

Treatment sequence in castration-resistant prostate cancer: A retrospective study in the new anti-androgen era

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Abstract. In recent years, abiraterone acetate (AA) and enzalutamide (EZL) have become available for the treatment of cancer. Prior clinical trials have demonstrated the benefits of these agents in males with castration-resistant prostate cancer (CRPC). The optimal sequencing of available therapies in the context of efficacy and known cross-resistance remains uncertain. Based on the mechanisms of action and accessible clinical data, AA and EZL may be indicated for the early stages of prostate cancer. Until clinical trials are conducted to determine the best treatment sequence, individualized therapy is required for each patient based on the clinicopathological characteristics. In the present study, 46 sequential patients (median age: 77, range 59-89; median serum PSA level: 56 ng/ml, range 1.5-3,211) with CRPC treated with EZL (160 mg/day) were retrospectively analyzed between June 2014 and July 2015 at the following institutions: Yamagata Prefectural Central Hospital (Yamagata, Japan); Yamagata Tokushukai Hospital (Yamagata, Japan); Ishinomaki Red Cross Hospital (Ishinomaki, Japan); Kan-etsu Hospital (Tsurugashima, Japan); Niigata Cancer Center Hospital (Niigata, Japan); Sakado Central Hospital (Sakado, Japan). A total of 18 patients were pre-treated with Docetaxel (DOC) and 28 patients were DOC-naïve. Once EZL therapy was initiated, increases in prostate specific antigen (PSA) levels were observed in 3/18 patients (17%) pre-treated with DOC and in 6/20 (30%) who were DOC-naïve. In total, 8/28 DOC-naïve patients were treated with AA without EZL. An increase in the PSA level was observed in only 1/8 (12%) cases following AA treatment in the DOC-naïve group. It was demonstrated that AA had a better efficacy in DOC-naïve patients. The efficacy

of EZL was limited in AA-pre-treated patients following DOC administration.

Introduction

Prostate cancer is the second most commonly diagnosed malignancy in males globally, with an estimated 1,111,700 novel cases and 307,500 mortalities per year (1). Metastatic prostate cancer is characterized by a period during which the suppression of serum testosterone using androgen deprivation therapy is sufficient to control the disease (2). However, this period is followed by a transition to castration resistance, during which progression occurs despite the continued suppression of testosterone. This is referred to as metastatic castration-resistant prostate cancer (mCRPC) (1). Formerly, this disease state was known as hormone-refractory prostate cancer. As it is now understood that androgen receptor (AR) signaling remains critical to disease progression in castration-resistant disease, this term is no longer used (3). The fact that prostate-specific antigen (PSA) rises during mCRPC progression exemplifies this point, as PSA is an androgen-regulated gene (1). The clinical relevance of targeting androgen signaling in mCRPC is demonstrated by the survival advantage conferred by abiraterone acetate (AA) and enzalutamide (EZL) in this disease state (1).

Docetaxel (DOC) was the first agent identified to prolong patient survival in mCRPC, and it gained regulatory approval from the FDA for this indication in 2004 (4). In recent years there has been a rapid increase in the number of drugs available to treat this disease, following the approval of cabazitaxel (2010) (5), sipuleucel-T (2010) (6), AA (post-DOC, 2011; chemotherapy-naïve, 2012) (7), EZL (post-DOC, 2012; chemotherapy-naïve, 2014) (8,9) and radium-223 (2013) (10). In the case of AA and EZL, approvals following DOC use were initially granted based on the COU-AA-301 and AFFIRM trials (9), respectively. Subsequent trials involving patients with chemotherapy-naïve mCRPC were conducted for AA (COU-AA-302) and EZL (PREVAIL), leading to an extension of the approval to the aforementioned population.

