Corticosteroids alleviate adverse events associated with enzalutamide in patients with metastatic castration-resistant prostate cancer

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Abstract. The aim of the present study was to investigate the impact of the combined use of corticosteroid on adverse events (AEs) induced by enzalutamide (Enz) in patients with metastatic castration-resistant prostate cancer (mCRPC). The cohort of the present study included 121 consecutive patients with mCRPC who sequentially received androgen receptor-axis-targeted (ARAT) agents, abiraterone acetate (AA) and Enz, in any order, without prior docetaxel therapy. Detailed assessments of AEs during treatment with Enz were conducted according to whether or not corticosteroid was administered. Of these patients, 63 and 58 received ARAT therapy with the Enz-to-AA sequence (group 1) and the AA-to-Enz sequence (group 2), respectively. No patient in group 1 received corticosteroid during treatment with Enz, while corticosteroid was continuously administered in combination with Enz to all patients in group 2 following AA failure. When ARAT therapy was initiated, no significant differences in the major baseline characteristics were observed between the two groups. During Enz therapy, there were no significant differences in the incidence of any AEs or AEs ≥ grade 3 between the two groups. However, the incidences of fatigue and appetite loss in group 1 were significantly higher when compared with those in group 2. Furthermore, the combined use of corticosteroid was revealed to be independently associated with the prevention of fatigue and appetite loss during Enz therapy. The results of the present study suggested that the combined use of corticosteroids could reduce the incidence of certain types of AE, particularly fatigue and appetite loss, in mCRPC patients treated with Enz.

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Introduction

Over the past few years, the therapeutic strategy for patients with metastatic castration-resistant prostate cancer (mCRPC) has markedly changed with the approval of several novel agents with different mechanisms of action based on the promising outcomes of pivotal clinical trials (1,2). Despite significant progress in the field of treatment for mCRPC patients, particularly prolonged overall survivals, a number of clinical issues remain unresolved (3). Of these, it is very important to appropriately manage adverse events (AEs) associated with the use of these agents in order to maintain the quality of life and further improve the prognostic outcomes of mCRPC patients (4).

Enzalutamide (Enz) is a potent direct inhibitor of the androgen receptor, reported to act by inhibiting the binding of androgens to the androgen receptor (AR), AR nuclear translocation and AR-mediated DNA binding (5). In the PREVAIL and AFFIRM trials, Enz was demonstrated to significantly improve the overall survival (OS) of patients with doctaxel-naïve and -refractory mCRPC, respectively, compared with a placebo (6,7). In the clinical practice as well, Enz has been widely introduced as one of the standard agents into mCRPC patients irrespective of the previous history of docetaxel therapy (8,9). To date, however, there have been several studies characterizing comparatively unfavorable AE and quality of life (QoL) profiles associated with the use of Enz for mCRPC patients (9-12). For example, Thiery-Vuillemin *et al* reported that significant differences favoring abiraterone acetate (AA), another AR axis-targeted agent selectively inhibiting CYP17A1, over Enz for cognitive outcomes and fatigue during the first 3 months of treatment initiation for mCRPC patients (10), while Khalaf *et al* directly compared the efficacies of AA and Enz in docetaxel-naïve mCRPC patients, and showed that a higher proportion of patients experienced clinically meaningful worsening with Enz than AA for the physical and functional well-being domains (11).

Considering these findings, it is an urgent requirement to develop an effective solution to resolve Enz-associated AEs; therefore, in this study, we retrospectively investigated whether the combined use of corticosteroid could alleviate AEs induced by the administration of Enz in a total of 121 consecutive docetaxel-naïve mCRPC patients who sequentially received AA and Enz, in either order.

Patients and methods

Study design and patients. The design of this study was approved by the Research Ethics Committee of our institution, and the need to obtain informed consent for involvement in it from all of the included patients was waived because of its retrospective design. This was performed as a retrospective study by reviewing clinicopathological data from a total of 121 consecutive Japanese mCRPC patients who were sequentially treated with 2 androgen receptor-axis-targeted (ARAT) agents, AA and Enz, in either order, without prior treatment with docetaxel at our institutions between August 2014 and July 2018 in a routine clinical setting. All the patients included in this study had been histologically diagnosed with adenocarcinoma of the prostate, and subsequently received primary androgen deprivation therapy (ADT). Disease progression during the primary ADT, indicating the development of CRPC, was defined as prostate-specific antigen (PSA) or radiographic progression assessed using the Prostate Cancer Working Group 2 (PCWG2) criteria (6) and the Response Evaluation Criteria in Solid Tumors (7), respectively, despite maintenance of the serum testosterone level <50 ng/dl.

