from prednisone to dexamethasone in Asians with metastatic castration-resistant prostate cancer (mCRPC) that progressed after docetaxel chemotherapy. ***Methods:*** This study included postdocetaxel patients with mCRPC treated with abiraterone acetate combined with prednisone (AA + P) who had experienced prostate-specific antigen (PSA) progression. All patients underwent a steroid switch from prednisone (10 mg/day) to dexamethasone (1 mg/day). The PSA level and clinical symptoms were recorded. Moreover, follow-up was conducted until patients were either lost to follow-up or death. ***Results:*** This study included 11 patients from a single center in Taiwan. The median follow-up time starting from AA + P treatment was 19.47 months. Seven patients (63.64%) had >30% PSA decline, and 6 patients (54.55%) had >50% PSA decline. The median percentage of PSA decline was 83.6%. The median time until PSA progression after the steroid switch was 11.38 months. No adverse events greater than grade 3 were noted. ***Conclusions:*** Steroid switching is a feasible and effective therapy in docetaxel-treated Asian patients with mCRPC.

Introduction

The first-line therapy for metastatic prostate cancer is androgen deprivation therapy (ADT) [1] with beneficial clinical responses observed in most patients. However, most of these patients progress to metastatic castration-resistant prostate cancer (mCRPC) within 2–3 years [2]. Nevertheless, abiraterone acetate (AA) can cause further androgen deprivation through inhibition of both 17α-hydroxylase (hydroxylase) and 17,20-lyase (lyase) reactions catalyzed by CYP17A1 [3]. However, AA should be used with prednisone (AA + P) to reduce the side effects of mineralocorticoid overproduction [3, 4]. A phase III study data (COU-AA-301) revealed that AA + P combined with ADT significantly prolonged overall survival

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time compared with ADT monotherapy in patients with docetaxel-treated mCRPC [5]. Furthermore, a survival benefit was observed in docetaxel-naïve mCRPC patients in the COU-AA-302 clinical trial [6]. AA + P is one of the standard treatments for mCRPC [1]. However, AA + P needs to be discontinued owing to cancer resistance or intolerable adverse effects. Moreover, limited choices are available that can be used in these vulnerable patients with metastatic cancer [1]. Therefore, a simple and acceptable subsequent treatment should be developed.

Compared with prednisone, dexamethasone provided better clinical and prostate-specific antigen (PSA) responses in patients with mCRPC [7]. Effects of "steroid switch" – changing from prednisone to dexamethasone – in patients treated with AA have been published [8]. Real-world data revealed that after switching to dexamethasone, 20–48.15% of patients had a >50% decrease in PSA, with time to PSA progression of 2.9–10.35 months, as well as limited side effects [9–11]. In addition, a phase II pilot study (SWITCH trial) demonstrated the feasibility of a steroid switch in patients with mCRPC who progressed while on AA + P treatment [11]. The possible mechanism could be related to medication potency and glucocorticoid receptor affinity [12]. However, the previous "steroid switch" studies had a limited study population and lacked clinical data from Asian countries. Notably, the incidence and mortality rate in Asian countries differed from those in Western countries [13]. Environmental factors play a significant role, and varying genetic backgrounds may be crucial too. Herein, we report a real-world experience of AA treatment plus a steroid switch through long-term follow-up in Taiwanese patients.

Material and Methods

Data Sources

This retrospective study was in patients with mCRPC treated with AA + P (AA 1,000 mg once daily plus prednisone 5 mg twice a day) from December 2014 to April 2016 at Changhua Christian Hospital. All patients were treated by the same doctor (Dr. H.J. Shih). This study was approved by the Institutional Review Board of Changhua Christian Hospital (Protocol No. 170218). The study was performed as per the Declaration of Helsinki.

