ORIGINAL RESEARCH

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Effectiveness of Current First-Line Treatments and Evaluation of Prognostic Factors Related to Survival in Castration-Resistant Prostate Cancer with Isolated Bone Metastasis

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ABSTRACT Objective: This study aimed to investigate the effectiveness of first-line treatments and survival-related prognostic factors in castration-resistant prostate cancer (CRPC) with isolated bone metastasis. Material and Methods: Clinicopathological characteristics of patients diagnosed with CRPC and isolated bone metastasis presenting to the Medical Oncology Clinic of Dicle University between January 2010 and December 2020, as well as the treatments received by them, were retrospectively evaluated. Results: Our study included 91 prostate cancer patients that were in the castration-resistant stage and had isolated bone metastases. As the first-line treatment, 43 (47.2%) of our patients received docetaxel (DOC), 27 (29.6%) received abiraterone acetate (AA), and 21 (23.2%) received enzalutamide (ENZA). The median progression-free survival (PFS) periods for the DOC, AA, and ENZA groups were 9 months [95% confidence interval (CI): 6.52-11.47], 8 months (95% CI: 3.54-12.45), and 13 months (95% CI: 8.09-17.90), respectively (p=0.047). The median overall survival (OS) periods among patients receiving DOC, AA, and ENZA during the hormone-refractory period were 13 months (95% CI: 8.48-17.51), 12 months (95% CI: 8.58-15.41), and 20 months (95% CI: 2.90-37.09), respectively (p=0.13). Multivariate analyses indicated that the choice of first-line treatment received by the patients was an independent prognostic factor for PFS, whereas lymph node metastasis was an important prognostic variable for OS. Conclusion: Our study involving CRPC patients with isolated bone metastases demonstrates similar OS among patients receiving DOC, ENZA, or AA as the first-line treatment for prostate cancer, although ENZA is associated with a better PFS.

Keywords: Castration-resistant prostate cancer; bone metastasis; abiraterone acetate; enzalutamide; docetaxel

Prostate cancer, which is the most common type of cancer in males, constitutes the second-leading cause of cancer-related deaths in males. The disease is often recorded in older men, with the median incidence age being 67 years.[1] Although the prognosis for localized disease is quite good, metastatic disease is associated with a poorer prognosis. Up to 80% of the patients present with localized disease, and the 5-year survival at this stage is almost 100%. The remaining 20% of the patients are admitted in the advanced or metastatic period. Among such patients, the 5-year survival rate is approximately 26%-30%.[2] Currently, androgen deprivation therapy (ADT) is included among the important standard treatments for prostate cancer. During the sensitive period of castration, cancer cells respond to changes in testosterone or metabolite levels. By maintaining testosterone levels at those found after castration (<50 ng/dL), the stimulus required for cancer cell growth is reduced, and prostate cancer cells die. However, ADT alone is not always sufficient to prevent disease progression. Although testosterone levels are kept low with ADT treatment during the hormone-sensitive disease course, the disease eventually becomes resistant to castration owing to changes in androgen receptors and somatic genomic changes.[3] Castration-resistant prostate cancer (CRPC) has been defined as disease progression, increase in prostate-specific antigen (PSA), or new metastatic development despite the maintenance of testosterone levels at castration levels. CRPC progresses rapidly, and death occurs within 2-4 years. In CRPC, treatment options in cases

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of unsuccessful curative treatments remain limited.[2] Both docetaxel (DOC) and next-generation anti-androgen therapies [enzalutamide (ENZA) and abiraterone acetate (AA)] are used in such cases today. These drugs have been approved and have demonstrated survival benefits.[4,5] AA and ENZA are next-generation anti-androgens with both pre and post-chemotherapy uses. AA is an agent that irreversibly inhibits cytochrome P450. By interacting with cytochrome P450 c17 and inhibiting androgen synthesis through the 17-hydroxylase and 17.20 lyase enzymes, AA improves overall survival (OS) both before and after DOC treatment.[6,7] On the other hand, ENZA, which is a second-generation androgen receptor signaling inhibitor, impairs the translocation of androgen receptors and DNA binding.[8] Phase-3 trials for both AA (COU-AA301 and COU-AA302) and ENZA (AFFIRM and PREVAIL) have shown positive results for OS, PSA response, and radiological responses regardless of previous chemotherapy.[9,10] The prognostic significance of different metastasis areas was evaluated thoroughly by several studies on metastatic castration-resistant prostate cancer (mCRPC).[11,12] The site of metastasis is an important parameter that influences the estimated survival in metastatic prostate cancer.[13] In a meta-analysis that reviewed 5 phase-3 trials on patients diagnosed with mCRPC, the median survival times for patients with bone, lung, and liver metastases were determined as 20, 17, and 12 months, respectively. Although CRPC with isolated bone metastases has several treatment options that have been demonstrated in phase-3 trials (such as DOC, AA, and ENZA), no clear information about the optimal ranking or combinations of these treatments is available.[14,15]The objective of this study was to investigate the effectiveness of first-line treatments and survival-related prognostic factors in CRPC.

