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Research Article

Clinical and Biochemical Outcomes of Hormonal Therapy among Elderly Patients with Prostate Cancer in Sulaimani City

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Abstract

Background: Androgens, such as testosterone and dihydrotestosterone (DHT), have a major impact on the progression of prostate cancer because they activate the androgen receptors (AR) of prostate cancer cells. This condition is one of the most common cancers in males worldwide. ***Objectives***: To evaluate the clinical and biochemical outcomes with bicalutamide, enzalutamide, and abiraterone in patients with prostate cancer. ***Methods***: This is a retrospective study that included patients with advanced prostate cancer who were divided into three groups: bicalutamide, enzalutamide, and abiraterone treated groups. Data were collected from patients' files at baseline, 6 and 12 months after treatment for measuring prostate specific antigen, liver function, renal function, and lipid profile. ***Results***: A remarkable decline in prostate size, prostate-specific antigen (PSA), back pain, and urinary symptoms was seen in all the groups after 12 months of treatment. Bicalutamide and abiraterone significantly attenuated total serum bilirubin (TSB). Meanwhile, enzalutamide significantly reduced alkaline phosphatase (ALP) level. Abiraterone resulted in a significant reduction in serum creatinine levels. A significant elevation of performance status (PS) score was noticed in the Enzalutamide and Abiraterone groups. ***Conclusions***: Bicalutamide, enzalutamide, and abiraterone improved the outcomes of prostate cancer. Bicalutamide was superior to enzalutamide and abiraterone in improving PS.

Keywords: Abiraterone, Bicalutamide, Enzalutamide, Prostate cancer, Prostate-specific antigen, PS score.

النتائج السريرية والكيميائية الحيوية للعلاج الهرموني بين المرضى المسنين المصابين بسرطان البروستاتا في مدينة السليمانية

الخاصة

الخلفية: الأندروجينات، مثل هرمون التستوستيرون وثنائي هيدروتستوستيرون (DHT)، لها تأثير كبير على تطور سرطان البروستاتا لأنها تنشط مستقبلات الأندروجين (AR) لخلايا سرطان البروستاتا. هذه الحالة هي واحدة من أكثر أنواع السرطان شيوعا عند الذكور في جميع أنحاء العالم. **الأهداف**: تقييم النتائج السريرية والكيميائية الحيوية مع بيكالوتاميد وإنزالوتاميد وأبيراتيرون في المرضى الذين يعانون من سرطان البروستاتا. **الطرائق**: هذه دراسة بأثر رجعي شملت مرضى سرطان البروستاتا المتقدم الذين تم تقسيمهم إلى ثلاث مجموعات: بيكالوتاميد، إنزالوتاميد، وأبيراتيرون المجموعات المعالجة. تم جمع البيانات من ملفات المرضى في خط الأساس وبعد 6 و 12 شهرا من العلاج لقياس مستضد البروستاتا النوعي ووظائف الكبد والوظيفة الكلوية وملف تعريف الدهون. **النتائج**: لوحظ انخفاض ملحوظ في حجم البروستاتا، PSA، آلام الظهر، وأعراض المسالك البولية في جميع المجموعات بعد 12 شهرا من العلاج. خفف بيكالوتاميد وأبيراتيرون بشكل كبير TSB. وفي الوقت نفسه، خفضت إنزالوتاميد بشكل كبير من مستوى ALP. أدى أبيراتيرون إلى انخفاض كبير في مستويات الكرياتينين في الدم. لوحظ ارتفاع كبير في درجة حالة الأداء (PS) في مجموعتي Enzalutamide و Abiraterone. **الاستنتاجات**: أدى بيكالوتاميد وإنزالوتاميد وأبيراتيرون إلى تحسين نتائج سرطان البروستاتا. كان بيكالوتاميد متفوقا على إنزالوتاميد وأبيراتيرون في تحسين PS.

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INTRODUCTION

Prostate cancer is one of the most common malignancies among men globally, and its growth is heavily driven by androgens, such as testosterone and dihydrotestosterone (DHT), which stimulate prostate cancer cells' androgen receptors (AR). One of the mainstays of treatment for prostate cancer is hormonal therapy, sometimes referred to as androgen deprivation therapy (ADT). It aims to reduce androgen production or block androgen receptors, thus depriving prostate cancer cells of the hormonal stimulation they need to grow and proliferate [1]. After lung cancer, prostate cancer is the second most common cause of cancer-related deaths among men.

