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Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer Patients

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Abstract

Background: The activity of enzalutamide after prior treatment with both abiraterone acetate (abiraterone) and docetaxel has been examined in several retrospective studies. However, limited data are available on the efficacy of enzalutamide following abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC).
Objective: To compare the activity of enzalutamide after abiraterone in docetaxel-experienced and docetaxel-naive mCRPC patients.
Design, setting, and participants: The British Columbia Cancer Agency Cancer Registry was searched for mCRPC patients who received enzalutamide after prior abiraterone. Clinicopathologic characteristics, confirmed prostate-specific antigen (PSA) response rates (PSA decline $\geq$50% confirmed $\geq$3 wk later), and survival data were collected.
Outcome measurements and statistical analysis: Outcomes on enzalutamide were compared between docetaxel-experienced and docetaxel-naive patients using chi-square for PSA response and log-rank test for time to PSA progression and overall survival (OS). Univariate analysis was performed to identify variables associated with confirmed PSA response on enzalutamide, using either chi-square for categorical variables or logistic regression for continuous variables.
Results and limitations: A total of 115 patients received enzalutamide after abiraterone: 68 had received prior docetaxel and 47 were docetaxel naive. Median time on enzalutamide was 4.1 mo. Confirmed PSA response rates (22% vs 26%; $p = 0.8$), median time to radiologic/clinical progression (4.6 mo vs 6.6 mo; $p = 0.6$), and median OS (10.6 mo vs 8.6 mo; $p = 0.2$) did not differ significantly between docetaxel-experienced and docetaxel-naive patients. No clinical variables (including prior response to abiraterone) were found to associate significantly with confirmed PSA response to enzalutamide.
Conclusions: Antitumour activity of enzalutamide following abiraterone was limited in mCRPC patients irrespective of prior docetaxel use. Identifying clinical and molecular factors predictive of response to enzalutamide remains a high priority for future research.
Patient summary: We looked at the effectiveness of enzalutamide after abiraterone acetate for treatment of advanced prostate cancer. We found that patients who had received docetaxel chemotherapy before abiraterone gained similar benefit from enzalutamide compared with patients who had not received docetaxel. These results suggest that earlier treatment with docetaxel does not have a large impact on the activity of enzalutamide after abiraterone.

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1. Introduction

The therapeutic armamentarium for metastatic castration-resistant prostate cancer (mCRPC) has rapidly expanded in recent years with several novel agents demonstrating a benefit on overall survival (OS) [1]. Among these agents are the novel androgen receptor (AR)-targeted therapies abiraterone acetate (abiraterone) and enzalutamide that inhibit CYP17 and AR, respectively. Both abiraterone and enzalutamide are increasingly being used in chemotherapy-naive mCRPC patients on the basis of positive data from the COU-AA-302 (abiraterone) and PREVAIL (enzalutamide) phase 3 studies [2,3]. Despite their efficacy, however, many questions regarding the use of abiraterone and enzalutamide remain unanswered including the optimal sequencing of treatment. Several prior studies have reported on outcomes in mCRPC patients treated with enzalutamide after abiraterone [4–9]. All but one of these studies [9] were restricted to patients previously treated with docetaxel, and currently little is known about the activity of enzalutamide following abiraterone in docetaxel-naive mCRPC patients. The aim of this study was to examine the activity of enzalutamide after abiraterone in mCRPC patients not previously treated with docetaxel chemotherapy and to compare outcomes with docetaxel-experienced patients.

2. Methods

2.1. Patient population

The British Columbia Cancer Agency (BCCA) consists of six distinct centres located throughout British Columbia, Canada. The Cancer Registry at BCCA was reviewed for mCRPC patients treated with enzalutamide following abiraterone. Patient demographics, prior treatments including docetaxel and abiraterone, clinicopathologic characteristics, and outcomes on postabiraterone enzalutamide (prostate-specific antigen [PSA] response and survival parameters) were documented from medical records of each patient. Patients who had previously received a minimum of one cycle of docetaxel were classified as docetaxel experienced; all other patients were classified as docetaxel naive. Research ethics board approval was obtained prior to commencing this study.