MATERIAL AND METHODS

PATIENTS AND STUDY DESIGN

Our study included prostate cancer patients with isolated bone metastases presenting to the Medical Oncology Clinic of Dicle University between January 2010 and December 2020. Following a diagnosis of castration-resistant disease with a histopathological diagnosis of prostate adenocarcinoma, 91 patients with isolated bone metastasis were included in this study. Patients receiving DOC and/or new antihormonal therapy (AA, ENZA) during the hormone-sensitive period or those who developed visceral organ metastases were not included in the study. Patients that showed cancer progression despite achieving castration-like levels of testosterone (<50 ng/dL) through medical or surgical intervention were considered to have CRPC. The age, performance status, comorbidities, basal PSA values, histopathological features of the tumor, and treatment details of patients were obtained from their respective files. Patients with radiologically verified metastasis were considered as having metastatic disease. For imaging, positron emission tomography (PET)/prostate-specific membrane antigen (PSMA) (gallium PSMA/PET) was used, while imaging methods such as computed tomography, bone scintigraphy, and magnetic resonance imaging were used when necessary. Radiological responses to treatment were evaluated as responses after three cycles of treatment according to the Response Evaluation Criteria in Solid Tumors guidelines. The Eastern Cooperative Oncology Group (ECOG) performance scale was used to evaluate patient performance. This study was approved by the Dicle University's Faculty of Medicine Ethics Committee (date: February 25, 2021; no: 127). The study was conducted according to the Declaration of Helsinki.

TREATMENTS

The effectiveness of treatment choices (DOC, AA, or ENZA) received by the 91 CRPC patients with isolated bone metastasis was evaluated. For this, 1,000 mg/day AA and 5 mg 2×1/day prednisone (in 28-day cycles), 160 mg/day ENZA (in 28-day cycles), or 75 mg/m^2/day DOC and 5 mg 2×1/day prednisone (once every 21 days) were used. Gonadotropin-releasing hormone analogs were continuously maintained in patients without orchiectomy. Second-generation anti-androgen therapies were continued until death unless there was a progression of cancer or severe toxicity. Up to 6 courses of DOC chemotherapy were given to surviving patients that did not show severe

side effects. Nine courses of therapy were completed for patients that did not show severe side effects after 6 courses. Treatment response was defined clinically, biochemically, and radiologically every 3 cycles.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, USA). Descriptive statistics were used to evaluate patient characteristics and parameter frequency. Student's t-test was used to compare normally distributed numerical variables. Mann-Whitney U test was used to compare non-normally distributed or non-parametric variables. Student's t-test, chi-square test, Fisher's exact test, and Mann-Whitney U test were used for univariate analysis. Kaplan-Meier survival analysis was used based on the log-rank p value. Cox regression analysis was used for the univariate and multivariate analyses in the survival analysis. The enter method was used for univariate analysis, while the forward stepwise likelihood ratio method was used for multivariate analysis.[16] The confidence range was 95%, and a p value of <0.05 was considered statistically significant.

DEFINITIONS

Progression-free survival (PFS) was defined as the period from the beginning of treatment until documented progression or death. Metastatic OS was defined as the time from metastatic disease to death, while hormone-refractory OS was defined as the time from refractory disease to death.

RESULTS

The median age of the patients was 66 years. A total of 69 (75.8%) patients were <75 years old, and 22 (24.2%) were ≥75 years old. The ECOG performance score of 18 (19.8%) patients was ≥2. The basal PSA value of 58 (67.4%) patients was <200 ng/mL, while that of 28 patients (32.6%) was ≥200 ng/mL. In total, 27 (29.7%) patients received third-line treatment, while 5 (5.5%) received fourth-line treatment. The baseline characteristics of the patients are presented in Table 1.