Patients

In Taiwan, the National Health Insurance benefits package has included postdocetaxel patients with mCRPC since December 2014 and patients with predocetaxel mCRPC since September 2017. This study included postdocetaxel patients with mCRPC who received AA + P and had PSA progression. For patients on AA + P treatment, PSA evaluation was performed every month, and a bone scan was performed if symptomatic progression was detected or every 6 months in our clinical practice. PSA progression was defined according to the COU-AA-301 clinical trial [5]. In brief, PSA progression was defined as a 25% rise above the baseline for patients without a PSA decrease, a 25% increase above the nadir for patients with <50% PSA decrease, and a 50% rise above the nadir for patients with >50% PSA decrease. All PSA levels increased to at least 5 ng/mL above the baseline or nadir, and a second rise was confirmed at least 1 week later. The switch from prednisone to dexamethasone 0.5 mg twice a day was performed if PSA progression was noted. The maximal values of PSA declines were recorded. The definition of PSA decline was confirmed based on the presence of a persistent PSA value at least 3 weeks later. The PSA response was defined as a >30% decline in the PSA value after the steroid switch. Durable response was defined as a continuous PSA response lasting >6 months, and durable response rate was recorded as per the previous report [14]. PSA progression after the steroid switch was defined as per the Prostate Cancer Working Group 2 (PCWG2) criteria; it was defined as a >25% increase above the nadir and an absolute PSA increase of 2 ng/mL or more from the nadir [15], and it was confirmed based on the presence of a second PSA value >2 weeks later. Time to PSA progression was defined as the duration from the date of the steroid switch to the date of PSA progression as per the PCWG2 criteria [15]. Patients who received the steroid switch were allowed to continue on AA and dexamethasone (AA + D) treatment if they had PSA progression. Adverse effects, reported in the medical record, before and after the steroid switch were recorded. The treatment was stopped in case of clinical progression.

Statistical Analyses

SPSS (v 21.0, SPSS Inc., IBM Corporation, Somers, NY, USA) was used for data analyses. The differences in the median PSA level at the time of the steroid switch, the time to PSA progression on AA + P, previous hormone-sensitive duration, and the percentage of PSA change while on AA + P treatment between the steroid switch responders and nonresponders were examined using the independent *t* test. A p value of <0.05 indicated statistical significance.

Results

Patient Characteristics

Overall, 11 patients with mCRPC received a steroid switch from prednisone 5 mg twice a day to dexamethasone 0.5 mg twice a day. All patients had received docetaxel plus prednisone (5 mg twice a day) treatment before AA + P treatment. Notably, prednisone was not used after completing docetaxel treatment. All patients had bone metastasis and were asymptomatic or had minimal symptoms. No visceral metastasis was noted. The median age at the steroid switch was 76 years. The median (range) Eastern Cooperative Oncology Group performance status (ECOG-PS) score at the time of AA + P treatment was 1 (1–2). All patients were followed up until loss to follow-up or death. The median (range) follow-up time from AA + P treatment until death or loss to follow-up was 19.47 months (10.03–50.17 months).

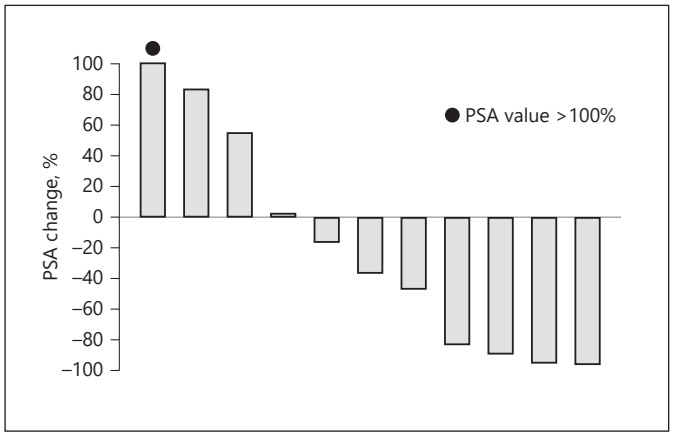

Fig. 1. Waterfall graph of PSA declines after steroid switch at 3 months.

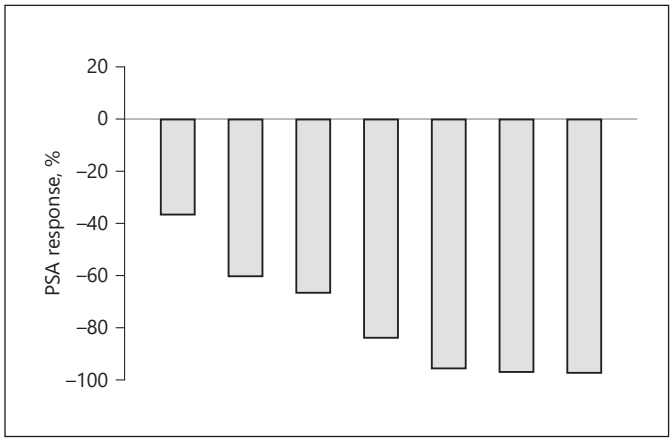

Fig. 2. Waterfall graph of maximum PSA declines after steroid switch.