Administration of ARAT agents and corticosteroid. In this study, the sequential administration of ARAT agents in either order after the progression of primary ADT was selected based on the preference of treating physicians without strictly-regulated criteria. These agents were generally administered according to the standard dosing schedule, as previously described (7,13); however, when introducing Enz following the failure of AA, corticosteroid was continuously administered considering the occurrence of steroid withdrawal syndrome. As a rule, treatment with either ARAT agent was continued until the development of progressive disease, judged by the same definition as that applied to primary ADT. In patients showing ARAT therapy-related AEs corresponding to grade ≥3, it was permitted to modify the dosing schedule of either agent.

Evaluation. Clinicopathological data of each patient were obtained from the medical records. Before initiating the treatment with the ARAT agent, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and serum values of PSA were assessed, and the detailed status of metastasis was generally evaluated by computed tomography and radionuclide bone scans. After the introduction of either ARAT agent, the serum PSA value and bone marrow, renal and liver functions were measured every 4-6 weeks, and the intervals of radiological examinations were determined by the treating physicians considering several conditions, such as the symptoms and findings of a blood test, in each patient. In addition, the AEs during treatment with Enz were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis. Statview 5.0 software (Abacus Concepts, Inc.) was employed in all statistical analyses, and $P<0.05$ was considered significant. Differences in various parameters between the two groups were examined by the unpaired *t*-test and Chi-square test. Forward stepwise logistic regression analyses were conducted to determine the association between several parameters and the incidence of some AEs during treatment with Enz.

Results

Patient characteristics. Of the 121 mCRPC patients included in this study, 63 (52.1%) and 58 (47.9%) received sequential ARAT therapy according to the Enz-to-AA sequence (group 1) and AA-to-Enz sequence (group 2), respectively. Table I summarizes the characteristics of these patients, when an ARAT agent was initially introduced. There were no significant differences in the major clinicopathological parameters between these two groups. However, no patient in group 1 received corticosteroid during the treatment with Enz, while corticosteroid was continuously administered to all patients in group 2 by combining with Enz after the failure of AA. When introducing Enz in group 2, 10 mg of prednisolone was orally given to all patients; however, during treatment with Enz, the dose of prednisolone was reduced in 33 patients (56.9%), and prednisolone was discontinued in 5 (8.6%).

Comparison of AE profiles. Comparison of AE profiles during treatment with Enz between groups 1 and 2 is presented in Table II. No significant difference in the incidence of all AEs or AEs ≥ grade 3 between the two groups was noted. Of several AEs analyzed in this study, both fatigue and appetite loss were more frequently observed in group 1 than group 2; however, there were no significant differences in the remaining AEs, irrespective of all or ≥ grade 3 AEs, between the two groups.

Impacts of corticosteroid on AEs. To precisely evaluate the impacts of corticosteroid on the incidences of fatigue and appetite loss during Enz therapy, forward stepwise logistic regression analyses were performed to determine the association between several parameters, including the administration of corticosteroid, and these 2 AEs (Table III). Univariate analyses identified the following significant parameters associated with the incidences of the 2 AEs: Age, PS and corticosteroid administration for fatigue, and age and corticosteroid administration for appetite loss. Furthermore, on multivariate analyses of these significant parameters, the following factors were shown to have independent impacts on the incidences of the 2 AEs: Age and corticosteroid administration on fatigue, and corticosteroid administration on appetite loss.

Discussion

Since the introduction of multiple novel agents shown to be effective for mCRPC, the prognostic outcomes of mCRPC patients have been markedly improved (1,2); therefore, mCRPC patients are currently living longer with this condition, and the consideration of patients experience related to therapy-induced AEs, treatment satisfaction and QoL has become important when providing systemic therapies (14,15). This is particularly true for mCRPC patients receiving Enz, since despite its powerful therapeutic activity against mCRPC, this agent has been reported to frequently cause comparatively

Table I. Baseline characteristics of docetaxel-naïve metastatic castration-resistant prostate cancer patients who received sequential therapy with androgen receptor-axis-targeted agents.