In the first-line treatment, 43 (47.2%) patients received DOC, 27 (29.6%) received AA, and 21 (23.2%) received ENZA. There were differences in the ages and comorbidities between the treatment groups. Patients receiving a new androgen pathway inhibitor (ENZA or AA) were younger and had fewer comorbidities (p<0.05) than those receiving DOC (Table 1). In total, 7 (16.3%) of DOC recipients, 14 (51.9%) of AA recipients, and 11 (52.4%) of ENZA recipients had a history of comorbidities (p<0.05) (Table 1).

The median OS of all patients was 13 months (95% confidence interval (CI): 9.39-16.60), and the median PFS was 10 months (95% CI: 8.56-11.43). The median OS of patients that received DOC, AA, and ENZA during the hormone-refractory period was 13 months (95% CI: 8.48-17.51), 12 months (95% CI: 8.58-15.41), and 20 months (95% CI: 2.90-37.09), respectively (p=0.13) (Table 2, Figure 1).

For the metastatic stage, the OS durations were 31 months, 40 months, and 49 months for the DOC, AA, and ENZA groups, respectively (p=0.66). The median PFS was 9 (95% CI: 6.52-11.47) months, 8 (95% CI: 3.54-12.45) months, and 13 (95% CI: 8.09-17.90) months (p=0.047) for the DOC, AA, and ENZA treatment groups, respectively (Figure 2). In the univariate analysis, DOC had no PFS advantage compared with either AA [hazard ratio (HR)=1.22, 95% CI: 0.71-2.11, p=0.46] or ENZA (HR=0.50, 95% CI: 0.25-1.02, p=0.06). However, in the multivariate analysis, ENZA showed a PFS advantage over DOC (13 months vs. 9 months, HR=0.42, 95% CI: 0.19-0.91, p=0.03). There was no statistically significant difference in OS between the DOC and AA groups (HR=1.44, 95% CI: 0.81-2.54, p=0.20) or between the DOC and ENZA groups (HR=0.70, 95% CI: 0.34-1.45, p=0.34). Correlations between the first-line treatment choices (DOC, AA, ENZA), age (<75 years, ≥75 years), Gleason score (<8, ≥8), ECOG performance score (0-1, ≥2), presence of comorbidity, basal PSA level (<200 ng/mL, ≥200 ng/mL), duration of ADT (<10 months, ≥10 months), and lymph node metastasis were evaluated by univariate and multivariate analyses. The results of the analysis are presented in Table 3, Table 4. Based on the multivariate analysis, the first-line treatment choices were independent prognostic factors for PFS. Meanwhile, the presence of lymph node metastasis was also an independent prognostic factor for OS.

TABLE 1: Baseline characteristics of patients.

Characteristic	All patients (n=91) % (n)	Docetaxel (n=43) % (n)	Abiraterone (n=27) % (n)	Enzalutamide (n=21) % (n)	p value*
Median age (range)	66 (42-85)	65 (42-77)	70 (51-84)	74 (50-85)	
Age (years)					**<0.05**
<75	75.8 (69)	93 (40)	63 (17)	57.1 (12)	
≥75 (%)	24.2 (22)	7 (3)	37 (10)	42.9 (9)	
ECOG PS					0.16
0-1	80.2 (73)	88.4 (38)	70.4 (19)	76.2 (16)	
≥2	19.8 (18)	11.6 (5)	29.6 (8)	23.8 (5)	
Gleason score at initial diagnosis					0.95
<8	49.5 (45)	51.2 (22)	48.1 (13)	47.6 (10)	
≥8	50.5 (46)	48.8 (21)	51.9 (14)	52.4 (11)	
Previous ADT time (months)					0.29
<10	27.5 (25)	32.6 (14)	29.6 (8)	14.8 (3)	
≥10	72.5 (66)	67.4 (29)	70.4 (19)	85.7 (18)	
Baseline PSA level					0.22
<200	67.4 (58)	59.5 (25)	80 (20)	68.4 (13)	
≥200	32.6 (28)	40.5 (17)	20 (5)	31.6 (6)	
Co-morbidities					**<0.05**
No	64.8 (59)	83.7 (36)	48.1 (13)	47.6 (10)	
Yes	35.2 (32)	16.3 (7)	51.9 (14)	52.4 (11)	
LN metastasis					0.75
No	54.9 (50)	53.5 (23)	51.9 (14)	61.9 (13)	
Yes	45.1 (41)	46.5 (20)	48.1 (13)	38.1 (8)	
Subsequent therapies					
3rd line	29.7 (27/91)				
4th line	5.5 (5/91)				

*Chi-square test; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ADT: Androgen deprivation therapy; PSA: Prostate-spesific antigen; LN: Lymph node.