The present review focuses on the use of AA in patients with chemotherapy-naïve mCRPC. In this retrospective

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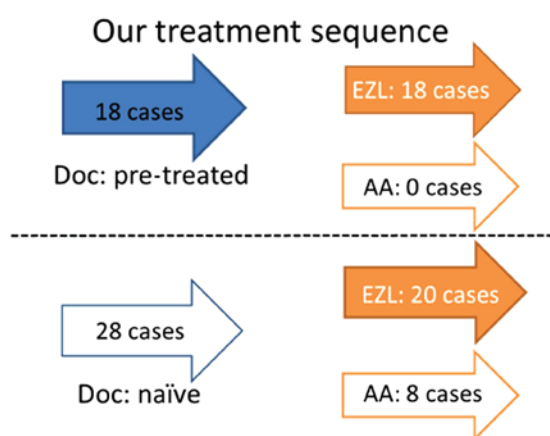


Figure 1. Initial treatment sequences. A total of 65 patients with CRPC treated with EZL (160 mg/day) were retrospectively analyzed from June 2014 to July 2015. A total of 42 patients were DOC-naïve and a further 23 patients were pre-treated with DOC. Following the initiation of EZL treatment, the PSA levels were evaluated in 46/65 cases. EZL, enzalutamide; AA, abiraterone acetate; DOC, docetaxel.

analysis, a variety of treatment sequences were evaluated in order to determine the optimal treatment sequence for patients with mCRPC.

Patients and methods

A total of 65 patients with CRPC treated with EZL (160 mg/day) were retrospectively analyzed at the

aforementioned institutions between June 2014 and July 2015. A total of 23 patients were pre-treated with DOC, and 42 patients were DOC-naïve. Following the initiation of EZL treatment, the PSA level was evaluated in 46/65 cases. This case series was conducted with those 46 sequential patients (median age: 77, range 59-89; median serum PSA level: 56 ng/ml, range 1.5-3211 ng/ml) with CRPC treated with EZL (160 mg/day) at the aforementioned institutions from June 2014 to July 2015 (Fig. 1).

Results

Pretreatment with DOC had been administered in 18/46 cases (Fig. 2), and the remaining 28 cases were DOC-naïve. EZL was administered to the aforementioned 18 patients following the pretreatment with DOC; subsequently, a reduction in PSA was observed in 15 of these cases. The remaining three cases, in which PSA reduction had not been recorded, received AA following EZL administration, and a reduction in PSA was later revealed in one of the three cases. Of the 28 DOC-naïve cases, EZL was prescribed for 20 patients, and a reduction in PSA was identified in 14 of these cases. Of the six cases who had not exhibited a reduction in PSA levels, and for whom AA was prescribed after EZL, only one case then revealed a reduction in PSA. Of eight cases without pretreatment with DOC for which AA was prescribed, seven cases exhibited a reduction in PSA levels; in the remaining one case without PSA reduction, EZL was prescribed following AA administration and a reduction in PSA was subsequently identified.