Only 6% of men are identified with distant metastases, while 13% of men are diagnosed with regional disease that has spread to regional lymph nodes, and 76% of men are diagnosed with localized disease that only affects the prostate. In addition to being incurable, metastatic prostate cancer is linked to substantial morbidity and a low quality of life. The majority of tumors are adenocarcinomas, which are caused by genetic changes in the prostate gland's epithelial cells. These tumors can appear in the organ in a variety of different locations [2]. Active surveillance, radiation therapy, and surgery are the standard of care for localized prostate cancer. Medical castration using front-line ADT agents is an option for patients with metastatic disease. Castrate levels of circulating testosterone, decreased tumor burden, increased survival, and symptom relief are all achieved by patients undergoing ADT. The majority of patients eventually progress on ADT, even though their serum testosterone levels reach castrate levels (<50 ng/dL). This progression is indicated by increasing serum PSA levels, the occurrence of new metastases (usually to bone and lymph nodes), or clinical progression (i.e., worsening symptoms). A well-known biomarker for prostate cancer is PSA, a protein encoded by the androgen-regulated KLK3 gene. Another piece of evidence of the often androgen-dependent character of castration-resistant prostate cancer (CRPC) is PSA levels, which indicate therapy failure [3]. Nonsteroidal anti-androgens inhibit androgen-induced receptor activation by binding to the AR with low affinity. Clinical care has improved as a result of the ongoing process of developing medicines that prevent AR activation in prostate cancer. Cyproterone acetate, a progestin, was the mainstay of medical treatment for prostate cancer decades ago. When antiandrogens are used to treat cancerous tissue, they may cause point mutations that change the drug's agonist/antagonist characteristics. However, routine testing to detect mutations is not part of clinical practice, and individualized treatment is not possible due to the agonistic effect of antiandrogens. Because prostate cancer is so varied, tissue from the same patient may contain a variety of ARs [4]. Huggins and Hodges approximately 80 years ago proposed hormonal therapy for the first time to treat prostate cancer [5]. During that period, surgical castration and/or estrogen therapy were the two main forms of hormonal therapy. ADT has been the cornerstone of systemic treatment for advanced prostate cancer [6]. The current standard of care for advanced prostate cancer includes gonadotropin-releasing hormone agonists (GnRH) such as leuprolide; first-generation nonsteroidal AR antagonists such as bicalutamide, flutamide, and nilutamide; second-generation nonsteroidal AR antagonists such as enzalutamide, apalutamide, and darolutamide; and the androgen biosynthesis inhibitor abiraterone [3]. In the management of prostate cancer, hormonal therapy is used in a variety of contexts, such as locally advanced disease that cannot be cured by radiation or surgery, metastatic disease as the first line of treatment, and recurrent disease following primary treatment (such as radiation or surgery). Several adverse reactions are associated with hormonal therapy, such as hot flashes, fatigue, osteoporosis, attenuation of libido, erectile dysfunction, and metabolic disturbances, including weight gain and insulin resistance. Hormonal therapy used for an extended period of time may raise the risk of cardiovascular disease and some metabolic diseases. Hormonal therapy patients need to be closely watched for adverse effects, and supportive measures may help control symptoms and improve quality of life [7]. The current study was designed to evaluate the clinical and biochemical significance of the use of different hormonal therapies in the management of prostate cancer.

METHODS

Study design and setting

This population-based retrospective study included patients recruited from Hiwa Cancer Hospital. This study complies with the Declaration of Helsinki. The protocol of the study has been approved by the Ethical Committee of the College of Pharmacy at 22/1/2025 with registration No. (PH 148-25). The full population database's medical records from April 2013 to June 2021 were used in the study.

Patient selection

The included patients were maintained on therapy with bicalutamide, enzalutamide, or abiraterone after being diagnosed with advanced prostate cancer.

