Clinics in Oncology

Research Article
Published: 19 Nov, 2022

Comparison of Clinical Efficacy between Abiraterone, Enzalutamide and Docetaxel in Patients with Metastatic Castrate-Resistant Prostate Cancer

Tomaš I[1], Sablić M[2], Drežnjak-Madunić M[3], Šambić-Penc M[1] and Matić M[1]*

[1]Department of Nuclear Medicine and Oncology, Josip Juraj Strossmayer University of Osijek, Croatia

[2]Department of Anatomy and Neuroscience, Josip Juraj Strossmayer University of Osijek, Croatia

[3]Department of Oncology, Josip Juraj Strossmayer University of Osijek, Croatia

Abstract

Comparison of clinical efficacy between abiraterone, enzalutamide and docetaxel in patients with metastatic castrate-resistant prostate cancer in the Clinical Hospital Center Osijek.

Objective: The goal of this study was to determine if there is a significant difference in the progression-free survival time between patients with castrate-resistant metastatic prostate cancer treated with abiraterone compared with those on enzalutamide.

Study Design: Historical prospective study.

Materials and Methods: This study was conducted on patients treated at the Institute of Oncology of Clinical Hospital Center Osijek from January 2015 until May 2021. Inclusion criteria were the confirmed diagnosis of metastatic castrate resistant prostate cancer and treatment with either medication.

Results: The study included 83 patients of which 29 (35%) had docetaxel as the first line treatment, 28 (34%) had enzalutamide and 26 (31%) abiraterone. Median age of patients was 75 years and the PSA at the time of diagnosis was on average 44 ng/mL. Gleason score ≤ 7 was present in 44 (53%) and a score ≥ 8 in 35 (42%) of patients. Bone metastases were present in 73 (87%) patients, visceral metastasis in 19 (23%). There were 60 (72%) patients that had undergone surgery of which 43 (52%) had an orchidectomy and 20 (24%) a prostatectomy. Curative radiation therapy was conducted in 45 (51%) patients with the median dose being 66 Gy. Kaplan-Meier survival analysis showed no significant difference in progression-free survival between enzalutamide and abiraterone as first or second line treatment (Log Rank, P=0.77). Median time for overall survival was 15 months (8-25) with no difference between studied groups (P=0.06).

Conclusion: There is no significant difference between progression-free survival time between abiraterone and enzalutamide as a first line treatment for metastatic castrate resistant prostate cancer.

Keywords: Prostate cancer; Abiraterone; MDV3100; Progression free survival

OPEN ACCESS

Correspondence:
Marko Sablić, Department of Anatomy and Neuroscience, Josip Juraj Strossmayer University of Osijek, Croatia,
E-mail: msablic@mefos.hr

Received Date: *31 Oct 2022*
Accepted Date: *15 Nov 2022*
Published Date: *19 Nov 2022*

Citation:
Tomaš I, Sablić M, Drežnjak-Madunić M, Šambić-Penc M, Matić M. Comparison of Clinical Efficacy between Abiraterone, Enzalutamide and Docetaxel in Patients with Metastatic Castrate-Resistant Prostate Cancer. Clin Oncol. 2022; 7: 1966.

ISSN: 2474-1663

Introduction

Prostate adenocarcinoma is the third most common malignant disease in the world, after lung and breast cancer, making it the second commonest in men. Prostate cancer is the fifth deadliest malignancy in men [1]. Prostate cancer is categorized as hormone-dependent or independent based on the effectiveness of testosterone deprivation therapy [2]. Some portion of hormone sensitive carcinomas becomes resistant to hormone therapy and continues growing. Such disease is considered castrate-resistant prostate cancer and calls for additional treatment [3]. The additional therapy in this case includes modified hormonal therapy, immunotherapy, chemotherapy with docetaxel or cabazitaxel or therapy with radium 223 isotope [4]. Abiraterone and enzalutamide are hormone-targeting drugs approved for the treatment of prostate cancer [5]. Abiraterone, the active form of the medication created by hydrolysis of abiraterone acetate, is an irreversible inhibitor of the CYP17 enzyme that catalyzes the creation of androgens and cortisol from cholesterol [6]. Enzalutamide irreversibly inhibits the androgen receptor, its translocation to the nucleus from the cytosol and

the interaction between the aforementioned receptor and cell DNA [7]. In an indirect comparison, therapy with enzalutamide showed significantly longer radiological and biochemical progression-free survival in patients with previous chemotherapy and in those without chemotherapy [8].