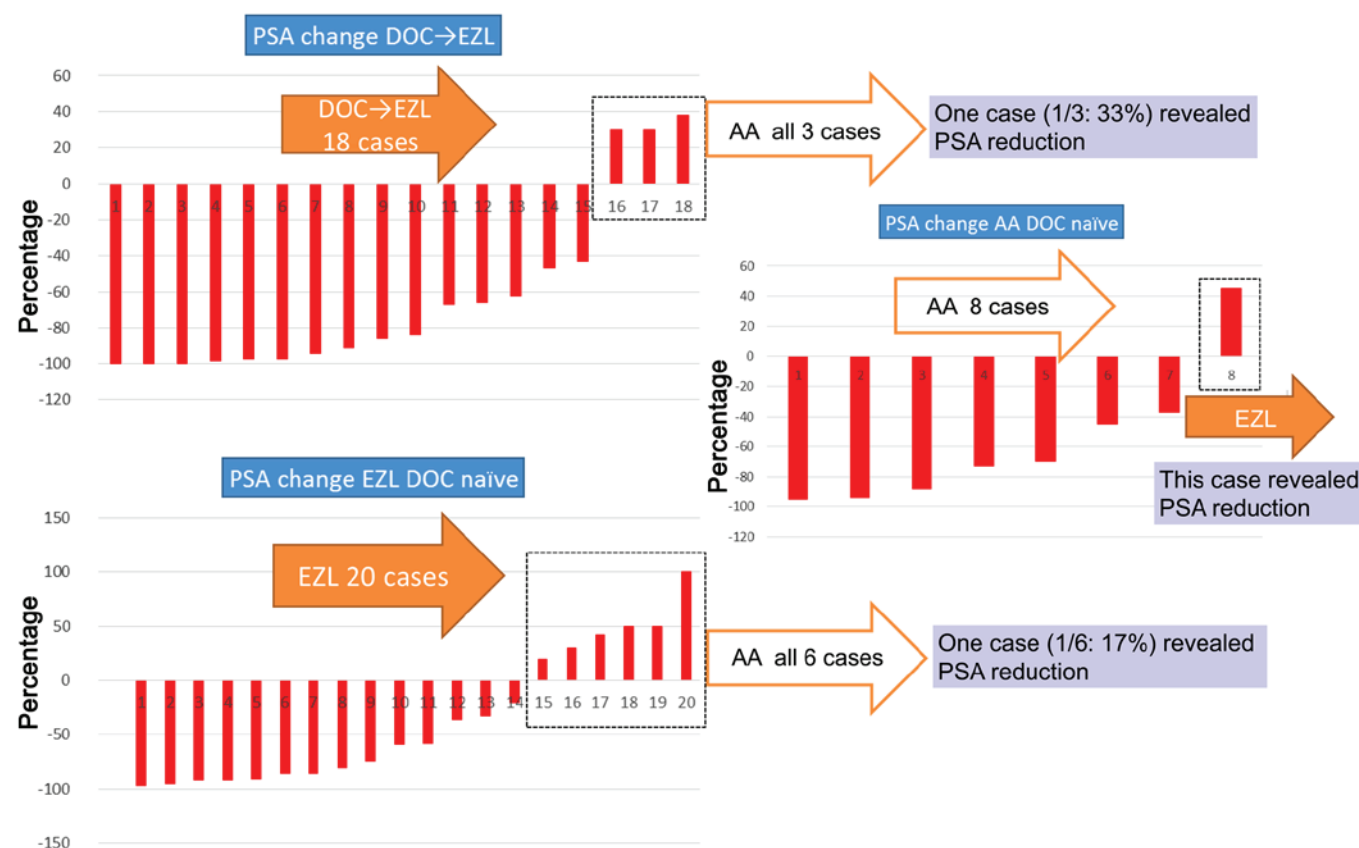


Figure 2. Treatment sequences: Within three months of the of treatment initiation, a decline in the PSA levels of $\geq 30\%$ was observed in 28/46 cases. EZL, enzalutamide; AA, abiraterone acetate; DOC, docetaxel; PSA, prostate specific antigen.

Discussion

During the study, the EZL dose was reduced in three cases due to adverse events (body weight loss, fatigue and nausea). In the single case of weight loss, the dose was gradually reduced, leading to the complete discontinuation of EZL; however, the decrease in the PSA level persisted for three months.

AA and EZL are currently available in Japan (11). A prior clinical trial has demonstrated the benefits of these agents in male patients with CRPC (11). The optimal sequencing of therapies in the context of drug efficacy and known cross-resistance remains uncertain. Due to the known mechanisms of action and the available clinical data, AA and EZL may be indicated for the treatment of the early stages of prostate cancer (11,12). Individualized therapy will remain a requirement for each patient based on the clinical and disease characteristics until further clinical trials are able to determine the optimal treatment sequence.

The efficacy of EZL was limited in AA-pre-treated patients following DOC administration. The possibility of DOC rechallenge in the treatment of patients with CRPC has been limited predominantly by the introduction of AA, EZL and cabazitaxel (5). However, it must be considered that the reintroduction of DOC may reduce the possibility that one of the novel treatment options available could then be administered. Furthermore, the situation is complicated by recent clinical trials that may lead to the early administration of DOC in combination with androgen-deprivation therapy, or to novel indications of AA and EZL in pre-DOC patients (13,14). In this setting, certain prior reports have indicated the possibility of the occurrence of cross-resistance when first-line chemotherapy with DOC was administered after the novel hormonal agent AA; by contrast, there have been few instances of DOC rechallenge following failure to respond to AA or other agents (15,16). The cross-resistance to AA and EZL, as well as EWS, has been attributed to the expression of an AR splice variant-7 (17,18). In conclusion, further prospective studies are required in order to determine the optimal treatment sequence in this new anti-androgen era.

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