TABLE 2: Survival outcomes of patients by treatment agent.

	Overall survival (months)			Progression free survival (months)		
	Median	95% CI	p value*	Median	95% CI	p value*
All patients	13	9.39-16.60	0.13	10	8.56-11.43	**0.047**
Docetaxel	13	8.48-17.51		9	6.52-11.47	
Abiraterone	12	8.58-15.41		8	3.54-12.45	
Enzalutamide	20	2.90-37.09		13	8.09-17.90	

*Kaplan-Meier survival analysis log-rank p value; CI: Confidence interval.

DISCUSSION

We observed no significant difference between DOC, ENZA, and AA regarding metastatic OS and refractory OS in CRPC patients with isolated bone metastasis (p=0.13). However, ENZA offered a significantly longer PFS than either DOC or AA (p=0.047). In the multivariate analysis, we observed that the first-line treatment option was a prognostic variable for PFS, and the presence of lymph node metastasis was a significant prognostic variable for OS.

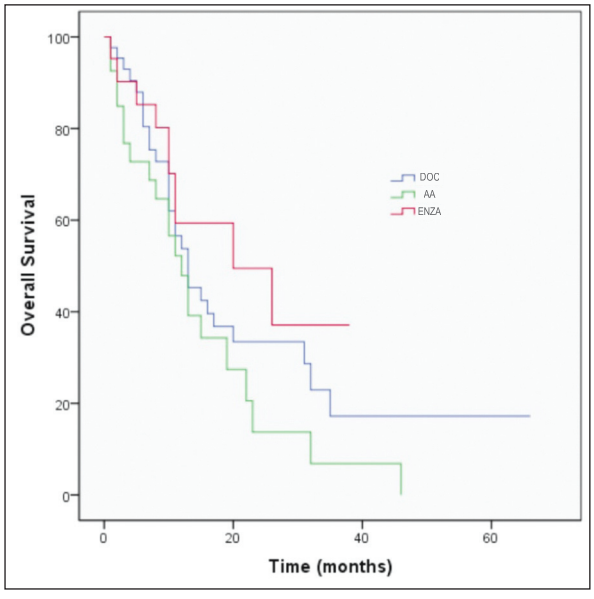

FIGURE 1: Progression-free survival of the three treatment groups.
DOC: Docetaxel; AA: Abiraterone acetate; ENZA: Enzalutamide.

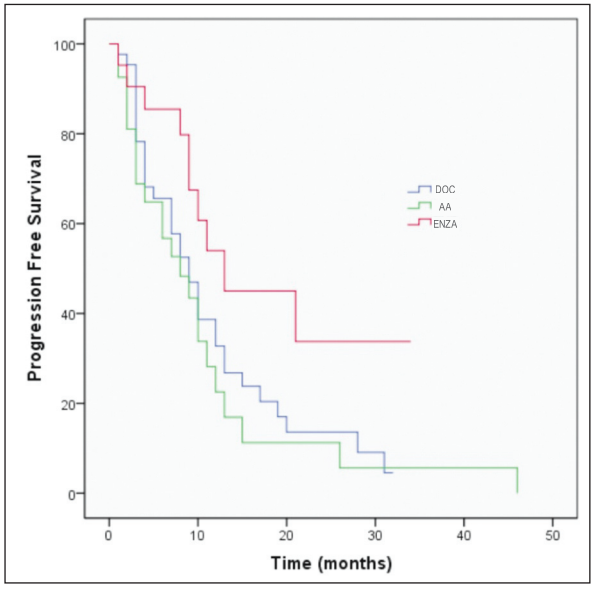

FIGURE 2: Overall survival of the three treatment groups.
DOC: Docetaxel; AA: Abiraterone acetate; ENZA: Enzalutamide.