Objectives

The objective of this study was to determine whether there is a difference in efficacy between the drugs abiraterone and enzalutamide, before and after docetaxel.

Material and Methods

This research was organized as a retrospective analysis of medical documentation of patients treated at the Department of Oncology of the Clinical Hospital Center Osijek in the period from March 2015 to May 2021. All patients with metastatic prostate cancer who had received treatment with abiraterone or enzalutamide were included in the study. The study was approved by the ethical committee of the medical faculty Osijek in May 2021.

Methods

This study included all patients with documented radiographic or PSA progression of the disease whilst having castration-levels of testosterone, who had abiraterone or enzalutamide in the course of their treatment. Patients who received previous cycles of chemotherapy as well as those without them were included. Patient age, type of cancer, Gleason score and PSA value at the time of diagnosis were taken from the medical documentation. For operated patients, the date and type of operation were recorded. For patients who underwent radiotherapy, the date and dose of radiation. Data on the date of metastatic disease diagnosis, PSA values and their date of measurement, the place of tumor metastasis and medications were all collected from patient histories. The patients had their PSA measured every 3 months with scintigraphy and CT follow-up every 6 months according to the clinical guidelines. All patients with noted biochemical (PSA) or radiographical (MRI, SPECT, CT, scintigraphy) worsening of the disease despite their current treatment were considered to have had progression. For the first and second line of treatment with abiraterone, or enzalutamide and docetaxel respectively, the start and end dates were recorded, as well as the number of received cycles, side effects and breaks in treatment. If the disease had not yet progressed, the date of the last control exam was categorized as "continued treatment", progressive as "on further processing" and "palliative" for progressives without any remaining viable therapeutic options. For the overall survival estimate, six weeks from the last exam for patients on palliative care and eight weeks for those waiting for further processing were taken as the cutoff dates.

Statistical methods

Categorical data are presented in absolute and relative frequencies. Differences between categorical variables were tested using the χ^2 test, and if necessary, with Fisher's exact test. The normality of the distribution of numerical variables was tested using the Shapiro-Wilk test. Numerical data were described using the arithmetic mean with standard deviation in case of normal distribution, and in other cases by the median and limits of the interquartile range. The differences of the normally distributed numerical variables between two independent groups were tested using the student's test, and in the case of deviations from the normal distribution by the Mann-Whitney U test or the Kruskal-Wallis test. All P values were two-sided. The significance level was set to α=0.05. The Kaplan-Meier test was used for the survival analysis and the Log-rank test for their comparison. The statistical analysis was done by using the following software: MedCalc Statistical Software version 19.6.4 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) (Figures 1-5).

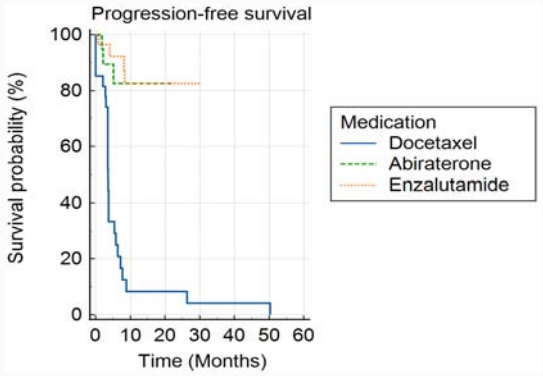

Figure 1: Kaplan-Meier progression-free survival graph based on the first line of treatment.

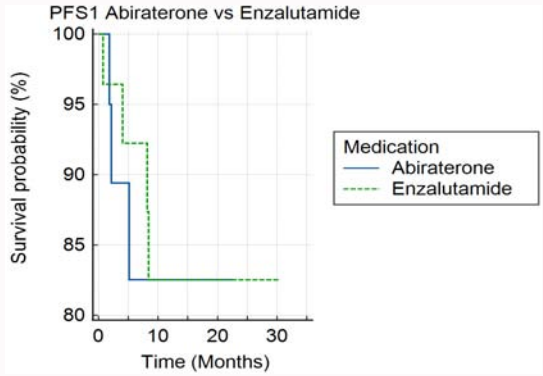

Figure 2: Kaplan-Meier progression-free survival graph based on the first line of treatment for abiraterone and enzalutamide.

