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Original Research

Enzalutamide versus Abiraterone Acetate as first-line treatment of castration resistant metastatic prostate cancer in geriatric (≥75) patients

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Abstract

Introduction: The efficacy and tolerability of Enzalutamide and Abiraterone Acetate have been reported in elderly patients with metastatic castration resistant prostate cancer (mCRPC). However, there is no randomized study directly comparing antitumor effects between these 2 agents in geriatric patients. We aimed to evaluate the efficacy of Enzalutamide (ENZA) and Abiraterone Acetate (AA) as a first-line treatment of mCRPC in elderly patients.

Materials and methods: The geriatric patients (≥75 years of age) with a diagnosis of mCRPC and treated with first-line ENZA or AA were included. The impacts of clinical parameters and treatment modalities on overall survival (mOS) were analyzed retrospectively and Cox regression analysis was performed.

Results: One hundred thirty-four mCRPC patients (77 in AA, 57 in ENZA), with a median age of 81 (75–93) were analyzed. The patient and disease characteristics were similar between arms. While there were more grade 1–2 toxicities in AA arm (45.5% vs 17.5%, *P* = 0.001), the discontinuation due to toxicity was similar between groups (8.5% vs 5.9%, *P* = 0.81). The mOS was 18.0 months (95% CI, 15.2–20.7) in AA, and 20.0 months (95% CI, 4.4–35.5) in ENZA arm (*P* = 0.47). In multivariate analysis, high Gleason score (≥8) (HR: 2.0 (95% CI, 1.1–3.4), *P* = 0.009) and high initial PSA values (≥100 ng/mL) (HR: 2.6 (95% CI, 1.5–4.8), *P* = 0.001) were poor prognostic factors. The choice of AA vs ENZA was insignificant as a predictor of OS (HR: 0.87 (95% CI, 0.48–1.56), *P* = 0.65).
Conclusion: In the first-line treatment of mCRPC in elderly (≥75) patients, AA and ENZA showed similar results in terms of mPFS and mOS. The clinical impacts of second-generation androgen receptor pathway inhibitors in the elderly population should be tested in prospective randomized studies.

Keywords
Metastatic castration-resistant prostate cancer; Enzalutamide; Abiraterone Acetate; Elderly

1. Introduction

Prostate cancer (PC) is the most common malignancy in men and 2nd most common cause of cancer-related deaths worldwide. It is a disease mostly affecting elderly men. The median age at diagnosis is 67 and the ones more than 75 years of age constitute 25% of prostate cancer cases [1]. In elderly patients, the prognosis of the PC is worse and more patients present with a metastatic stage. In addition, 70.6% of prostate cancer deaths occur in men older than 75 [2]. The standard treatment modality of PC is androgen deprivation therapy. However, due to adaptations in androgen receptor signaling and somatic genomic alterations, the disease turns into a castration-resistant state [3]. The term metastatic castration-resistant prostate cancer (mCRPC) is defined as prostate-specific antigen (PSA) progression according to Prostate Cancer Clinical Trials Working Group 2 or radiographic progression in soft tissue or bone with or without PSA progression while the patient is under ongoing androgen deprivation with a serum testosterone level of less than 50 ng per deciliter [4].