Data collection and outcome measurements

The following information has been extracted from the database: age, blood pressure (BP), PS, residence, prior treatments (none, radical prostatectomy, radiotherapy, chemotherapy, and hormonal therapy), and metastatic site (bone, viscera, and lymphadenopathy). Pre-examination was required every three months to authorize administering bicalutamide, enzalutamide, or abiraterone. When the pre-examination was applied, a few documents needed to be attached. Each patient underwent PSA, ALP, complete blood count (CBC), erythrocytes sedimentation rate (ESR), serum creatinine (S. Cr), blood urea, TSB, total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), echocardiography, and imaging (either MRI, CT scan, PET scan, or bone scan). The patients were allocated into three groups, each group contained 30 patients, and the reported clinical and biochemical data at baseline, after six months and 12 months of hormonal therapy were obtained, as follows: Group 1; treated with a bicalutamide tablet 50 mg once daily. Group 2; treated

with an enzalutamide tablet 160 mg once daily. Group 3; treated with an abiraterone tablet 1000 mg once daily.

Statistical analysis

GraphPad Prism 8 was used for the statistical analysis. Data are presented as frequency, percentage, and mean ± standard deviation (S.D.). For the comparison between the groups, one-way ANOVA was used, followed by Tukey's test to compare each group with the positive control group. The level of significance was considered at $p < 0.05$.

RESULTS

Table 1 shows the characteristics of the study sample, including age, medication history, residency, line of treatment, and metastasis. The current study showed that among patients with prostate cancer, the range of age distribution among study groups was 50-95 years.

Table 1: Characteristics of the patient groups studied (n=30 in each group)

Variables		Drug Treatment		
		Bicalutamide	Enzalutamide	Abiraterone
Age group	< 70 years	13(43.3)	12(40)	14(46.7
	≥ 70 years	17(56.7)	18(60)	16(53.3)
History	No HT and DM	11(36.7)	13(43.3)	8(26.7)
	HT	8(26.7)	9(30)	9(30)
	HT and DM	2(6.7)	2(6.7)	7(23.3)
	HT and Heart disease	2(6.7)	0(0.0)	2(6.7)
	HT and Hyperlipidemia	2(6.7)	1(3.3)	0(0.0)
	Hyperlipidemia	2(6.7)	0(0.0)	3(10)
	Heart disease	3(10)	3(10)	0(0.0)
	DM	0(0.0)	2(6.7)	0(0.0)
	HT, DM, and Hyperlipidemia	0(0.0)	0(0.0)	1(3.3)
Imaging	MRI	12(40)	20(66.7	24(80)
	CT scan	14(46.7)	6(20)	6(20)
	Bone Scan	4(13.3)	4(13.3)	0(0.0)
Residency	Urban	22(73.3)	13(43.3)	11(36.7)
	Rural	8(26.7)	17(56.7)	19(63.3)

Values were expressed as frequency and percentage.

The majority of prostate cancer among age groups was equal and greater than 70 years. Regarding the residency, urban clusters (51%) were slightly higher than rural areas among the three groups. In terms of comorbid conditions, the majority of patients had HT (28.9%), while patients with no HT and DM were 35.5% among the three groups (Table 1). As a diagnostic work-up for illness staging, all patients in this study underwent either an MRI, CT scan, or bone scan; among the three groups, the majority of patients (62.2%) used an MRI. (Table 1). In the current study, the use of bicalutamide for 6 and 12 months revealed a significant decrease in PSA (p-value < 0.0001). Meanwhile, no significant changes were observed in PS after 12 months of treatment with bicalutamide, (p-value > 0.05). Prostate size was significantly attenuated throughout the treatment period (p-value < 0.0001). Additionally, the study showed only a significant decrease in TSB (p-value = 0.033), with no substantial changes in the other parameters, including the biochemical tests, EF, metastasis %, and BP (p-value > 0.05) (Table 2).

Table 2: Multivariable analysis in Bicalutamide group, at the baseline, after six and 12 months