2.2. Outcome measures

The primary objective of this study was to compare the efficacy of enzalutamide following abiraterone in docetaxel-experienced and docetaxel-naive patients. Data were collected for the following end points: confirmed PSA response rate (PSA decline $\geq$50% from baseline maintained $\geq$3 wk), time to progression, and OS (time from initiation of enzalutamide to death of any cause or censoring on March 31, 2014). Progression was defined as radiologic (Prostate Cancer Working Group 2 [PCWG2] criteria) or clinical (worsening disease-related symptoms requiring a change in antineoplastic therapy or a decrease in Eastern Cooperative Oncology Group performance status of two or more levels). Reasons for discontinuation of enzalutamide were recorded as follows: PSA progression (PCWG2 criteria), radiologic progression (PCWG2 criteria), clinical progression, and toxicity. Patients who stopped enzalutamide due to toxicity were censored for time to progression analysis.

2.3. Statistics

Outcomes on enzalutamide were compared between docetaxel-naive and docetaxel-experienced patients using chi-square for PSA response and log-rank test for time to PSA progression and OS. Univariate analysis was performed to identify variables associated with confirmed PSA response to enzalutamide, using either chi-square for categorical variables or logistic regression for continuous variables. Progression-free survival (PFS) and OS were calculated using Kaplan-Meier estimates.

3. Results

3.1. Patient population

A total of 115 patients were treated with enzalutamide following abiraterone: 68 had received at least one cycle of docetaxel previously (“docetaxel experienced”); the remaining 47 patients were docetaxel naive. Table 1 lists the patient characteristics at the initiation of enzalutamide. Docetaxel-experienced and docetaxel-naive patients were matched for all clinicopathologic characteristics with the exception of age and serum lactate dehydrogenase (LDH).

3.2. Enzalutamide treatment

Median duration of enzalutamide treatment was 4.1 mo and did not significantly differ between docetaxel-experienced and docetaxel-naive patients (Table 2). Overall, 21% of patients (24 of 115) received enzalutamide $\geq$6 mo. Median time between cessation of abiraterone and initiation of enzalutamide was 21 d (interquartile range: 2–68). A total of 13% of patients (15 of 115) received another systemic agent between stopping abiraterone and starting enzalutamide. Seven of these 15 patients were docetaxel experienced and were rechallenged with docetaxel between abiraterone and enzalutamide. The remaining patients received BEZ235 (n = 2), PX-866 (n = 2), mitoxantrone (n = 1), and AZD2171 (n = 1); two patients were enrolled in the Study of Cabozantinib (XL184) versus Mitoxantrone Plus Prednisone in Men with Previously Treated Symptomatic Castration-resistant Prostate Cancer (COMET-2) trial (cabozantinib vs mitoxantrone).

A total of 61% of patients (70 of 115) were on corticosteroids at the start of enzalutamide and 28% (32 of 115) remained on corticosteroids at the cessation of enzalutamide. Reasons for enzalutamide discontinuation (more than one could apply) were clinical progression (43%), PSA progression (25%), radiologic progression (10%), and toxicity (9%); 28% of patients (32 of 115) remained on treatment as of March 31, 2014. Among patients stopping enzalutamide due to toxicity (n = 10), four were docetaxel experienced and six were docetaxel naive. Postenzalutamide systemic treatment was administered to 25% (17 of 68) and 16% (7 of 45) of docetaxel-experienced and docetaxel-naive patients, respectively (p = 0.3; chi-square).

3.3. Prostate-specific antigen response

Confirmed PSA declines $\geq$90%, $\geq$50%, and $\geq$30% were seen in 4% (5 of 115), 23% (27 of 115), and 35% (40 of 115) of patients, respectively. Waterfall plots of maximal PSA decrease on enzalutamide are presented in Figure 1A and