Since prostate cancer is mostly seen at an advanced age when comorbidities are also common, most patients do not have the opportunity to receive effective treatment at the desired level.[17,18] The median age at diagnosis among our patients was 66 years, which was consistent with that reported in the literature. Overall, 32 (35.2%) patients showed additional comorbidities. Survival times are shorter in older patients due to the Gleason score and aggressive tumor histology.[19,20] It has been reported that the next generation of androgen synthesis pathway inhibitors (ENZA and AA) can be used without causing severe toxicity and that they improve survival in CRPC patients with advanced age, poor performance, and comorbidities, who cannot tolerate chemotherapy.[17,18] There are currently no biomarkers for mCRPC that can help predict an appropriate first-line treatment and its effectiveness, and there is no consensus on this issue.[21] Therefore, in clinical practice, factors such as the age of the patient, performance status, and comorbidities, as well as tumor load and sites of metastasis (visceral or non-visceral organ involvement), can help decide the treatment course.[4,5] Studies on CRPC with isolated bone metastasis are rare. Although factors such as the number of bones affected and the tumor site partially influence tumor density, there are no clear data on whether DOC, ENZA, or AA should be used for this group of patients. In our study involving CRPC patients with isolated bone metastases, 43 (47.2%) received DOC, 27 (29.6%) received AA, and 21 (23.2%) received ENZA as the first-line treatment. Compared with the patients that received either ENZA or AA, those receiving DOC were younger and generally had fewer comorbidities ($p<0.05$).

In the TAX-327 study, the median OS after DOC therapy was determined as 18.9 months and 13.1 months for patients with bone and/or lymph node metastases and those with visceral metastases, respectively. Although the OS was shorter in patients with visceral metastases, treatment with DOC positively contributed to OS.[22,23] Evans et al. prospectively evaluated visceral and non-visceral patient groups in the PREVAIL study. While median OS was not determined in the non-visceral group, it was 27.8 months in the visceral group.[24] Numerous studies have investigated the first-line therapies in prostate cancer. However, there is no phase-3 study demonstrating which treatment choice (DOC, AA, or ENZA) is more effective in mCRPC patients with visceral metastases. A meta-analysis of 23 studies indirectly compared DOC, AA, and ENZA therapies and reported no significant differences between them. However, DOC is recommended in first-line therapy

TABLE 3: Univariate and multivariate analysis for progression-free survival of patients.

Variables	Univariate HR	Analysis 95% CI	p value*	Multivariate HR	Analysis 95% CI	p value**
Primary treatment option			0.07			**0.04**
Docetaxel	Reference			Reference		
Abiraterone	1.22	0.71-2.11	0.46	1.17	0.66-2.07	0.57
Enzalutamide	0.50	0.25-1.02	0.06	0.42	0.19-0.91	**0.03**
Age years (<75, ≥75)	0.98	0.55-1.75	0.95			
Gleason score (<8, ≥8)	0.88	0.54-1.43	0.61			
Performance status (0-1, ≥2)	1.20	0.68-2.12	0.51			
Comorbidity (no, yes)	0.63	0.37-1.35	0.08			
Baseline PSA level (<200, ≥200)	0.92	0.54-1.57	0.77			
ADT time months (<10, ≥10)	0.59	0.36-0.99	0.04			
LN metastasis (no, yes)	0.59	0.35-0.98	0.04			

*Cox regression analysis enter method; **Cox regression analysis forward stepwise (likelihood ratio) method; HR: Hazard ratio; CI: Confidence interval; PSA: Prostate-spesific antigen; ADT: Androgen deprivation therapy; LN: Lymph node.

TABLE 4: Univariate and multivariate analysis for overall survival of patients.

Variables	Univariate HR	Analysis 95% CI	p value*	Multivariate HR	Analysis 95% CI	p value**
Primary treatment option			0.15			
Docetaxel	Reference					
Abiraterone	1.44	0.81.2.54	0.20			
Enzalutamide	0.70	0.34-1.45	0.34			
Age years (<75, ≥75)	1.19	0.66-2.14	0.56			
Gleason score (<8, ≥8)	0.79	0.47-1.32	0.38			
Performance status (0-1, ≥2)	1.62	0.91-2.89	0.10	1.72	0.94-3.15	0.07
Comorbidity (no, yes)	0.88	0.52-1.50	0.65			
Baseline PSA level (<200, ≥200)	0.74	0.42-1.32	0.31			
ADT time months (<10, ≥10)	0.70	0.41-1.19	0.19			
LN metastasis (no, yes)	0.56	0.32-0.96	0.04	0.55	0.31-0.96	0.04