Variable	Baseline	6 Months	12 Months	*p*-value
PSA (ng/ml)	102.0±164.4[a]	4.715±16.38[b]	2.039±5.48[b]	<0.0001*
PS	1.0±0.0[a]	1.0±0.0[a]	1.067± 0.25[a]	0.132[#]
Prostate Size (n=29)	58.76±24.86[a]	33.21±10.16[b]	28.45±7.28[b]	<0.0001*
ALP (IU/L)	71.45±20.38[a]	73.53±26.25[a]	78.77±26.66[a]	0.497*
Hb (g/dl)	13.71±1.40[a]	13.58±1.42[a]	13.30±1.56[a]	0.538*
ESR (mm/hr)	17.5±6.8[a]	17.7±8.2[a]	17.4±9.2[a]	0.987*
S. Creatinine (mg/dl)	0.97±0.22[a]	0.91±0.23[a]	0.92±0.19[a]	0.521*
Blood. Urea (mg/dl)	33.72±13.9[a]	31.85±7.7[a]	31.22±7.6[a]	0.615*
TSB (mg/dl)	0.64±0.26[a]	0.52±0.19[a]	0.50±0.2[b,a]	0.033*
T. Chol. (mg/dl)	203.1±54.8[a]	211.4±47.9[a]	210.4±42.5[a]	0.773*
TG (mg/dl)	182.8±90.8[a]	215.3±146.3[a]	224.3±155.2[a]	0.452*
LDL-c (mg/dl)	116.2±27.44[a]	117.7±26.93[a]	125.7±29.72[a]	0.337*
EF (%)	60.13±4.92	61.00±3.95	60.97±4.11	0.787[#]
Metastasis n(%)	14(46.7)	14(46.7)	16(53.3)	0.356†
SBP (mmHg)	140.4±13.5[a]	145.7±24.1[a]	148.0±22.5[a]	0.349*
DPB (mmHg)	81.40±9.3[a]	87.97±17.3[a]	83.47±11.3[a]	0.143*

Values were expressed as mean±SD. * One-way ANOVA; [#] Kruskal-Wallis test. † Chi square test. Values with non-identical superscripts (a,b) are significantly different (p<0.05; *post hoc* analysis).

Regarding the effect of enzalutamide, the study showed significant effects on PSA, PS, and prostate size after 12 months of treatment (p-value < 0.0001). ALP level also decreased significantly (p-value = 0.022) with no significant changes noticed in other biochemical tests, EF, metastasis %, and BP (p-value > 0.05) (Table 3). In

the present study, the use of abiraterone revealed significant effects on PSA, PS, and prostate size after 12 months of treatment (p-value < 0.0001) along with a significant reduction in TSB.

Table 3: Multivariable analysis in Enzalutamide group, at the baseline, after six and 12 months

Variable	Baseline	6 Months	12 Months	p-value
PSA (ng/ml)	492.9± 768.9[a]	10.53± 21.46[b]	2.143± 3.55[b]	<0.0001*
PS	1.133±0.35[a]	1.133±0.34[a]	1.733±0.69[b]	<0.0001[#]
Prostate Size	43.93±15.84[a]	31.57±8.9[b]	26.53±10.45[b]	<0.0001*
ALP (IU/L)	195.2±188.9[a]	117.2±92.3[a]	109.9±80.43[b,a]	0.022*
Hb (g/dl)	15.08±13.33[a]	13.00±1.76[a]	12.85±1.21[a]	0.467*
ESR (mm/hr)	32.87±24.86[a]	30.6±17.7[a]	29.37±16.71[a]	0.792*
S. Creatinine (mg/dl)	1.24±0.99[a]	0.95±0.49[a]	0.97±0.47[a]	0.191*
Blood. Urea (mg/dl)	42.46±19.36[a]	38.75±16.9[a]	40.62±15.43[a]	0.709*
TSB (mg/dl)	0.663±0.402[a]	0.569±0.257[a]	0.543±0.255[a]	0.301*
T. Chol. (mg/dl)	169.2±45.98[a]	183.9±41.38[a]	235.9±197.9[a]	0.082*
TG (mg/dl)	143.1±72.83[a]	173.4±86.76[a]	184.4±89.69[a]	0.146*
LDL-c (mg/dl)	112.1±30.35[a]	117.9±29.40[a]	123.8±30.98[a]	0.329*
EF (%)	62.60±3.67[a]	61.93±4.59[a]	61.33±5.07[a]	0.287[#]
Metastasis n(%)	30(100)	30(100)	30(100)	N/A†
SBP (mmHg)	149.6±23.40[a]	149.3±18.24[a]	150.5±23.55[a]	0.974*
DPB (mmHg)	80.27±13.75[a]	83.00±8.47[a]	80.63±11.82[a]	0.612*

Values were expressed as mean±SD. * One-way ANOVA; [#] Kruskal-Wallis test. † Chi square test. Values with non-identical superscripts (a,b) are significantly different (p<0.05; *post hoc* analysis).