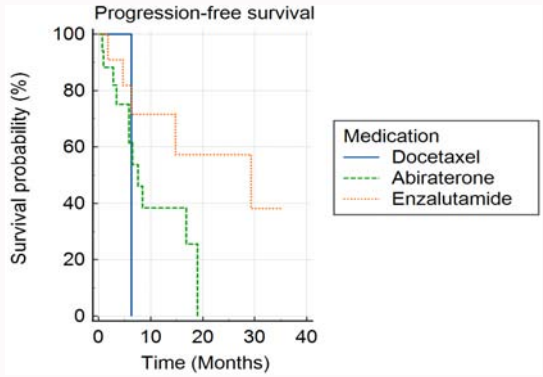

Figure 3: Kaplan-Meier progression-free survival graph based on the second line of treatment.

Results

Baseline population characteristics

The study was conducted on 83 patients with metastatic castration-resistant prostate adenocarcinoma treated at the Department of Oncology of the Clinical Hospital Center Osijek in the period from March 2015 to May 2021. Five patients had an additional oncological

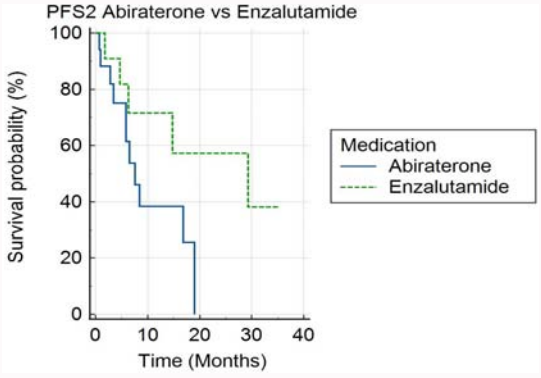

Figure 4: Kaplan-Meier progression-free survival graph based on the second line of treatment for abiraterone and enzalutamide.

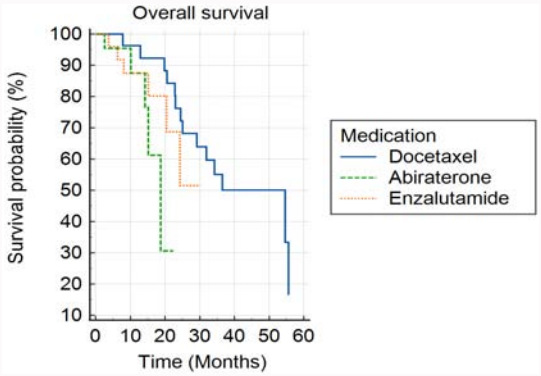

Figure 5: Kaplan-Meier overall survival graph.

Table 1: Median age of the observed groups based on the first line of treatment.

	Median (interquartile range)			
	Docetaxel	**Abiraterone**	**Enzalutamide**	**P***
Age (years)	73 (69-75)	73 (70-81)	77 (70-80)	0.30

*Kruskal-Wallis

Table 2: Differences in nadir PSA value between observed groups.

	Median (interquartile range)			
	Docetaxel	**Abiraterone**	**Enzalutamide**	**P***
PSA value (/dL)	62 (33-150)	24 (11-61)	29 (10-100)	0.09

*Kruskal-Wallis

diagnosis before starting treatment: two patients had bladder cancer, and one each with malignant melanoma, squamous cell carcinoma of the skin and sigmoid colon cancer. Two individuals were diagnosed with a brain tumor (one of unknown genesis and one glioblastoma) during the course of treatment. The median (median) age is 75 years, with limits in the interquartile range of 70 to 80 years. There are no significant differences between the observed groups (Table 1). The median PSA value in the diagnosis of prostate adenocarcinoma (nadir) is 44 ng/mL, with an interquartile range of 12-100. PSA is of unknown value for 12 individuals. There were no significant differences between groups based on the first-line treatment (Table 2). Forty-four (53%) patients had a Gleason score ≤ 7 and 35 (42%) had a Gleason score ≥ 8. The Gleason score was unknown for 4 patients. Differences between groups based on first-line treatment were not significant (Table 3). All observed patients had metastases. Bone metastases were present in 73 (87%) patients while visceral metastases were present in 19 (23%) patients. The differences between the observed groups were not significant (Table 4). Sixty (72%) patients were operated on,

Table 3: Distribution of the Gleason score values for the observed groups.

