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Original article

Prognostic factors of oncologic outcomes in metastatic chemotherapy-naïve castration-resistant prostate cancer treated with enzalutamide in actual clinical practice in East Asia

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Abstract

Objectives: We aimed to evaluate the prognostic factors for chemotherapy-naïve castration-resistant prostate cancer (CRPC) treated with enzalutamide in actual clinical practice using easily accessible clinical variables.

Methods and materials: We retrospectively reviewed the following data from 113 patients with chemotherapy-naïve CRPC treated with enzalutamide: serum levels of prostate-specific antigen (PSA), testosterone, hemoglobin, total protein, albumin, and alkaline phosphatase (ALP); platelet, neutrophil, and lymphocyte counts; neutrophil-to-lymphocyte ratios (NLRs); and liver profiles. PSA progression-free survival (PFS), radiological PFS, and overall survival were estimated by Cox regression analysis.

Results: Compared with baseline levels, laboratory values at 2 months showed significantly lower PSA (160.2 ± 351.5 ng/ml vs. 47.4 ± 117.1 ng/ml) and ALP levels (201.86 ± 223.77 IU/l vs. 148.25 ± 146.81 IU/l) and a significantly higher percentage of lymphocytes (28.1% ± 10.6% vs. 31.2% ± 9.7%); those at 1 month showed a significantly lower percentage of neutrophils (61.0% ± 11.0% vs. 57.1% ± 12.5%). In the multivariate analysis, poor prognostic factors for PSA PFS were Gleason score ≥ 9 (hazard ratio [HR] 2.022; $P = 0.0250$); visceral metastasis (HR 3.143; $P = 0.0002$); high NLR (HR 1.205; $P = 0.0126$); and high ALP (HR 1.002; $P = 0.0015$). For radiological PFS, high NLR (HR 1.249; $P = 0.0002$) and high ALP (HR 1.002; $P = 0.0001$) were associated with poor outcomes. The predictors of poor overall survival were visceral metastasis (HR 3.155; $P < 0.0001$); high NLR (HR 1.341; $P < 0.0001$); and high ALP (HR 1.001; $P = 0.0017$).

Conclusion: Enzalutamide is less effective in patients with metastatic chemotherapy-naïve CRPC with Gleason scores ≥ 9, visceral metastasis, high NLR, and high ALP. © 2018 Elsevier Inc. All rights reserved.

Keywords: Castration-resistant prostate cancer; Enzalutamide; Neutrophil-to-lymphocyte ratio; Prognosis; Biomarker

1. Introduction

Androgen deprivation therapy (ADT) is the first-line therapy for metastatic prostate cancer. Although the disease has a generally favorable initial response to ADT, it progresses to castration-resistant prostate cancer (CRPC) [1]. The TAX-327 study showed that docetaxel for metastatic CRPC patients increased overall survival (OS) up to 2.9 months. Therefore, docetaxel is widely used for treating metastatic CRPC [2]. The PREVAIL study showed that in chemotherapy-naïve metastatic CRPC patients, the androgen receptor (AR)-targeting agent enzalutamide reduced radiological progression and mortality risks [3]. In 2012, the United States Food and Drug Administration approved enzalutamide for treating metastatic CRPC patients. The effectiveness and safety of enzalutamide in this patient

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population have also been reported in Japan, Korea, and Singapore [4]. However, no definitive data support either docetaxel or enzalutamide as the best first-line therapy for metastatic CRPC.

Resistance mechanisms of AR-targeting agents include AR splice variants, AR mutations, AR gene amplification, and up-regulated glucocorticoid receptor signaling [5]. Identifying biomarkers predicting drug resistance can help in selecting appropriate agents and reducing opportunity costs. The AR splice variant 7 (AR-V7) messenger RNA, resulting in ligand-binding domain loss, is a known biomarker of resistance to enzalutamide [6]. Detection of AR-V7 in the circulating tumor cells of CRPC patients has been associated with enzalutamide resistance [6]. However, AR-V7 value confirmation in clinical situations remains challenging due to economic and technological limitations. Prostate-specific antigen (PSA) response during the early period of enzalutamide administration can also predict radiological progression-free survival (PFS) and OS, but developing the response takes several weeks following enzalutamide administration [7]. This study aimed to evaluate the prognostic factors among easily accessible clinical variables in chemotherapy-naïve CRPC patients receiving enzalutamide.