Furthermore, no significant changes were observed in BP after 12 months of treatment (Table 4). Concerning metastatic sites, either bone metastases or visceral metastases among different groups. In the bicalutamide and abiraterone groups, metastasis increased from 46.7% to 50% and from 76.7% to 83.3%, respectively, after 12 months. Bicalutamide was used as a 1st-line treatment, while in the Enzalutamide group, 20%, 73.3%, and 6.7% were used as 1^{st-}, 2$^{nd-,}$ and 3rd-line treatments, respectively.

Table 4: Multivariable analysis in Abiraterone group, at the baseline, after six and 12 months

Variable	Baseline	6 Months	12 Months	p-value
PSA (ng/ml)	354.0±404.4[a]	9.923±14.99[b]	11.04±20.7[b]	<0.0001*
PS	1.0±0.0[a]	1.0±0.0[a]	1.33±0.48[b]	<0.0001[#]
Prostate Size	42.13±15.34[a]	30.93±5.15[b]	26.40±2.44[b]	<0.0001*
ALP (IU/L)	153.5±197.1[a]	119.7±126.9[a]	112.4±95.14[a]	0.512*
Hb (g/dl)	13.51±1.13[a]	13.54±1.08[a]	13.32±1.01[a]	0.689*
ESR (mm/hr)	30.17±11.14[a]	34.63±10.69[a]	38.90±15.1[b,a]	0.029*
S. Creatinine (mg/dl)	0.98±0.31[a]	0.86±0.19[a]	0.83±0.18[b,a]	0.031*
Blood. Urea (mg/dl)	35.95±11.46[a]	37.74±8.7[a]	36.16±11.32[a]	0.775*
TSB (mg/dl)	0.52±0.2[a]	0.71±0.23[b]	0.66±0.23[a,b]	0.005*
T. Chol. (mg/dl)	179.2±51.25[a]	200.8±65.58[b]	217.9±68.62[b,a]	0.06*
TG (mg/dl)	174.3±102.1[a]	189.0±115.0[a]	236.4±150.9[a]	0.136*
LDL-c (mg/dl)	118.6±45.89	125.8±52.59	132.5±57.1	0.588*
EF (%)	62.1±4.38[a]	62.4±3.66[a]	63.0±3.1[a]	0.768[#]
Metastasis n(%)	23(76.7)	23(76.7)	25(83.3)	0.356†
SBP (mmHg)	140.2±13.1[a]	154.9±21.21[b]	147.8±15.83[a,b]	0.005*
DPB (mmHg)	82.7±9.75[a]	87.83±7.3[b]	85.1±7.23[a,b]	0.057*

Values were expressed as mean±SD. * One-way ANOVA; [#] Kruskal-Wallis test. † Chi-square test. Values with non-identical superscripts (a,b) are significantly different (p<0.05; *post hoc* analysis).

In the Abiraterone group, 66.7% and 33.3% were used as 1^{st-} and 2nd-line treatments, respectively (Tables 2, 3, and 4). A dramatic reduction in PSA levels was observed in the bicalutamide, enzalutamide, and abiraterone-treated groups after 12 months of treatment (p-value < 0.0001).After 12 months of treatment, no discernible differences among the groups were observed (Figure 1). Regarding prostate size, there was a highly significant attenuation in the bicalutamide, enzalutamide, and abiraterone groups after 12 months (p-value < 0.0001). However, there were no discernible variations among the treatment groups (p-value > 0.05) (Figure 2). After 12 months of intervention, significant reductions in back pain incidence were noticed in the bicalutamide (6% *vs.* 2%), enzalutamide (25% *vs.* 10%), and abiraterone (16% *vs.* 11%) treated groups when compared to the baseline value (p-value < 0.0001) (Figure 3).

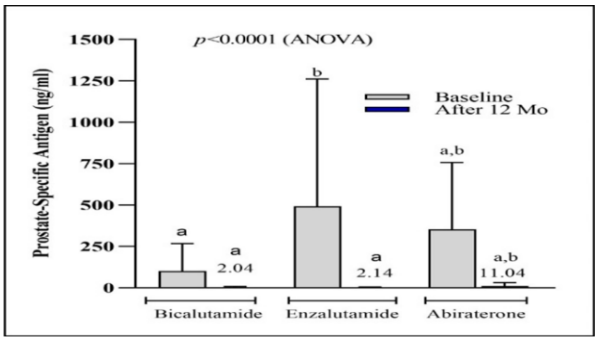

Figure 1: Effect of Bicalutamide, Enzalutamide and Abiraterone on PSA after 12 months of treatment. Values with non-identical superscripts (a,b) are significantly different (p<0.05; *post hoc* analysis).