The survival efficacy of cytotoxic drugs and new generation anti-androgen drugs have been reported and those drugs are actively used in mCRPC. Abiraterone Acetate (AA) and Enzalutamide (ENZA) are two new generation anti-androgen drugs used in pre/post-chemotherapy settings. AA is an inhibitor of cytochrome P450c17 interfering with androgen synthesis through inhibition of 17 hydroxylase and 17, 20 lyase enzymes. The survival benefit of AA has been shown in the second-line (after docetaxel) [5] and first-line [6]. In the first-line study, in the AA arm, there were 185 (34%) patients who were ≥75 years of age. The sub-group analysis showed that the radiographic progression-free survival (PFS) was better in AA when compared to prednisolone arm (14.9 vs 8.1 months, HR: 0.64 (95% CI 0.48–0.84)). The median overall survival (mOS) was better in AA (NR vs 23.8 months, HR: 0.71 (95% CI 0.51–1.00)) [6]. The efficacy and safety of AA in patients aged >80 years were also demonstrated in second-line mCRPC [7]. ENZA is an androgen receptor signaling inhibitor that inhibits androgen receptor translocation and its DNA binding [8]. In the PREVAIL study in which ENZA was tested in first-line treatment of mCRPC, the elderly (≥75) group constituted 37.3% of the ENZA arm [9]. Subgroup analysis of radiographic PFS has favored ENZA instead of placebo (NR vs 3, 7 months, HR: 0.17 (95% CI 0.12–0.25)) and the mOS was longer in the ENZA arm (32.4 vs 25.1 months, HR: 0.60 (95% CI 0.47–0.79)).

In a recent retrospective study, comparing them in the first line of mCRPC showed that ENZA had better mOS compared to AA (HR 0.90, 95% CI 0.85, 0.96; mOS, 31.7 months for AA and 34.2 months for ENZA) [10]. A meta-analysis by Wang *et al.* [11] concluded that ENZA was associated with a higher PSA response rate compared to AA in patients with mCRPC, and no significant difference was found in terms of toxicity profiles. These anti-androgens are generally preferred instead of docetaxel in geriatric patients who have numerous comorbidities. Unfortunately, there is no data in the elderly (≥75) mCRPC patients in which we tend to use ENZA or AA in the first-line setting. In this study, we aimed to evaluate the efficacy of ENZA and AA as first-line treatment of mCRPC in elderly (≥75) patients.

2. Material/methods

The study was conducted as a retrospective study in 16 cancer centers in Turkey. It was approved by the institutional review board or ethics committee at each center and conducted according to the Helsinki Declaration and good clinical practice. The patients with a diagnosis of mCRPC, treated between 09/2013–06/2020 were analyzed retrospectively. The eligibility criteria were an age of 75 and more, histopathologically confirmed diagnosis of prostate adenocarcinoma, meeting the diagnosis of castration-resistant metastatic prostate cancer according to PSA increase, radiological progression or symptoms [4], being treated with AA or ENZA in the first-line setting. The patients who were treated with docetaxel or other anti-androgen modalities in the first line and who had only locoregional lymph nodes were excluded.

The patients' ages, comorbidities, performance scores before therapy, Gleason score of the primary pathology, the extent of disease, number of bony metastases, the involvement

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of other solid organs, the treatment modality of androgen deprivation, PSA levels before the therapy were recorded from medical records. In addition, the first-line treatment modality (AA or ENZA), the toxicities recorded during therapy, the date of therapy start and date of cessation of therapy, the cause of cessation, and the date of death were recorded.

3. Statistical methods

Baseline characteristics of the patient group were described using proportions for dichotomous and categorical variables. The chi-square or Fisher exact tests were used to compare categorical and dichotomous variables. To further evaluate the effect of age, the patients were subgrouped into 75–79 and ≥80. In addition, the number of bone metastases was grouped into <5, 5–10, and ≥10 according to previous studies. The median PSA value of ≥100 (ng/mL) was used to group patients into high/low initial PSA. The mPFS was defined as the time between the date of therapy start and progression. Progression was defined as a 25% increase in the serum PSA level (to at least 5 ng/mL) over the nadir, which was confirmed by a second value, progression in measurable disease as defined by RECIST criteria, or the appearance of new lesions on bone scan. The mOS was defined as the time between the date of therapy start and the date of death. The effects of regimens on mPFS and mOS were investigated by using the log ranks test. The Kaplan-Meier survival estimates were calculated. Also, the factors associated with mOS were analyzed and the Cox proportional-hazards model was used to estimate the hazard ratio and its associated confidence interval. In multivariate analysis; the age ≥80, presence of comorbidity, performance score, gleason score of 8–10, the number of bone metastasis, pre-treatment PSA value, and treatment modality (ENZA vs AA) were analyzed All analyses were performed using SPSS 17.0 for Windows (IBM Corp., Armonk, NY). A *P*-value of less than 0.05 was considered statistically significant.