Gleason score	Overall	Docetaxel	Abiraterone	Enzalutamide	P*
5 (2+3)	1 (1)	0/29	1/26	0/28	0.86
6 (3+3)	6 (7)	2/29	0/26	4/28	
7 (3+4)	18 (22)	6/29	6/26	6/28	
7 (4+3)	19 (23)	7/29	6/26	6/28	
8 (3+5)	2 (2)	1/29	1/26	0/28	
8 (5+3)	1 (1)	0/29	1/26	0/28	
8 (4+4)	15 (18)	6/29	4/26	5/28	
9 (4+5)	13 (16)	4/29	5/26	4/28	
9 (5+4)	3 (4)	1/29	1/26	1/28	
10 (5+5)	1 (1)	0/29	0/26	1/28	
Unknown	4 (5)	2/29	1/26	1/28	
Overall	83 (100)	29	26	28	

*Kruskal-Wallis

Table 4: Location of the metastasis based on the observed groups.

	Number (%) of patients				P*
	Overall	Docetaxel	Abiraterone	Enzalutamide	
Bone	73 (88)	26 (90)	23 (88)	24 (85)	0.52
Lymph nodes	36 (43)	11 (37)	14 (54)	11 (39)	0.86
Lungs	10 (12)	3 (10)	4 (15)	3 (11)	0.95
Liver	8 (10)	1 (3)	4 (15)	3 (11)	0.45
Spleen	1 (1)	0 (0)	0 (0)	1 (4)	0.35

*χ^2 test

Table 5: Patient distribution in regard to the operative treatment based on the observed groups.

	Number (%) of patients			P*
	Docetaxel	**Abiraterone**	**Enzalutamide**	
Operated	25 (86)	16 (62)	19 (68)	0.10
Not operated	4 (14)	10 (38)	9 (32)	
Overall	29 (100)	26 (100)	28 (100)	

*χ^2 test

Table 6: Type of operation based on the observed groups.

Type of operation	Number (%) of patients			P*
	Docetaxel	Abiraterone	Enzalutamide	
Orchidectomy	20 (69)	9 (35)	14 (50)	0.03
Prostatectomy	7 (24)	7 (27)	6 (21)	0.89
Lymphadenectomy	2 (7)	2 (8)	1 (4)	0.79
Other operations	3 (1)	1 (4)	3 (11)	0.59

*χ^2 test

Table 7: Patient distribution based on radiation treatment.

	Number (%) of patients			P*
	Docetaxel	Abiraterone	Enzalutamide	
Curative	17 (59)	13 (50)	12 (43)	0.49
Palliative	6 (21)	2 (8)	2 (7)	0.21

*χ^2 test

with 43 (52%) orchiectomized, 20 (24%) prostatectomies and 5 (6%) lymphadenectomies. Other operations were performed on 7 patients (two hemicolectomies, sigmoid bowel resection, three bladder resections and craniotomy). There was a statistically significant difference only in the number of orchiectomized patients (Table 5, 6). Forty-four (53%) patients were irradiated, 42 (51%) were in some point curatively, and 10 (12%) patients palliatively irradiated.

Table 8: Differences in radiation doses between observed groups.

	Median (interquartile range)			P*
	Docetaxel	Abiraterone	Enzalutamide	
Dose (Gy)	66 (66-74)	71 (66-74)	66 (66-70)	0.305

*Kruskal-Wallis

Table 9: Patient distribution based on the drug received.

Therapy	Number of patients on the 1st line of treatment	Number of patients on the 2nd line of treatment
Docetaxel	29 (35)	4 (11)
Abirateronee	26 (31)	19 (54)
Enzalutamide	28 (34)	12 (34)
Overall	83 (100)	35 (100)

Table 10: Patient distribution based on the drugs administered on the second line of treatment.

Ist line	IInd line		
	Docetaxel	Abiraterone	Enzalutamide
Enzalutamide	3	1	/
Abiraterone	1	/	2
Docetaxel	/	18	10
Overall	4	19	12

Table 11: Cases summary for the first line of treatment.

	Number of events[a]		Number censored[b]		Total sample size
	N	%	N	%	
Docetaxel	26	96.3	1	3.7	27
Abiraterone	3	13.6	19	86.4	22
Enzalutamide	4	14.3	24	85.7	28
Overall	33	42.9	44	57.1	77

[a]Progression = 1
[b]No progression = 0

Table 12: Mean and median survival for the first line of treatment.