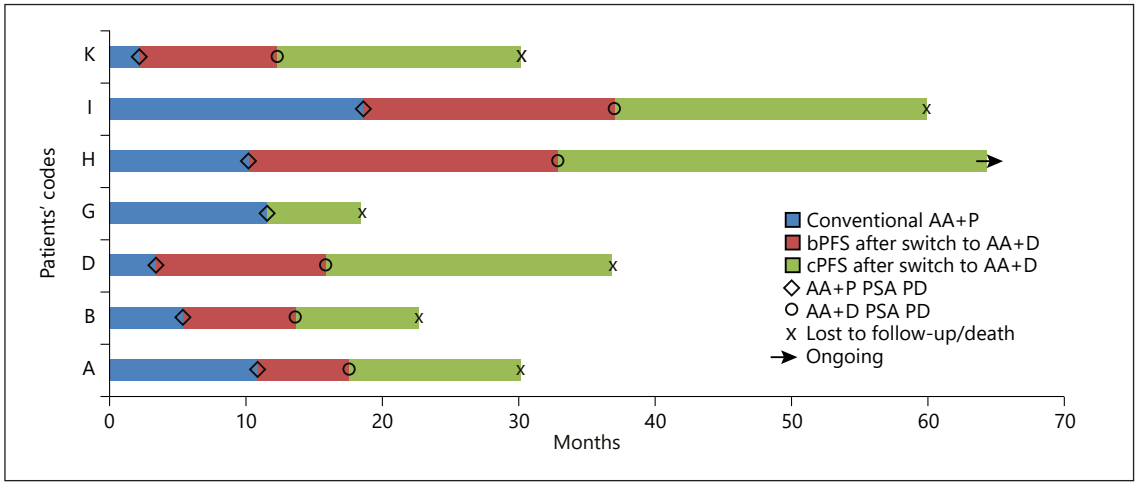

Fig. 3. Swim lanes represented the 7 patients with PSA response to steroid switch. AA + P, abiraterone plus prednisone; AA + D, abiraterone plus dexamethasone; PD, progression.

Treatment Response

After starting AA + P treatment, PSA decline was observed in 10 patients, including 9 patients (81.82%) with a >30% PSA decline and 7 patients (63.64%) with a >50% PSA decline. The median (range) time to PSA progression on AA + P was 6 months (2.1–18.67 months). Only 1 patient had no PSA decline.

All 11 patients received the steroid switch from prednisone to dexamethasone when PSA progression occurred. The median (range) PSA at the time of the steroid switch was 61.17 ng/mL (5.7–2,031.32 ng/mL). Seven patients had a PSA response, with the median (range) percentage of PSA decline of 83.6% (37–97.4%). Overall, 7 of 11 patients (63.64%) had a PSA response (PSA decline of >30%). Moreover, a PSA decline of >50% was observed in 6 patients (54.55%). Six of 7 patients with PSA response achieved durable response for >6 months, and the durable response rate was 85.71%. One patient with no PSA response on AA + P treatment had a PSA decline of 97.4% after the steroid switch to dexamethasone. The PSA declines at 3 months and maximum PSA declines are presented in Figures 1 and 2, respectively. Regarding the PSA response to the steroid switch, the median (range) nadir PSA after the steroid switch was 8.48 ng/mL (0.24–785.58 ng/mL), and the median (range) time to nadir PSA was 3.7 months (2.73–11.63 months). The median (range) time to PSA progression after the steroid switch was 11.38 months (6.6–22.83 months). One patient was still receiving AA + D therapy at the time of analysis without clinical progression. Six patients died from prostate cancer, 1 patient died

Table 1. Prognostic factors related to response to the steroid switch

	Responders	Nonresponders	*p* value[a]
Patients, *n*	7	4	
PSA level at the time of switch, median (range)	184.48 (5.7–2,031.32)	37.89 (8.35–200.47)	0.181
The time to PSA progression on AA + P, months, median (range)	5.37 (2.1–18.67)	6.23 (4.67–11.47)	0.811
Previous hormone-sensitive duration, months, median (range)	25.47 (4.77–49)	19.35 (13.3–100.73)	0.58
PSA decline percentage after AA + P, median (range)	44.25 (14.5–99.8)	91.75 (75.8–92.6)	0.069

PSA, prostate-specific antigen; AA + P, abiraterone acetate combined with prednisone. [a] Tested by the independent *t* test.

from heart disease, and 3 patients were lost to follow-up. All patients received the best supportive care after clinical progression. The clinical courses of 7 patients with response to steroid switch are listed in Figure 3.