4. Results

One hundred thirty-four CRPC patients (77 in AA, 57 in ENZA), were analyzed. The patient and disease characteristics are summarized in Table 1. The median age was 81 (75–93) and 82 (61.2%) patients were ≥80 years of age. Most of them (69.4%) had at least one comorbidity and the most common co-morbidity was hypertension. 76 (56.7%) patients had disease with a Gleason score of 8–10 and bony metastases were present in 96.3% of patients. Androgen deprivation modalities were orchiectomy, LHRH analog, and LHRH analog plus bicalutamide in 16.4%, 38.8%, and 44.8% of patients, respectively. Only a small group of patients (3%) had a history of docetaxel therapy in the hormone-naïve period. The statistical analysis showed that there was no difference between AA and ENZA arms in terms of the patient and disease characteristics.

4.1 Safety

During treatment, there were more grade 1–2 toxicities in AA arm (45.5% vs 17.5%, $P = 0.001$) (Table 2). Grade 3–4 toxicities were present in 9.1% of the AA arm and 1.8% of the ENZA arm, $P = 0.076$. While the grade 3–4 toxicities in AA were hypertension and hypokalemia, 1 patient had grade 3 hypertension and malaise. There were more dose reductions in AA arm (2.6% vs 0%, $P = 0.002$). However, discontinuation due to toxicity was similar between groups (8.5% vs 5.9%, $P = 0.81$). There were no deaths related to drug toxicity.

4.2 Efficacy

The PSA decrease of ≥50% was present in 56 (75.7%) patients in AA and 40 (81.6%) patients in ENZA arms ($P = 0.56$). The mPFS was 16.0 months (95% CI, 11.7–20.2) in AA and 11.0 months (95% CI, 6.2–15.7) in ENZA treated patients ($P = 0.22$) (Fig. 1). The mOS was 18.0 months (95% CI, 15.2–20.7) in AA, and 20.0 months (95% CI, 4.4–35.5) in ENZA arm ($P = 0.47$) (Fig. 2). There were only 11 patients (14.3%) in AA and 5 (8.8%) patients in ENZA who had second-line therapy ($P = 0.24$). In ENZA arm, 4 had docetaxel and 1 had AA. In the AA arm, 5 patients had docetaxel, 2 had ENZA and 4 patients were treated with hormonal manipulation. The multivariate analysis of factors associated with survival showed that high Gleason score (≥8) (HR: 2.0 (95% CI, 1.1–3.4), $P = 0.009$) and high initial PSA values (≥100 ng/mL) (HR: 2.6 (95% CI, 1.5–4.8), $P = 0.001$) were poor prognostic factors. The choice of AA vs ENZA was insignificant as a predictor of OS (HR: 0.87 (95% CI, 0.48–1.56), $P = 0.65$).

5. Discussion

In the current study, we tried to compare the results of AA and ENZA in elderly mCRPC patients. We found that the mPFS and mOS of these anti-androgens were similar in first-line treatment.

Aging is a physiological process that results in increased susceptibility to diseases and decreased organ reservoir [12]. In literature, the data concerning the elderly is limited, because in most of the clinical trials; elderly patients, those with comorbidities, reduced performance scores, and impaired organ capacity are excluded. So, we should be cautious while generalizing the trial results and integration of our clinical practice [13]. Due to the nature of the disease, while dealing with prostate cancer, we care for elderly patients. In mCRPC, due to problems with the primary disease and comorbidities, the treatment plan is challenging. The tolerability and efficacy of taxane-based treatment have been shown in the elderly (≥75) patients [14, 15]. However, the analysis of Wallis *et al.* showed that docetaxel in CRPC was associated with increased risk of hospitalizations (HR: 1.69 (95% CI 1.46–1.96), $P < 0.001$) and emergency visits (HR: 1.52 (95% CI 1.33–1.74), $P < 0.001$) to manage complications [16]. The prospective analysis of patients with mCRPC found that the patients were more concerned about reduced quality of life from side effects of treatment rather than the extension of survival. Consistent with the literature, in our daily prac-

TABLE 1. The baseline characteristics of the patients.