*Cox regression analysis enter method; **Cox regression analysis forward stepwise (likelihood ratio) method; HR: Hazard ratio; CI: Confidence interval; PSA: Prostate-spesific antigen; ADT: Androgen deprivation therapy; LN: Lymph node.

as it offers better outcomes in terms of both OS and PFS. Another study recommended ENZA because it showed the best secondary results as a non-chemotherapeutic agent.[25] In a retrospective study of 115 chemo-naïve mCRPC patients with or without poor prognosis, the survival outcomes for AA and DOC were compared and found to be similar. In the patient group with a poor prognosis, the AA group had a median OS of 7.8 months, and the DOC group had a median OS of 15.7 months (p=0.16). In the group with a good prognosis, the OS was 20.5 months, whereas the subgroup that received DOC showed an OS of 18.2 months (p=0.78).[26] In the current study, DOC and AA did not show a relative advantage in terms of survival in patients with either good or poor prognoses. Until now, no study has directly compared the efficacy of AA and ENZA. However, no differences were observed between ENZA and AA in terms of OS before or after treatment with DOC. Nevertheless, ENZA was superior regarding secondary outcomes.[27] Our study showed that ENZA offered a PFS advantage over DOC (HR=0.42, 95% CI: 0.19-0.91, p=0.03). No statistically significant differences were observed while comparing DOC

with AA (p=0.20) or with ENZA (p=0.34) regarding the OS.

Previous studies have evaluated several parameters that might be related to survival in mCRPC.[28-31] Conflicting data have emerged in several studies on the effect of age on survival. While some studies have reported that age affects survival, other studies have not found this effect.[30-32] Several studies have indicated that high PSA levels are an independent marker for poor prognosis. Although there is no clear upper limit on the PSA level, some studies have stated that high PSA constitutes values between 39-406 ng/mL.[11,28] A high Gleason score is associated with poor differentiation and aggressive tumor biology, thus negatively affecting the prognosis. Survival was shorter among patients with a Gleason score of ≥8.[33] Comorbidities such as hypertension and diabetes mellitus also negatively affect survival. Visceral metastases with bone and lymph node involvement were also reported to negatively affect survival. In a study conducted by Halabi et al. on mCRPC, median OS was found to be 36 months and 46 months in patients with and without visceral metastasis, respectively.[4] In a study that evaluated 8,820 patients receiving DOC, patients with nodal metastasis, bone metastasis, lung metastasis, and liver metastasis had OS durations of 31.6 months, 21.3 months, 19.4 months, and 13.5 months, respectively.[13] Isolated nodal metastasis is associated with better survival compared to bone and visceral organ involvement. In our study, the multivariate analysis revealed that the first-line treatment option was an independent prognostic factor for PFS, while lymph node metastasis was an independent prognostic factor for OS. Due to the small number of patients, other parameters may not have been statistically significant. Besides, the choice of treatment according to risk factors may have affected the results of the statistical analysis. These findings suggest that we can use next-generation therapies that give comparable results as DOC in terms of survival in patients with comorbidities.

The limitations of our study include its single-center, retrospective nature, and the relatively low number of patients. As the study was retrospective, discrepancies in patient records may have affected the prognosis. Such discrepancies include records related to the localization of bone metastasis, number of metastases, laboratory parameters (hemoglobin, alkaline phosphatase, lactate dehydrogenase, etc.), bisphosphonate use, the status of radiotherapy, and toxicity. Moreover, compared with DOC, fewer patients received AA or ENZA, which may have affected the statistical comparisons.

CONCLUSION

In conclusion, this study evaluated CRPC patients with isolated bone metastases and found similar OS outcomes for patients treated with DOC, ENZA, or AA as the first-line therapy. However, the presence of lymph node metastasis was a poor prognostic factor for OS. On the other hand, treatment with ENZA offered a better PFS. For CRPC patients with isolated bone metastases, prospective randomized clinical studies with larger patient cohorts are needed to gain a clear understanding of first-line treatments and determine the factors affecting prognosis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zuhat Urakçı, Zeynep Oruç;* ***Design:*** *Senar Ebinç, Muhammet Ali Kaplan;* ***Control/Supervision:*** *Zuhat Urakçı;* ***Data Collection and/or Processing:*** *Zeynep Oruç, Senar Ebinç;* ***Analysis and/or Interpretation:*** *Zuhat Urakçı, Mehmet Küçüköner;* ***Literature Review:*** *Senar Ebinç, Zuhat Urakçı;* ***Writing the Article:*** *Zuhat Urakçı, Senar Ebinç;* ***Critical Review:*** *Zuhat Urakçı, Abdurrahman Işıkdoğan;* ***References and Fundings:*** *Mehmet Küçüköner;* ***Materials:*** *Muhammet Ali Kaplan, Abdurrahman Işıkdoğan.*