The incidence of urinary problems declined to 0% of all the treatment groups after 12 months when compared to baseline values (Figure 4).

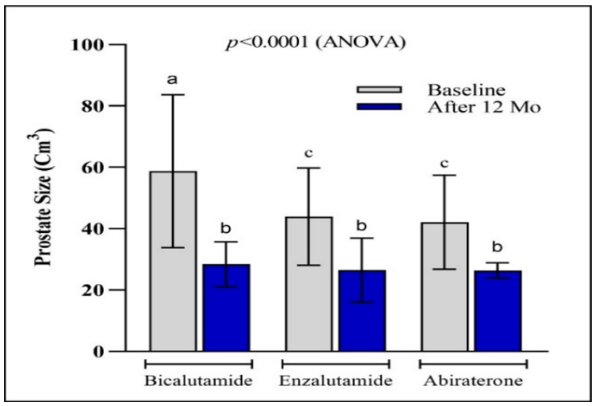

Figure 2: Effect of Bicalutamide, Enzalutamide and Abiraterone on prostate size after 12 months. Values with non-identical superscripts (a,b,c) are significantly different ($p<0.05$; *post hoc* analysis).

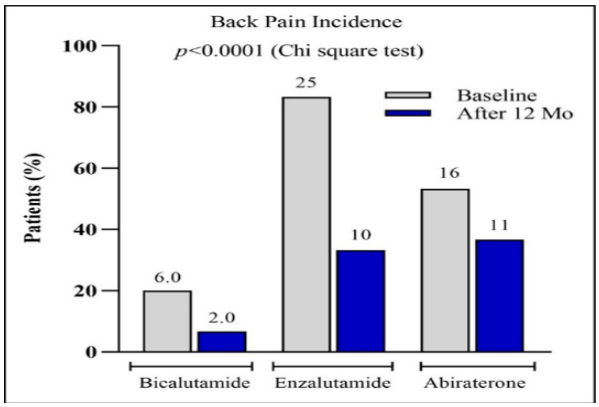

Figure 3: Effect of Bicalutamide, Enzalutamide and Abiraterone on the incidence of back pain after 12 months. Values are expressed as percentages.

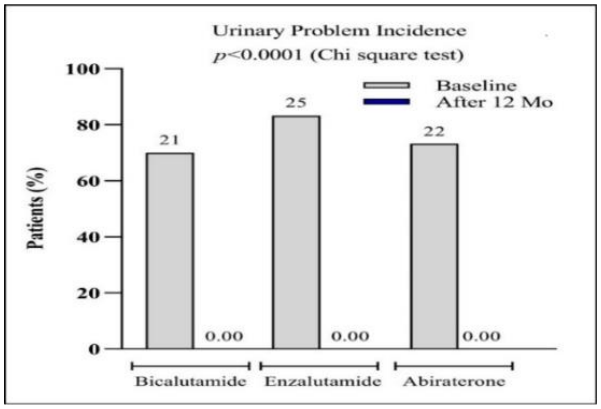

Figure 4: Effect of Bicalutamide, Enzalutamide and Abiraterone on the incidence of urinary problems after 12 months. Values are expressed as percentages.