	Mean	SE	95% CI for the mean	Median	95% CI for the median
Docetaxel	6.667	2.13	2.497 to 10.838	3.567	3.500 to 5.400
Abiraterone	19.05	1.77	15.577 to 22.522	-	
Enzalutamide	25.95	1.96	22.113 to 29.787	-	
Overall	25.11	3.78	17.694 to 32.520	26.367	6.367 to 50.333

Differences between groups were not statistically significant (Table 7). The median dose of curative radiation is 66 Gy with the limits of the interquartile range of 66 Gy to 74 Gy. The differences between the observed groups are not significant (Table 8). Ten patients were palliatively irradiated, three of them with a dose of 30 Gy, the others with 24 Gy.

Treatment results

Of the 83 patients on the first line of treatment, 29 (35%) received docetaxel, 26 (31%) abiraterone, and 28 (34%) enzalutamide.35 patients had second-line treatment due to progression or drug intolerance, of which 4 (12%) received docetaxel, 19 (54%) abiraterone and 12 (34%) enzalutamide. During the treatment with docetaxel, seven patients had a break in therapy; two patients had a break on abiraterone and one patient on enzalutamide. All breaks lasted one cycle of treatment, and were most often the result of drug intolerance, poor laboratory findings, or hospitalization because of other causes. A total of 14 patients had side effects. Of these seven on docetaxel, two on abiraterone and five on enzalutamide. The most common side effects of docetaxel were poor general condition, diffuse erythema throughout the body, nausea, vomiting and loss of appetite. Side effects of enzalutamide: Diffuse rash on the body, irregular stools and itching. The most common side effects on abiraterone were fatigue, weakness, and nausea. One patient on abiraterone was discontinued from the first line of treatment because of side effects. The median duration of the first line of treatment was 5 months, with an interquartile range of 3 to 12 months. The progression-free survival time for the first-line treatment was significantly longer in patients treated with abiraterone and enzalutamide in comparison to docetaxel (Tables 9-12). The progression-free survival did not differ significantly between abiraterone and enzalutamide in first-line treatment (Log Rank, P=0.77) (Table 13). The progression-free survival for the second line of treatment did not differ significantly between drugs (Table 14). Progression-free survival between abiraterone and enzalutamide as the second line of therapy did not differ statistically significantly (Log rank test, P=0.06). The median overall survival time is 15 (8-25) months. Overall survival did not differ significantly between first-line treatment groups (Table 15).

Table 13: Comparison of survival curves (Log rank test) for the first line of treatment.

Chi-squared	38.3380
DF	2
Significance	P<0.0001

Table 14: Hazard ratios with 95% confidence interval.

	Docetaxel	Abiraterone	Enzalutamide
Docetaxel	-	0.1291	0.1036
		0.05181 to 0.3216	0.04605 to 0.2333
Abiraterone	7.7474	-	0.803
	3.1098 to 19.3011		0.3468 to 1.8592
Enzalutamide	9.6484	1.2454	-
	4.2865 to 21.7170	0.5379 to 2.8835	

Table 15: Case summaries for the second line of treatment.

	Number of events[a]		Number censored[b]		Total sample size
	N	%	N	%	
Docetaxel	1	25	3	75	4
Abiraterone	11	57.9	8	42.1	19
Enzalutamide	5	45.5	6	54.6	11
Overall	17	50	17	50	34

[a]Progression = 1
[b]No progression = 0

Discussion

The efficacy of abiraterone in prostate cancer is consistent with studies COU-AA-301 and COU-AA-302 [9,10]. Enzalutamide was approved primarily based on randomized clinical trials AFFIRM and PREVAIL [11,12]. Their comparison was also performed by a systematic literature review in the work by Zhang et al. [13], which was primarily based on four previous randomized clinical trials.

In the current study, most patients who had either abiraterone or enzalutamide in the second line were switched from docetaxel in the first line. The main disadvantage of this study is the small number of patients. Randomized clinical trials on the basis of which the studied drugs were approved had significantly larger samples with >1000 individuals [9-12].

Table 16: Mean and median survival for the second line of treatment.