A previous study found the PSA level at the time of the steroid switch, the time to PSA progression on AA + P, and previous hormone-sensitive duration to be the prognostic factors for progression-free survival in patients on AA + D treatment [10]. Our study analyzed the prognostic factors related to the response to the steroid switch (Table 1). The median (range) previous hormone-sensitive duration in AA + D responders and nonresponders was 25.47 (4.77–49) and 19.35 (13.3–100.73) months, respectively (p = 0.58). The median (range) PSA level at the time of steroid switch in AA + D responders and nonresponders was 184.48 (5.7–2,031.32) and 37.89 (8.35–200.47) ng/mL, respectively (p = 0.181). The median (range) duration of AA + P treatment in AA + D responders and nonresponders was 5.37 (2.1–18.67) and 6.23 (4.67–11.47) months, respectively (p = 0.811). No significant difference was observed in these prognostic factors between AA + D responders and nonresponders. However, we noted that all steroid switch nonresponders experienced an excellent PSA response with AA + P treatment (all >50%), and 4 of the 7 steroid switch responders experienced a <50% PSA response with AA + P treatment. The median (range) PSA decline percentage after AA + P treatment in AA + D responders and AA + D nonresponders was 44.25% (14.5–99.8%) and 91.75% (75.8–92.6%), respectively (p = 0.069).

Safety

All patients tolerated AA + P and AA + D treatment without dose adjustment. Regarding possible abiraterone-specific adverse events, only 1 patient experienced grade 2 hypertension after AA + P treatment, and it was well controlled with antihypertensive medication. However, blood pressure was stable after the steroid switch, and antihypertensive medication was discontinued. No electrolyte imbalance or leg edema was observed.

Discussion

Our study retrospectively evaluated the therapeutic effects of AA with a steroid switch in postdocetaxel Taiwanese patients with mCRPC. Our study results demonstrated that 7 of 11 patients (63.64%) had a PSA response (PSA decline of >30%), and 6 of 11 patients (54.55%) had a >50% PSA decline after steroid switch from prednisone to dexamethasone. Notably, in AA + D therapy responders, abiraterone treatment was prolonged to approximately 1 year (11.38 months) after biochemical failure with AA + P therapy. Nonetheless, these elderly and fragile patients still have limited treatment options. Nevertheless, the steroid switch provides hope for patients who have failed AA + P treatment.

Steroids have been used as the secondary hormone therapy for patients with mCRPC [7]. Clinical studies demonstrated a better response rate and longer time to PSA progression with dexamethasone than with prednisone [7, 16]. Moreover, the same trend was identified in a randomized phase 2 trial [7]. According to previous study findings, dexamethasone with AA is a better combination. This concept is supported by the results of a randomized phase 2 study (SWITCH study) [11]. The combination of AA with dexamethasone (0.5 mg once daily) was more active than that with prednisone (5 mg twice daily) [11]. Because of the limited treatments available for patients treated with AA + P who had disease progression, a steroid switch is considered a reasonable subsequent treatment. In 2014, Lorente et al. [9] reported the clinical result of a steroid switch in 4 chemonaïve and 26 postchemotherapy patients with mCRPC. As per their report, 20% of patients had a >50% PSA decline and 39%

of patients had a >30% PSA decline [9]. In addition, the mean time to PSA progression was 11.7 weeks [9]. Furthermore, similar results were reported in a phase 2 pilot study (SWITCH study) [11]. This study included 14 chemonaïve and 12 postchemotherapy patients, of which 34.6% of patients had a >50% PSA decline with the time to PSA progression of 5.3 months [11]. Our study included 11 consecutive postchemotherapy patients who were treated with AA and received a steroid switch. A >50% PSA decline was observed in 54.55% of patients, and time to PSA progression was 11.38 months. As per our study results, a steroid switch is an effective and tolerable treatment for postchemotherapy patients with mCRPC who had received AA + P treatment.

