Original Study

Efficacy of Eplerenone in the Management of Mineralocorticoid Excess in Men With Metastatic Castration-resistant Prostate Cancer Treated With Abiraterone Without Prednisone

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Abstract

Prednisone is typically coadministered with abiraterone in the treatment of castrate-resistant prostate cancer to prevent the toxicities of secondary mineralocorticoid excess. However, many patients do not desire or cannot tolerate chronic glucocorticoid therapy. In the present retrospective study, we report that eplerenone, a mineralocorticoid antagonist, can be safely used with abiraterone, obviating the need for concomitant prednisone in this patient population.

Background: Abiraterone acetate has been approved for metastatic castration-resistant prostate cancer (mCRPC). Coadministration with prednisone has been recommended to prevent the toxicity from secondary mineralocorticoid excess, such as hypertension, hypokalemia, and edema. However, the use of prednisone is often not desired by patients because of the potential for detrimental effects of long-term therapy with corticosteroids, especially in those with comorbidities such as diabetes or who have received previous immunotherapeutic agents. Eplerenone is a nonsteroidal mineralocorticoid antagonist demonstrated to abrogate mineralocorticoid excess. In the present retrospective study, we report our real-world experience with the use of eplerenone with abiraterone in men with mCRPC who wished to avoid concomitant prednisone therapy. **Patients and Methods:** The incidence and grade (Common Terminology Criteria for Adverse Events, version 4) of mineralocorticoid excess toxicities, baseline demographics, disease characteristics, and progression-free survival (PFS) were collected retrospectively. The patient population included men with mCRPC treated with abiraterone, who were not willing to receive corticosteroids, and thus received eplerenone. Their data were compared with the data from those treated with abiraterone and prednisone during the same period. Continuous variables were assessed using the Wilcoxon rank sum test or Student *t* test, and categorical variables were assessed using Fischer's exact test or χ^2 test, as appropriate. PFS was compared using the Kaplan-Meier method. **Results:** Of the 106 men treated with abiraterone, 40 received eplerenone and 66 received prednisone. The baseline and disease characteristics, incidence and grade of adverse events related to the syndrome of mineralocorticoid excess, and the median PFS were similar in both cohorts. **Conclusion:** In a real-world population of men with mCRPC treated with abiraterone, corticosteroids can be avoided by concomitant treatment with eplerenone. These data require further validation.

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Introduction

Abiraterone acetate is an approved agent for men with metastatic castration-resistant prostate cancer (mCRPC) and one of the most commonly used. Abiraterone targets cytochrome P450 17A1 (CYP17A1), the rate-limiting hydroxylase in the androgen and steroid biosynthetic pathway.[1]

Abiraterone suppresses nongonadal androgen synthesis (ie, testosterone, cortisol) downstream of CYP17A1. This leads to an elevation in

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adrenocorticotrophic hormone (ACTH), leading to secondary excess in mineralocorticoids. This secondary excess manifests as hypertension, hypokalemia, and fluid overload, which often presents as lower extremity edema.[2] To suppress the hypothalamic-pituitary-adrenal axis and diminish the symptoms of mineralocorticoid excess, abiraterone was approved with concurrent prednisone administration.[3] At present, abiraterone is the most commonly prescribed drug in the first-line setting of mCRPC, a population comprising predominantly asymptomatic or minimally symptomatic men with mCRPC. The median overall survival in this patient population is approximately 3 years.[4,5] The long-term use of prednisone is often not desired by these relatively asymptomatic patients because of concerns of detrimental effects, especially in those with previous immunotherapy or in the presence of comorbidities such as diabetes.

Earlier phase I investigations of abiraterone used peripheral inhibition of mineralocorticoid excess with the mineralocorticoid receptor antagonist eplerenone.[2] Further clinical investigations used central suppression with prednisone and other low-dose glucocorticoids. However, eplerenone remains a potentially viable option to mitigate secondary mineralocorticoid excess in clinical practice in men reluctant to be treated with long-term prednisone.[6-9]

We report our real-world experience with the use of eplerenone with abiraterone in men with mCRPC who wished to avoid concomitant therapy with prednisone. We also compared the patient and disease characteristics, clinical outcomes, and incidence and grade of mineralocorticoid excess for these men with those of the men treated with abiraterone and prednisone during the same period.