	Mean	SE	95% CI for the mean	Median	95% CI for the median
Docetaxel	6.3	0	6.300 to 6.300	6.3	
Abiraterone	10.052	1.885	6.357 to 13.746	7.567	3.433 to 19.000
Enzalutamide	22.403	4.349	13.878 to 30.927	29.3	4.667 to 29.300
Overall	15.978	2.681	10.723 to 21.234	14.767	6.300 to 29.300

Table 17: Comparison of survival curves (Log rank test) for the second line of treatment.

Chi-squared	3.6293
DF	2
Significance	P=0.1629

Table 18: Hazard ratios with 95% confidence interval.

	Docetaxel	Abiraterone	Enzalutamide
Docetaxel	-	0.9415	0.3776
		0.07562 to 11.7231	0.03069 to 4.6472
Abiraterone	1.0621	-	0.4011
	0.08530 to 13.2248		0.1518 to 1.0597
Enzalutamide	2.6481	2.4932	-
	0.2152 to 32.5884	0.9437 to 6.5870	

Table 19: Case summaries for the calculation of overall survival.

	Number of events[a]		Number censored[b]		Total sample size
	N	%	N	%	
Docetaxel	14	50	14	50	28
Abiraterone	5	20	20	80	25
Enzalutamide	6	21.4	22	78.6	28
Overall	25	30.9	56	69.1	81

[a]Died = 1
[b]Alive = 0

The median age of the patients included in the current study was 75 years, and the observed groups based on first-line treatment did not differ significantly. In studies examining the effect of abiraterone, the median age ranged from 69 (COU-AA-301) to 70 years (COU-AA-302), while the mean age for enzalutamide was 72 and 69 years (PREVAIL, AFFIRM). Patient age in the current study ranged from at least 69 to a maximum of 81 years, while the range in previously listed studies was much wider and included people aged 40 to 90 years.

In the current study, the mean PSA value at the time of diagnosis was about 50 ng/mL which most closely correlates with the PREVAIL and COU-AA-302 studies, where those values were 39 and 54 ng/mL. It should be noted that, in contrast to the current study, the range of nadir PSA values in others (AFFIRM and COU-AA-301) was very wide, ranging from 0.1 to several thousand (PREVAIL). There were no statistically significant differences based on PSA values between the groups.

Fifty-three percent of patients had a Gleason score ≤ 7, while 42% of patients had a GS value ≥ 8 and the rest unknown, indeterminate. The observed groups did not differ significantly from each other. In the current study, GS was on average lower than in abiraterone and enzalutamide approval studies [9-12], where the proportion of patients with GS ≤ 7 ranged around 49% for enzalutamide and 46% for abiraterone, respectively.

There was a statistically significant difference between the observed

Table 20: Mean and median survival for the calculation of overall survival.

	Mean (units?)	SE	95% CI for the mean	Median	95% CI for the median
Docetaxel	39.973	3.32	33.467 to 46.479	54.633	25.067 to 55.600
Abiraterone	17.409	1.54	14.388 to 20.431	18.767	14.233 to 18.767
Enzalutamide	23.965	2.06	19.932 to 27.997	-	
Overall	36.006	2.85	30.412 to 41.600	34.267	24.300 to 55.600

Table 21: Comparison of survival curves (Log rank test) for the calculation of overall survival.

Chi-squared	5.5843
DF	2
Significance	P=0.0613

Table 22: Hazard ratios with 95% confidence interval for the calculation of overall survival.

	Docetaxel	Abiraterone	Enzalutamide
Docetaxel	-	2.8048	1.5368
		0.7034 to 11.1838	0.5679 to 4.1584
Abiraterone	0.3565	-	0.5479
	0.08942 to 1.4216		0.1137 to 2.6394
Enzalutamide	0.6507	1.8251	-
	0.2405 to 1.7608	0.3789 to 8.7921	

groups only in the number of orchiectomized patients. Ultimately, this did not change the predictive value of the study in which castration-resistant cancer was studied. All patients underwent either medical or surgical castration during a certain period of their treatment. In the first line of treatment, 90% of operated patients received docetaxel, 88% abiraterone and 85% enzalutamide. In contrast, the percentages of patients operated on in the AFFIRM and COU-AA-302 studies was 66% and 47%, respectively, for the two observed drugs, which is less than the observed sample. The percentage of patients treated with radiation ranged from about 38% for enzalutamide and around 52% for abiraterone in the approval studies, while in the current study, the percentages were: 59% docetaxel, 50% abiraterone and 43% for enzalutamide. The stated characteristics of the observed population before treatment did not differ much from those reported in the studies [9-12].