Variables	Group 1 (n=63)	Group 2 (n=58)	P-value
Mean age, years (range)	75.7 (59-88)	75.3 (59-84)	0.41
Mean duration of ADT, months (range)	18.1 (4-182)	18.5 (3-144)	0.39
Previous listing of corticosteroid use	3 (4.8)	2 (3.4)	0.72
ECOG performance status, n (%)			
0 or 1	47 (74.6)	45 (77.6)	0.70
≥2	16 (25.4)	13 (22.4)	
Serum albumin concentration, g/dl (range)	3.8 (3.1-5.2)	3.9 (3.2-5.1)	0.74
Serum sodium concentration, mEq/l (range)	138 (133-148)	138 (132-148)	0.57
Serum choline esterase level, U/l (range)	311 (220-507)	307 (222-513)	0.61
Symptom n (%)			
Negative	48 (76.2)	47 (81.0)	0.52
Positive	15 (23.8)	11 (19.0)	
Mean value of baseline PSA, ng/ml (range)	23.9 (2.7-419.6)	23.3 (3.6-427.2)	0.66
Gleason score n (%)			
≤7	14 (22.2)	13 (22.4)	0.98
≥8	49 (77.8)	45 (77.6)	
Bone metastasis n (%)			
Negative	13 (20.6)	10 (17.2)	0.63
Positive	50 (79.4)	48 (82.8)	
Lymph node metastasis n (%)			
Negative	40 (63.5)	36 (62.1)	0.87
Positive	23 (36.5)	22 (37.9)	
Visceral metastasis n (%)			
Negative	58 (92.1)	52 (89.7)	0.65
Positive	5 (7.9)	6 (10.3)	

ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Table II. Major adverse events during treatment with enzalutamide in docetaxel-naïve metastatic castration-resistant prostate cancer patients who received sequential therapy with androgen receptor-axis-targeted agents.

	Group 1 (n=63)		Group 2 (n=58)		P-value	
Variables	All grades, n (%)	≤ Grade 3, n (%)	All grades, n (%)	≤ Grade 3, n (%)	All grades	≤ Grade 3
All adverse events	48 (76.2)	8 (12.7)	39 (67.2)	5 (8.6)	0.27	0.47
Fatigue	23 (36.5)	3 (4.8)	10 (17.2)	2 (3.4)	0.017	0.72
Appetite loss	14 (22.2)	2 (3.2)	5 (8.6)	1 (1.7)	0.040	0.61
Liver toxicity	4 (6.3)	1 (1.6)	3 (5.2)	1 (1.7)	0.78	0.95
Hypertension	4 (6.3)	0 (0)	4 (6.9)	0 (0)	0.90	-
Arthralgia	4 (6.3)	0 (0)	2 (3.4)	0 (0)	0.46	-
Diarrhea	3 (4.8)	0 (0)	2 (3.4)	0 (0)	0.72	-
Asthenia	3 (4.8)	0 (0)	3 (5.2)	0 (0)	0.92	-
Nausea	2 (3.2)	1 (1.6)	2 (3.4)	1 (1.7)	0.93	0.95
Anemia	2 (3.2)	0 (0)	2 (3.4)	0 (0)	0.93	-

severe AEs directly associated with impairment of the QoL, such as fatigue (6-12). Collectively, these findings suggest that it is a pressing issue to develop an efficacious strategy for the alleviation of AEs induced by the administration of Enz.

To date, there have been several studies showing the significant effect of steroids on the improvement of cancer-related fatigue (16-18). For example, Yennurajalingam *et al* conducted a placebo-controlled randomized trial targeting patients with

Table III. Uni- and multivariate analyses of several parameters predicting the occurrence of fatigue and appetite loss during treatment with enzalutamide in docetaxel-naïve metastatic castration-resistant prostate cancer patients who received sequential therapy with androgen receptor-axis-targeted agents.

	Fatigue				Appetite loss			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value
Age <75 years	0.29	0.017	0.32	0.037	0.36	0.042	0.56	0.089
Duration of ADT <18 months	1.79	0.34	-	-	1.62	0.39	-	-
ECOG performance status ≤1	0.31	0.042	0.59	0.027	0.45	0.094	-	-
Symptom, negative	0.47	0.079	-	-	0.51	0.13	-	-
PSA <25 ng/ml	0.57	0.13	-	-	0.60	0.21	-	-
Bone metastasis, negative	0.58	0.20	-	-	0.62	0.31	-	-
Lymph node metastasis, negative	0.72	0.42	-	-	0.77	0.52	-	-
Visceral metastasis, negative	0.66	0.37	-	-	0.55	0.19	-	-
Co-administration of corticosteroid, yes	0.28	0.009	0.30	0.025	0.32	0.029	0.40	0.046

ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

advanced cancer, and showed that dexamethasone was more effective than a placebo in improving the cancer-related fatigue and QoL of these patients (17). Since fatigue is regarded as one of the most frequent and potent AEs associated with the use of Enz (6-12), it is worthwhile to investigate whether the combined use of steroids could alleviate Enz-induced AEs. In this study, therefore, we focused on the cohort of mCRPC patients continuously receiving corticosteroid combined with Enz after the failure of AA in order to prevent steroid withdrawal syndrome, and compared the AE profiles between this cohort and that receiving Enz without corticosteroid followed by the introduction of AA and corticosteroid.