REFERENCES

1. Ferlay J, Colombet M,Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40countries and 25 major cancers in 2018. Eur J Cancer. Nov 2018;103:356-387. [Crossref] [PubMed]
2. Steele CB, Li J, Huang B, Weir HK.Prostate cancer survival in the United States by race and stage (2001-2009): Findings fromthe CONCORD-2 study. Cancer. 2017;123 Suppl 24(Suppl 24):5160-5177. [Crossref] [PubMed] [PMC]
3. Pienta KJ, Bradley D. Mechanismsunderlying the development of androgen-independent prostate cancer. Clin Cancer Res.2006;12(6):1665-1671. [Crossref] [PubMed]
4. Halabi S, Lin CY, Kelly WK, et al.Updated prognostic model for predicting overall survival in first-line chemotherapy forpatients with metastatic castration-resistant prostate cancer. J Clin Oncol.2014;32(7):671-677. Erratum in: J Clin Oncol. 2014;32(13):1387. [Crossref] [PubMed] [PMC]
5. Nuhn P, De Bono JS, Fizazi K, etal. Update on systemic prostate cancer therapies: management of metastaticcastration-resistant prostate cancer in the era of precision oncology. Eur Urol.2019;75(1):88-99. [Crossref] [PubMed]
6. Ryan CJ, Smith MR, Fizazi K, etal; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plusprednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer(COU-AA-302): final overall survival analysis of a randomised, double-blind,placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-160. [Crossref] [PubMed]
7. Ryan CJ, Smith MR, de Bono JS, etal; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previouschemotherapy. N Engl J Med. 2013;368(2):138-148. Erratum in: N Engl J Med. 2013;368(6):584. [Crossref] [PubMed] [PMC]
8. Tran C, Ouk S, Clegg NJ, et al.Development of a second-generation antiandrogen for treatment of advanced prostate cancer.Science. 2009;324(5928):787-790. [Crossref] [PubMed] [PMC]
9. Scher HI, Fizazi K, Saad F, et al;AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer afterchemotherapy. N Engl J Med. 2012;367(13):1187-1197. [Crossref] [PubMed]
10. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators.Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med.2014;371(5):424-433. [PubMed] [PMC]
11. Halabi S, Kelly WK, Zhou H, etal. The site of visceral metastases (mets) to predict overall survival (OS) incastration-resistant prostate cancer (CRPC) patients (pts): A meta-analysis of five phaseIII trials. J Clin Oncol. 2014;32(suppl 15):5002. [Crossref]
12. Cui PF, Cong XF, Gao F, et al.Prognostic factors for overall survival in prostate cancer patients with differentsite-specific visceral metastases: A study of 1358 patients. World J Clin Cases.2020;8(1):54-67. [Crossref] [PubMed] [PMC]
13. Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact ofsite of metastasis on overall survival in men with castration-resistant prostate cancer. JClin Oncol. 2016;34(14):1652-1659. [PubMed] [PMC]
14. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men withmetastatic castration-resistant prostate cancer:American Society of Clinical Oncology andCancer Care Ontario clinical practice guideline. J Clin Oncol. 2014;32(30):3436-3448. [PubMed] [PMC]
15. Lorente D, Mateo J, Perez-LopezR, de Bono JS, Attard G. Sequencing of agents in castration-resistant prostate cancer.Lancet Oncol. 2015;16(6):e279-292. [Crossref] [PubMed]
16. Hair JF, Black WC, Babin BJ, Anderson RE. Multivariate Data Analysis.7th ed. New York, USA: Pearson; 2010.
17. Scosyrev E, Messing EM, Mohile S,Golijanin D, Wu G. Prostate cancer in the elderly: frequency of advanced disease atpresentation and disease-specific mortality. Cancer. 2012;118(12):3062-3070. [Crossref] [PubMed]
18. Shelke AR, Mohile SG. Treatingprostate cancer in elderly men: how does aging affect the outcome? Curr Treat Options Oncol.2011;12(3):263-275. [Crossref] [PubMed]