Patients and Methods

Patient Selection

We queried the University of Utah Huntsman Cancer Institute electronic medical database for the records of men with mCRPC treated with abiraterone and either prednisone or eplerenone from January 2013 to August 2016. The inclusion criteria were prostate adenocarcinoma, documented castrate level of testosterone, disease progression in accordance with the Prostate Cancer Working Group 2 criteria before beginning abiraterone therapy, performance status of 0 to 2, and documented evidence of metastatic disease on imaging studies. The exclusion criteria were the absence of follow-up data during treatment or discontinuation of treatment for factors unrelated to mCRPC progression or toxicity. Before the initiation of eplerenone therapy, the patients agreed to transition from eplerenone to prednisone should they develop any drug-related toxicity or mineralocorticoid excess.

Data Acquisition

We retrospectively analyzed the patients' medical records to collect data on patient characteristics. These included age, previous therapies, Charlson comorbidity index (CCI), disease characteristics (ie, prostate-specific antigen [PSA] level at the initiation of abiraterone therapy, Gleason score, the presence of visceral metastasis), and data on the incidence and grade of mineralocorticoid excess-related toxicities during abiraterone therapy. These toxicities included hypertension, hypokalemia, and lower extremity edema. Additionally, the baseline body mass index, diabetes mellitus, and change of weight during therapy were recorded. Progression was determined by PSA progression (in accordance with the Prostate Cancer Working Group 2 criteria), clinical progression, or imaging progression (when imaging studies had been consistently performed). The grade of secondary mineralocorticoid excess was determined using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The data for men transitioning from therapy with eplerenone to prednisone because of grade 3 or 4 effects attributable to eplerenone were analyzed in the abiraterone plus eplerenone group. Only toxicities secondary to the syndrome of mineralocorticoid excess were recorded. The University of Utah institutional review board approved the present study.

Statistical Analysis

The data were analyzed using R statistical computing software.[10] Fisher's exact test was used for categorical variables with 2 or 3 categories (visceral metastasis, hypertension, edema, hypokalemia, any toxicity), and the Wilcoxon test was used for continuous variables and ordered categorical variables with ≥ 4 categories (age, PSA level, Gleason score, previous lines of therapy, CCI). The median PFS was estimated using the Kaplan-Meier method, and the log-rank test was used to compare the PFS between the 2 groups. We controlled the baseline prognostic factors for PFS by running a multivariate Cox proportional hazards model adjusted for previous lines of treatment, age, Gleason score, PSA level, and CCI.

Results

Patient Characteristics

A total of 106 men met the criteria for the present study and were included in the analysis. Of the 106 men, 66 were treated with abiraterone and prednisone (10 mg daily) and 40 were treated with abiraterone and eplerenone (50 mg daily). Age, comorbidities, Gleason score, PSA level, and baseline body mass index on the initiation of abiraterone were not significantly different statistically between the 2 groups (Table 1). A greater number of therapy lines preceded abiraterone for those treated with abiraterone plus eplerenone than for those treated with abiraterone plus prednisone. No difference was found in PFS between those who received eplerenone and those who received prednisone (Figure 1).

Toxicities of Secondary Mineralocorticoid Excess

No significant differences between hypertension, hypokalemia, or lower extremity edema were found comparing prednisone and eplerenone for the management of secondary mineralocorticoid excess. Four men required transition from eplerenone to prednisone because of mineralocorticoid excess toxicity. All 4 men had grade 3 hypertension, and all 4 continued to have grade 2 hypertension after transitioning to prednisone. Each was successfully treated with optimization of antihypertensive medications on an outpatient basis without hospitalization. Overall, the incidence of grade 1 to 2 and grade 3 to 4 hypertension was similar in both groups. No grade 3 or 4 hypokalemia or edema toxicities developed in any patient, regardless of the treatment received. Weight loss during therapy was significantly different between the treatment arms, with nearly a 5 kg loss in the eplerenone arm compared with no change in those treated with prednisone. A complete list of the observed toxicities is provided in Table 2.