As described above, both groups included in this study were sequentially treated with 2 ARAT agents either with the Enz-to-AA or AA-to-Enz sequence without previous treatment with docetaxel; accordingly, they were likely to be composed of patients with similar characteristics. In fact, there were no significant differences in baseline clinicopathological parameters prior to the initiation of ARAT therapy following the failure of primary ADT. Taken together, it might be suitable to assess the impact of corticosteroid on the tolerability of Enz by comparing the AE profiles during Enz therapy between these 2 groups.

In this series, although there was no significant difference in the incidence of all AEs or AEs ≥ grade 3 between the 2 groups, the incidences of fatigue and appetite loss in the group receiving Enz combining corticosteroid were significantly lower than those in the group receiving Enz alone, respectively. In addition, combined administration of corticosteroid was shown to have independent impacts on the prevention of both fatigue and appetite loss during treatment with Enz. As is well known, fatigue is a quite common and distressing AE in patients with malignant diseases, developing as a consequence of the disease itself as well as a side effect of treatment, and it significantly impairs the QoL (19). Unfortunately, no definitive therapy has been established for the management of fatigue in cancer patients, including those with mCRPC, and non-pharmacological treatment is generally conducted for patients complaining of fatigue (20). However, the outcomes of this study clearly showed that the co-administration of corticosteroid significantly reduced the occurrence of Enz-induced fatigue in mCRPC patients, and that the QoL of these patients could also be improved by considering the simultaneous reduction of the incidence of appetite loss. Collectively, these findings suggest that despite not being required, the co-administration of corticosteroid should be conducted with Enz for mCRPC patients for the management or prevention of fatigue and appetite loss.

It is of interest to explore the mechanism mediating this alleviating effect of steroids, including corticosteroid, on Enz-induced fatigue and related symptoms in mCRPC patients. A number of previous studies reported the involvement of chronic inflammation in the regulation of cellular events in prostate cancer progression through modification of the tumor microenvironment (21). Moreover, proinflammatory cytokines have been shown to mediate the pathophysiology of cancer-related fatigue (22). Considering these findings, steroids may be able to reduce fatigue by having a peripheral impact on mediators of inflammation. However, it should also be recognized that cumulative corticosteroid exposure could result in a high risk of developing a wide range of adverse events in CRPC patients (23).

Here, we would like to describe several limitations of this study. Firstly, this was conducted as a retrospective study including a small number of patients; thus, the findings presented in this study should be confirmed in a prospective study with a larger sample size. Secondly, this study targeted docetaxel-naïve mCRPC patients who sequentially received 2 ARATs after the failure of primary ADT. However, this may not be a standard sequential therapeutic approach for

mCRPC (2); therefore, considering the actual clinical significance of this sequential treatment, the present findings should be carefully interpreted. Detailed outcomes of cancer control following sequential treatment of mCRPC patients with ARAT agents, AA and Enz, in either order, was reported in our previous study (9,24), which may give additional information on this treatment. Thirdly, although only prednisolone was orally administered in this series, there are several unresolved issues with respect to the use of corticosteroids for mCRPC patients receiving Enz, such as the type, dosage and route. Finally, the role of pharmacological treatments of patients with Enz-induced fatigue other than steroids should also be considered in a future study.

In conclusion, we compared AE profiles between docetaxel-naïve mCRPC patients receiving Enz combined with or without corticosteroid, and found that the incidences of both Enz-related fatigue and appetite loss in patients treated with Enz and corticosteroid were significantly lower than in those treated with Enz alone. Furthermore, the co-administration of corticosteroid was shown to be independently associated with the prevention of both fatigue and appetite loss during Enz therapy. Collectively, these findings suggest that it might be beneficial to administer corticosteroid for the alleviation of some types of Enz-related AE in mCRPC patients, particularly fatigue and appetite loss.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KT and HM conceived the present study. KT designed the present study, performed statistical analysis and wrote the main manuscript. YM, HW, DM, TS, AO, HM and TI collected the patient data and reviewed the article. TS, AO and HM supervised the study and improved the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The design of the present study was approved by the Research Ethics Committee of Hamamatsu University School of Medicine (Hamamatsu, Japan). Informed consent was waived for individual participants included in the study given the retrospective nature of this work.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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