Characteristics	Abiraterone-77	Enzalutamide-57	*P*	Total-134
	N (%)	N (%)		N (%)
Median age, years (range)	82.0 (75–93)	80.0 (75–92)	0.52	81 (75–93)
Age, years				
75–79	27 (35.1)	25 (43.9)		52 (38.8)
≥80	50 (64.9)	32 (56.1)	0.19	82 (61.2)
Comorbidity present	54 (70.1)	39 (68.4)	0.49	93 (69.4)
Hypertension	37 (48.1)	26 (45.6)	0.45	63 (47.0)
Diabetes Mellitus	13 (16.9)	12 (21.1)	0.34	25 (18.7)
Coronary artery disease	18 (23.7)	17 (29.8)	0.27	35 (26.3)
Other	30 (45.4)	23 (43.4)	0.66	53 (44.5)
Performance Score (ECOG)				
0–1	45 (58.4)	27 (47.4)		72 (53.7)
2–3	32 (41.6)	30 (52.6)	0.13	62 (46.3)
Gleason Score				
3 + 3	4 (5.2)	5 (8.8)		9 (6.7)
3 + 4	15 (19.5)	5 (8.8)		20 (14.9)
4 + 3	15 (19.5)	14 (24.6)		29 (21.6)
8–10	43 (55.8)	33 (57.9)	0.31	76 (56.7)
8–10	43 (55.8)	33 (57.9)		76 (56.7)
<8	34 (44.2)	24 (42.1)	0.47	58 (43.3)
Docetaxel in hormone naïve period	1 (1.3)	3 (5.3)	0.20	4 (3.0)
Metastases in				
Only bone	54 (70.1)	39 (68.4)		93 (69.4)
Only solid organ	4 (5.2)	1 (1.8)		5 (3.7)
Bone + Solid organ	19 (24.7)	17 (29.8)	0.65	36 (26.9)
Number of bone metastasis				
None	4 (5.2)	1 (1.8)		4 (3.0)
<5	17 (22.1)	15 (26.3)		33 (24.6)
5–10	28 (36.4)	18 (31.6)		46 (34.3)
≥10	28 (36.4)	23 (40.4)	0.71	51 (38.1)
Pulmonary metastasis	13 (16.9)	12 (21.1)	0.60	57 (16.7)
Hepatic metastasis	11 (14.3)	3 (5.3)	0.08	32 (9.4)
Regional lymph node metastasis	30 (39.0)	29 (50.9)	0.17	165 (48.4)
Castration by				
Orchiectomy	15 (19.5)	7 (12.3)		22 (16.4)
LHRH analog	25 (32.5)	27 (47.4)		52 (38.8)
LHRH + bicalutamide	37 (48.1)	23 (40.4)	0.18	60 (44.8)
PSA level before therapy (median, range)	100.8 (1.4–3700)	77.0 (1.4–2752)	0.41	100 (1.4–3700)
PSA ≥100 (ng/mL)	42 (54.5)	27 (47.4)	0.25	69 (51.5)
Antiresorptive therapy				
Zoledronate	76 (98.7)	56 (98.2)		132 (98.5)
Denosumab	1 (1.3)	1 (1.8)	0.67	2 (1.5)

TABLE 2. Toxicities of the study arms.

Characteristics	Abiraterone-77	Enzalutamide-57	*P*	Total-134
	N (%)	N (%)		N (%)
Dose reduction (>10%)	2 (2.6)	0 (0)	0.002	2 (1.4)
Grade 1–2 toxicity	35 (45.5)	10 (17.5)	0.001	45 (33.6)
Grade 3–4 toxicity	7 (9.1)	1 (1.8)	0.076	8 (6.0)

tice, there is a tendency to use non-taxane modalities in the first line, especially in octogenarians with poor performance scores and multiple co-morbidities.