Notably, prognostic factors are needed to predict the treatment outcomes after the steroid switch. Our study determined that steroid switch nonresponders experienced an excellent PSA response to AA + P treatment, and most steroid switch responders had a poor PSA response to AA + P treatment. However, studies with more patients are needed to confirm our findings. Fenioux et al. [10] demonstrated that previous long (>5 years) hormone sensitivity duration, low PSA level (<50 ng/mL) at the time of the switch, and short time (<6 months) to PSA progression on AA + P treatment were the prognostic factors of excellent responses in patients treated with AA + D. However, our study results revealed that previous hormone sensitivity duration, PSA level at the time of the switch, and time to PSA progression on AA + P were not significantly different between steroid switch responders and nonresponders. The inconsistency between the findings of our study and previous study may be because of the small sample size and varying basic characteristics of patients included. Moreover, the study populations included different ethnicities (Western vs. Asian) and different previous treatment (100 vs. 14.58% patients, respectively, received prior docetaxel treatment in our study and that of Fenioux et al. [10]).

Our study is the first clinical case series reporting the treatment response to steroid switch in postdocetaxel Asian patients with mCRPC. In 2018, a case report in Japan revealed an excellent PSA response to a steroid switch (97.24% PSA decline from baseline) [12]. Furthermore, the results from our study demonstrated better PSA response rates (83.6% PSA decline from baseline), longer treatment duration (11.38 months), and durable treatment response (durable response rate 85.71%) after the steroid switch compared with previous reports in Western countries [8–11]. Nevertheless, genetic factors may play a crucial role in treatment response differences between Western and Asian countries. A meta-analysis of genetic studies confirmed that the prostate cancer predisposition loci differed between Western and Asian countries [17]. Notably, the racial differences of somatic alteration and single nucleotide polymorphisms in prostate tumors between Western and Asian populations have been reported [18]. Nonetheless, further studies are needed to elucidate the definite mechanisms underlying the differences between Western and Asian populations regarding treatment response to a steroid switch.

Oral glucocorticoids were used to prevent the secondary mineralocorticoid excess induced by AA [4]. However, long-term oral glucocorticoids may increase the risk of adverse effects. Atarrd et al. [19] conducted a randomized, open-label phase 2 study to evaluate the safety of the combination of oral glucocorticoid regimens (prednisone 5 mg, twice daily; prednisone 5 mg, once daily; prednisone 2.5 mg, twice daily; dexamethasone 0.5 mg, once daily) with AA in predocetaxel patients with mCRPC in European countries. Increase in serum insulin and decrease in bone mineral density were noted in patients treated with dexamethasone and AA [18]. However, there was no detectable reduction of patient-reported quality of life in all treatment groups [18]. In our study, no glucocorticoid-related side effects were reported in postdocetaxel patients with mCRPC. However, limited patients were included in Atarrd et al. [19] and our studies. Therefore, further studies are required to evaluate the possible side effects induced by oral glucocorticoids.

Our retrospective clinical study revealed an excellent PSA response and durable treatment duration with the steroid switch after AA + P treatment failure in postdocetaxel Taiwanese patients with mCRPC. Hence, this simple and feasible alternative treatment can be safely used in these fragile patients. Nonetheless, our study had some limitations. First, our study had a small sample size. Hence, a large sample size involving patients from Asian countries is needed to obtain conclusive results. Second, the dose of dexamethasone used in our study (1 mg) is different than that used in most previous studies (0.5 mg). Therefore, further studies are needed to evaluate the treatment outcomes with varying doses of dexamethasone.

Conclusions

In postdocetaxel patients with mCRPC who received AA + P treatment, a steroid switch from prednisone to dexamethasone can prove to be an effective and durable alternative treatment in the case of PSA progression.

Statement of Ethics

This study was approved by the Institutional Review Board of Changhua Christian Hospital (Protocol No. 170218). The study was performed as per the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

H.J.S., K.H.L., Y.C.W., Y.C.F., P.S.T., and C.J.H. have made substantial contributions to the conception of the work, data acquisition, data analysis and interpretation, drafting of work, manuscript review, and final approval of the submitted version.

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