In the current study, during treatment with docetaxel, seven patients had a break in therapy, two patients on abiraterone and one patient on enzalutamide. All breaks lasted 1 cycle of treatment and were most often the result of intolerance to therapy, poor findings or hospitalization due to other causes. A total of 14 patients had adverse reactions, of which 7 on docetaxel, 5 on enzalutamide and 2 on abiraterone. The most common side effects of docetaxel were poor general condition, diffuse erythema throughout the body, nausea, vomiting and loss of appetite, less common oral canker sores, low red blood cells, and swelling of the legs. Side effects of enzalutamide included diffuse body rash, irregular stools, itching, pain, and swelling of the legs.

In contrast with PREVAIL and AFFIRM studies, no serious cardiac side effects such as atrial fibrillation or neurological side effects such as convulsions were observed [11,12]. On abiraterone, the most common side effects were fatigue, weakness, and nausea, and no serious side effects such as hypokalemia, cardiac events, or elevated liver enzymes reported were observed in this group [9,10].

Progression-free survival time for the first-line treatment

was significantly (P<0.001) longer in subjects on abiraterone or enzalutamide compared to docetaxel. Such results are confirmed by a study by the Poon-led Urological Oncology Society comparing abiraterone and docetaxel [14]. In contrast, a comparison of docetaxel and enzalutamide after abiraterone therapy showed no differences for this drug [15].

In a systematic literature review, which made an indirect comparison of abiraterone and enzalutamide based on the four randomized clinical trials (COU-AA-301, COU-AA-302, PREVAIL, AFFIRM), significant differences between the two drugs were found. Overall survival was not significantly longer for enzalutamide in patients without visceral progression, while in other subgroups, it was almost equal to survival on abiraterone. The time to radiographic and PSA progression was significantly longer in the enzalutamide group in subjects with and without prior chemotherapy [8].

In contrast, the current study showed that there was no significant difference between abiraterone and enzalutamide in the time to biochemical progression of the disease (P=0.77) in patients without prior chemotherapy. On average, the duration to progression for enzalutamide was longer, 12 compared to 5 months for abiraterone, but with a relatively wide range of reliability for both drugs (Table 12). These results are consistent with the work of Beer et al. [12] where the radiographic PFS for enzalutamide without prior chemotherapy was also 12 months, with a significantly higher number of patients.

Time to the progression of PSA values for enzalutamide in the current study ranged from 3.7 to 20 months which was significantly longer than the values obtained in this paper, but with a large range, while for abiraterone the time to radiographic progression was about 6 months (for PSA 10 months). This is consistent with the values in previous studies [16].

In an analysis conducted by Cesca et al. [17], enzalutamide showed a longer time to progression, but no change in overall survival compared with abiraterone.

The small number of patients studied limits analysis of the time to disease progression based on the second line of treatment, i.e., in patients who have progressed, who have had the drug replaced due to side effects or who had previously received docetaxel. Thus, for example, only four individuals had received docetaxel as a second-line treatment. The median time to death, biochemically or radiologically proven progression since the initiation of second-line treatment was 6 months for docetaxel and abiraterone and 29 months for enzalutamide. There was no significant difference progression-free survival between these drugs (P=0.16), which was potentiated with a wide range of reliability (Table 14).

The second line of treatment showed no significant difference between abiraterone and enzalutamide, although there was a tendency for a slightly longer survival on enzalutamide (P=0.06). These results are consistent results of enzalutamide treatment after abiraterone, as outlined in the December 2019 Chung and Kang study [18]. In addition, the authors of that paper stated that there was no significant difference in overall survival between the two sequences, which is concordant with results of the current study.

In terms of overall survival, the current study shows that there was no difference in survival regardless of the drug used as the first line of treatment, confirming previous results [8]. However, the overall survival deviated significantly from that obtained in other works. In efficacy studies of abiraterone compared with placebo, the percentage of progressed patients on first-line treatment for this drug was 68%, while overall survival ranged from 32 to 36 months (COU-AA-302). Earlier studies have shown progression in 42% of patients and a total survival of 5.8 months (COU-AA-301).