Besides Radium 223 and Sipuleucel-T, anti-androgen therapy options are effective and well-tolerated in the treatment of mCRPC. The efficacy of ENZA against placebo was tested with PREVAIL study and long-term data showed a radiographic PFS of 20.0 months (18.9–22.1) and mOS of 35.3 months (32.2-NYR) [17]. We found worse mPFS and mOS in our study, 11 and 20 months, respectively. However, in the

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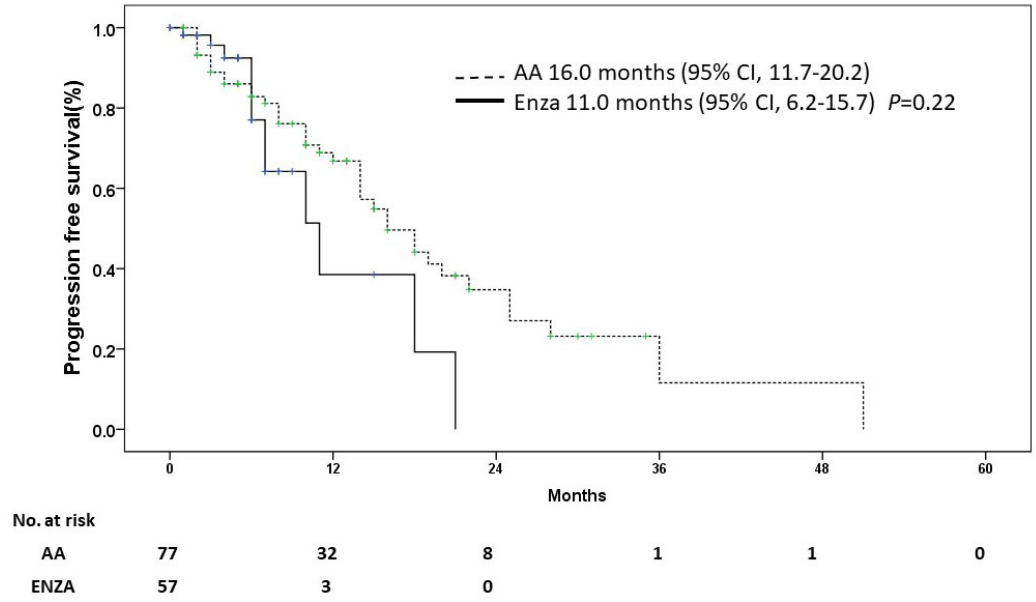

FIG. 1. Kaplan-Meier curve for Progression-free survival of AA and ENZA.