19. Mandel P, Kriegmair MC, KamphakeJK, et al. Tumor characteristics and oncologic outcome after radical prostatectomy in men 75years old or older. J Urol. 2016;196(1):89-94. [Crossref] [PubMed]
20. Tosoian JJ, Alam R, Gergis C, etal. Unscreened older men diagnosed with prostate cancer are at increased risk of aggressivedisease. Prostate Cancer Prostatic Dis. 2017;20(2):193-196. [Crossref] [PubMed] [PMC]
21. Ingrosso G, Detti B, Scartoni D,et al. Current therapeutic options in metastatic castration-resistant prostate cancer. SeminOncol. 2018;45(5-6):303-315. [Crossref] [PubMed]
22. Pond GR, Sonpavde G, de Wit R,Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site inmen with metastatic castration-resistant prostate cancer. Eur Urol. 2014;65(1):3-6. [Crossref] [PubMed]
23. Berthold DR, Pond GR, Soban F, deWit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisonefor advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol.2008;26(2):242-245. [Crossref] [PubMed]
24. Evans CP, Higano CS, Keane T, etal The PREVAIL study: primary outcomes by site and extent of baseline disease forenzalutamide-treated men with chemotherapy-naïve metastatic castration-resistant prostatecancer. Eur Urol. 2016;70(4):675-683. [Crossref] [PubMed]
25. Zheng H, Chen J, Qiu W, et al.Safety and efficacy of first-line treatments for chemotherapy-naive metastaticcastration-resistant prostate cancer: a systematic review and indirect comparison. BiomedRes Int. Dec 2017;2017:3941217. [Crossref] [PubMed] [PMC]
26. Poon DMC, Chan K, Lee SH, et al;Hong Kong Society of Uro-Oncology (HKSUO). Differences in clinical outcome between docetaxeland abiraterone acetate as the first-line treatment in chemo-naïve metastaticcastration-resistant prostate cancer patients with or without the ineligible clinicalfactors of the COU-AA-302 study. Prostate Int. 2018;6(1):24-30. [Crossref] [PubMed] [PMC]
27. Zhang W, Wu TY, Chen Q, et al.Indirect comparison between abiraterone acetate and enzalutamide for the treatment ofmetastatic castration-resistant prostate cancer: a systematic review. Asian J Androl.2017;19(2):196-202. [Crossref] [PubMed] [PMC]
28. Saad F, de Bono J, Shore N, etal. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial.Eur Urol. 2015;67(2):223-230. [Crossref] [PubMed]
29. de Bono JS, Smith MR, Saad F, etal. Subsequent chemotherapy and treatment patterns after abiraterone acetate in patientswith metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-302. EurUrol. 2017;71(4):656-664. [Crossref] [PubMed] [PMC]
30. Siemens DR, Klotz L, HeidenreichA, et al. Efficacy and Safety of Enzalutamide vs Bicalutamide in Younger and Older Patientswith Metastatic Castration Resistant Prostate Cancer in the TERRAIN Trial. J Urol.2018;199(1):147-154. [Crossref] [PubMed]
31. Afriansyah A, Hamid ARAH, MochtarCA, Umbas R. Prostate specific antigen (PSA) kinetic as a prognostic factor in metastaticprostate cancer receiving androgen deprivation therapy: systematic review and meta-analysis.F1000Res. Feb 2018;7:246. [Crossref] [PubMed] [PMC]
32. Mukherji D, Pezaro CJ,Shamseddine A, De Bono JS. New treatment developments applied to elderly patients withadvanced prostate cancer. Cancer Treat Rev. 2013;39(6):578-583. [Crossref] [PubMed]
33. Miller K, Carles J, Gschwend JE,Van Poppel H, Diels J, Brookman-May SD. The phase 3 COU-AA-302 study of abiraterone acetateplus prednisone in men with chemotherapy-naïve metastatic castration-resistant prostatecancer: stratified analysis based on pain, prostate-specific antigen, and gleason score. EurUrol. 2018;74(1):17-23. [Crossref] [PubMed]