The median survival from the start of first line abiraterone to death in the current study was 18 months, a value between the two previously mentioned. According to our data in the current study, the percentage of progressives was around 14% for the first and 58% for the second line. The overall survival for enzalutamide was 18 months in AFFIRM and 32 months in the PREVAIL study. In the current study, overall survival was much lower than expected and amounted to 11 months for first-line treatment with a 95% confidence range of 5 to 17 months. The percentage of progressed on first- line enzalutamide treatment was 14%, while in people treated with this drug as a second line it was 45%.

The stated overall survival data were not sufficiently predictive due to the estimated date of death and a small observed population. A recently published study by Tagawa et al. [19] found that survival was longer on enzalutamide.

The current study showed that there was no significant difference in the choice of abiraterone over enzalutamide for the first-line treatment of metastatic castration-resistant prostate cancer. By extending the study to a larger number of subjects, marginal statistical values could become significant in favor of enzalutamide. Different mechanisms of action, very small differences between the levels of significance in the study and more research in which the risk ratio favors enzalutamide, should make it the drug of choice. Lastly, further research in this field is needed to confirm the efficacy of abiraterone (Tables 16-22).

Conclusion

There is no significant difference in progression free survival time between abiraterone and enzalutamide as first line of treatment.

The overall survival is not significantly different between abiraterone, enzalutamide or docetaxel.

References

1. Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health. 2019;9(4):217-22.
2. Hoang DT, Iczkowski KA, Kilari D, See W, Nevalainen MT. Androgen receptor-dependent and -independent mechanisms driving prostate cancer progression: Opportunities for therapeutic targeting from multiple angles. Oncotarget. 2017;8(2):3724-45.
3. Vellky JE, Ricke WA. Development and prevalence of castration-resistant prostate cancer subtypes. Neoplasia. 2020;22(11):566-75.
4. Cornford P, Bellmunt J, Bolla M, Briers E, Santis MD, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630-42.
5. Dong L, Zieren RC, Xue W, de Reijke TM, Pienta KJ. Metastatic prostate cancer remains incurable, why? Asian J Urol. 2019;6(1):26-41.
6. Reid AH, Attard G, Barrie E, de Bono JS. CYP17 inhibition as a hormonal strategy for prostate cancer. Nat Clin Pract Urol. 2008;5(11):610-20.
7. Schalken J, Fitzpatrick JM. Enzalutamide: Targeting the androgen signaling pathway in metastatic castration-resistant prostate cancer. BJU Int. 2016;117(2):215-25.

8. Zhang W, Wu TY, Chen Q, Shi XL, Xiao GA, Zhao L, et al. Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: A systematic review. Asian J Androl. 2017;19(2):196-202.

9. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.

10. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48.

11. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.

12. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33.

13. Zhang W, Wu TY, Chen Q, Shi XL, Xiao GA, Zhao L, et al. Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: A systematic review. Asian J Androl. 2017;19(2):196-202.

14. Poon DMC, Chan K, Lee SH, Chan TW, Sze H, Lee EKC, et al. Differences in clinical outcome between docetaxel and abiraterone acetate as the first-line treatment in chemo-naïve metastatic castration-resistant prostate cancer patients with or without the ineligible clinical factors of the COU-AA-302 study. Prostate Int. 2018;6(1):24-30.

15. Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. Prostate. 2014;74(13):1278-85.

16. Armstrong AJ, Lin P, Higano CS, Iversen P, Sternberg CN, Tombal B, et al. Prognostic association of prostate-specific antigen decline with clinical outcomes in men with metastatic castration-resistant prostate cancer treated with enzalutamide in a randomized clinical trial. EurUrol Oncol. 2019;2(6):677-84.

17. Cesca MG, Silveira MT, Pandolfi NC, Oliveira TB, Rinck JA, Da Costa AA, et al. Comparison of enzalutamide versus abiraterone in castration-resistant prostate cancer before docetaxel: Results of a propensity score-matched analysis. J Clin Oncol. 2019;37(15_suppl):e16540.

18. Chung DY, Kang DH, Kim JW, Kim DK, Lee JY, Hong CH, et al. Comparison of oncologic outcomes between two alternative sequences with abiraterone acetate and enzalutamide in patients with metastatic castration-resistant prostate cancer: A systematic review and meta-analysis. Cancers (Basel). 2019;12(1):8.

19. Tagawa ST, Ramaswamy K, Huang A, Mardekian J, Schultz NM, Wang L, et al. Survival outcomes in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. Prostate Cancer Prostatic Dis. 2021;24(4):1032-40.