2. Materials and methods

This study was approved by the ethics board of our institution. A retrospective review was performed between April 2014 and April 2017 to identify 285 prostate cancer patients who had received enzalutamide. After excluding patients who had received chemotherapy before enzalutamide administration, 113 chemotherapy-naïve CRPC patients treated with enzalutamide were included. All the patients were diagnosed with adenocarcinoma by prostate needle biopsy and underwent at least 1 type of ADT. Enzalutamide (160 mg) was routinely administered once daily until disease progression was determined or severe adverse events occurred.

Data on pathological characteristics of the tumor at the time of diagnosis were collected. Clinical characteristics of the patients, including Eastern Cooperative Oncology Group (ECOG) performance status and prior medical history upon first use of enzalutamide, were also collected. Serum laboratory measurements of PSA, testosterone, hemoglobin, platelets, white blood cells (WBCs), neutrophils, lymphocytes, monocytes, creatinine, cholesterol, total protein, albumin, aspartate aminotransferase, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels were conducted every 4 weeks. Data on serum laboratory values, except PSA, were collected during 3 months of enzalutamide use. PSA measurements were performed monthly when patients were prescribed enzalutamide, whereas radiological assessments were performed every 3 to 6 months at the discretion of the clinicians. Progression in PSA and radiological parameters was evaluated using the Prostate Cancer Clinical Trials Working Group 2 guidelines [8]. OS was defined as time between first administration of enzalutamide and patient death.

Baseline characteristics of patients and tumors were described as mean ± standard deviation with interquartile ranges (IQR) or as numbers with percentages. Changed serum laboratory values were compared with baseline levels before administrating enzalutamide using Student's *t* test. PSA PFS, radiological PFS, and OS were estimated using the Kaplan–Meier methods, with log-rank tests according to PSA, neutrophil-to-lymphocyte ratio (NLR), and ALP levels stratified by established cutoff values. Cox regression was used to analyze prognostic factors for predicting PSA and radiological PFS and OS at the time of enzalutamide administration. The significant factors in univariate analysis ($P < 0.20$) were entered into the multivariate analysis. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using R (version 3.4.1; R Project for Statistical Computing, Vienna, Austria) and SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). The R package "maxstat" was used to determine the cut-point resulting in maximal separation of the Kaplan–Meier curves when stratified by interest variables [9].

3. Results

A total of 113 patients were included after ADT failure. The baseline characteristics are shown in Table 1. The median age at the first enzalutamide administration was 73.0 years (IQR 67.0–78.0). Upon initial diagnosis, 60.6% and 64.2% of the cases were in N1 and M1 stages, respectively. Twenty-five (22.1%) patients had undergone prior radical prostatectomy and 28 (24.8%) had prior definitive radiation therapy; 101 (89.4%) patients had received antiandrogen therapy and 7 patients (6.2%) had been receiving abiraterone before using enzalutamide. The median duration from diagnosis to first enzalutamide administration was 2.0 years (IQR 1.4–4.0). At the first enzalutamide administration, 102 (90.3%) patients had bone metastasis, 58 (51.3%) had lymph node metastasis, and 28 (24.8%) had visceral metastasis. At the last follow-up, bone metastases in 51 (51.0%) of the patients were due to disease progression. In soft tissue lesions, 10 (14.2%) patients showed a partial response, 37 (52.9%) had stable disease, and 23 (32.9%) developed progressive disease.

Fig. 1 shows the changes in various serum laboratory levels during enzalutamide administration. The PSA levels decreased significantly over 2 months, from 160.2 ± 351.5 ng/ml to 47.4 ± 117.1 ng/ml ($P = 0.002$). Testosterone levels did not vary during the 3 months. Hemoglobin levels and platelet counts did not change despite enzalutamide administration; however, WBC counts decreased after 2 months of enzalutamide administration ($6.405 \pm 1.925 \times 10^3/\mu l$ to $5.757 \pm 1.487 \times 10^3/\mu l$; $P = 0.041$). The proportion of neutrophils decreased over 1 month (61.0% ± 11.0%–57.1%

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