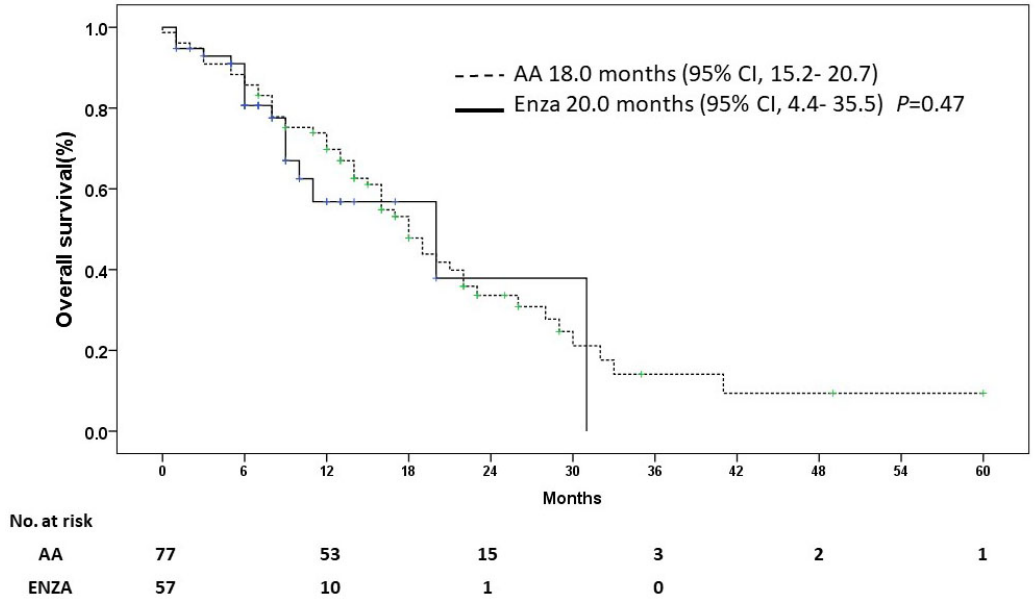

FIG. 2. Kaplan-Meier curve for Overall survival of AA and ENZA.

PREVAIL study, only 36.3% of the patients were ≥75 years of age and there were no patients with an ECOG performance score of ≥2. However, 56.2% of our study population had ECOG ≥2. In addition, we had more patients with hepatic/pulmonary metastasis (26.4% vs 11.2%), the number of patients with ≥10 bone metastasis was also higher (40.4% vs 32.7%) and baseline median PSA was worse (77.0 vs 54.1 ng/mL). The first-line study of AA in mCRPC showed 16.5 months of radiographic PFS and better mOS when compared to placebo + prednisone [6]. We found worse mPFS and mOS in our study, 16 and 18 months, respectively. However, in the reference study, only 34% of the patients were ≥75 years of age, and the patients with solid organ metastases were excluded (29.9% of our AA arm). In addition, our patients had worse baseline PSA (100.8 vs 42.0 ng/mL). When compared to reference phase III studies, our patients in both AA and ENZA arms had worse basal clinical and disease characteristics, leading to worse mPFS and mOS. Although there were more patients in AA, who had second-line therapy, the mOS in AA and ENZA arms were comparable. Unfortunately, there is no study directly comparing the efficacy of AA and ENZA in the first-line setting. There are still ongoing studies [18, 19].

Because of dealing with fragile patients, the toxicity of drugs is essential. There are numerous studies comparing the impacts of ENZA/AA on quality of life and neurocognitive functions. REAAcT study showed more fatigue and neurocognitive with ENZA compared to AA [20]. The AQUARiUS study which was a prospective observational study found an advantage of AA over ENZA on fatigue and

cognitive functions [21]. Also, in some of the comparison studies, patient-reported outcomes favored AA compared with ENZA with differences in quality of life and depression scores [22]. In our study, the toxicity profiles of the drugs were our secondary endpoints. Probably, due to the inevitable data collection bias of retrospective study, we detected less toxicity compared to previous reference studies. Although more patients had dose reductions in the AA arm, discontinuations due to toxicity were similar.

Due to the retrospective design, we had some limitations. As a result of inadequate medical records about toxicities, we couldn't provide detailed data about the toxicity profiles of the drugs. In addition, because of better toxicity profiles of AA and ENZA, there was an inevitable selection bias. The patients had more comorbidities, worse disease characteristics, more solid organ metastases, and poor performance scores when compared to similar studies in the literature. Although there was an inevitable selection bias, the study reflects real life better than the trials in the first-line. Due to documentation problems, we couldn't approach the exact objective response data of the patients.

6. Conclusions

AA and ENZA were equally effective for elderly patients more than 75 years old with mCRPC. The treatments were safe and were discontinued for less than ten percent of the patients. The clinical impacts of anti-androgens in the elderly population should be tested in prospective randomized studies.

Author contributions

All of the authors contributed to study design, data collection and data analysis. AA, GT, BK and YÜ contributed to manuscript writing, submission and revision process.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the institutional review board or ethics committee at each center.

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Conflict of interest

The authors declare no competing interests.

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