DISCUSSION

In the Western world, the most prevalent non-cutaneous tumor in men is prostate cancer. Anti-androgens like bicalutamide, enzalutamide, and abiraterone are used as a treatment for non-organ-confined prostate cancer. The expression of the AR occurs during the growth and dissemination of tumors [4]. In the present study elders (> 70 years) were shown to be more prone to prostate cancer; likewise, a study done by Rawla (2019) in the USA found that age has a significant impact on prostate cancer incidence and mortality rates, with older men (over 65) having the highest incidence. This could be attributed to alterations in the DNA of the prostate cells leading to a rapid proliferation of the cells [8]. The residency of the study sample consisted of almost similar percentages of both urban and rural. A study conducted by Stolzenbach *et al.* (2021) found that people in rural areas are more prone to prostate cancer than urban clusters [9]. Concerning metastatic sites, it involved either bone metastases or visceral metastases among different groups. In the present study patients in the Enzalutamide group had free radiological progression and improved clinical symptoms. Meanwhile, in the bicalutamide and abiraterone groups, after 12 months of treatment, two patients had radiologically progressed to metastasis. A study done by Tsujino *et al.* (2023) in Tokyo showed that non-metastatic CRPC patients treated with abiraterone plus prednisone were more likely to result in death than those treated with enzalutamide. In addition, enzalutamide was superior to abiraterone in non-metastatic CRPC [10]. In this study, all patients did either an MRI, CT scan, or bone scan, whereas the majority of patients did MRI as imaging because the best imaging technique for prostate cancer is MRI, which produces a clear image of the prostate gland and surrounding organs. While whole-body MRI (WB-MRI) has a high specificity, modern PET/CT has a high overall sensitivity [11]. Compared to CT or scintigraphy, MRI is more accurate in detecting and quantifying bone disease. MRI and PET-CT provide objective proof of therapeutic benefits by enabling the quantification of disease and the classification of patients into "complete response," "partial response," "stable disease," or "progressive disease." Future imaging of metastatic bone disease may benefit greatly from the use of hybrid PET/MRI scanners [12]. An outstanding reduction of PSA levels was observed in the three treatment groups after 12 months compared to baseline; this finding is comparable to the study in the US, which showed that PSA levels significantly reduced in bicalutamide- and enzalutamide-treated groups after seven months [6]. Another study done by Li *et al.* (2022) in Taiwan showed the PSA level in the Enzalutamide group was significantly greater than in the Abiraterone group [13]. The majority of patients with prostate cancer ultimately progress on ADT, with the progression of the disease including rising serum PSA levels, new metastases, and/or worsening clinical symptoms [3]. The goal of hormone therapy for prostate cancer is to prevent the production of testosterone or its entry into prostate cancer cells. Testosterone is essential for the growth of most prostate cancer cells. Prostate cancer cells either

die or grow more slowly as a result of hormone therapy. Thus, it inhibits the growth of both healthy and cancerous prostatic tissue by blocking the effects of androgens derived from the adrenal glands and the testes [14]. A patient's level of functioning in terms of daily activities, physical ability (walking, working, etc.), and self-care is described by their personal status score [15]. A highly significant elevation of PS score was seen in this retrospective study; the PS score of the bicalutamide group did not significantly differ from the baseline, while the groups treated with enzalutamide and abiraterone had significant changes after 12 months. This is comparable to the study done by Vaishampayan *et al*. (2021) in the US, which showed a significant change in the PS score in the enzalutamide group but no significant change in the bicalutamide group [6]. Studies revealed an inverse relationship between prostate size and the incidence and aggressiveness of prostate cancer [16]. Prostate size greatly reduced in all treatment groups compared to baseline, which is comparable to a study done by Zhaoyang *et al*. (2020) in China, which showed that prostate volume significantly reduced in bicalutamide-treated patients (three months after treatment compared with the pretreatment value) [17]. Moreover, a study conducted by Azad *et al*., (2022), in Australia showed that prostate size was significantly reduced in the enzalutamide-treated group [18]. ALP is a prognostic biomarker in mCRPC that forecasts disease outcomes independent of treatment. Moreover, higher ALP levels have also been connected to the severity of metastatic bone disease. ALP levels may fluctuate in response to changes in osteoblastic activity and bone turnover [19]. The Enzalutamide group in this retrospective analysis had a significantly lower ALP level than the baseline; however, the Bicalutamide and Abiraterone groups did not show a significant reduction in ALP level. This result is in tune with a study done by Sakamoto *et al*. (2019) in Japan regarding Enzalutamide, which showed that ALP level significantly reduced in Enzalutamide and Abiraterone treated for 12 months [20]. This may be because enzalutamide has an affinity for blocking AR that is more than 30 times greater than that of bicalutamide. However, abiraterone functions by inhibiting Cyp17; therefore, its mechanism differs from that of enzalutamide and bicalutamide [11]. Furthermore, no significant change in Hb level was observed in all the treated groups after 12 months compared to baseline. A study done by Machidori *et al*. (2021) in Japan showed the prognostic significance of CBC data in CRPC patients treated using androgen receptor pathway inhibitors (ARPIs), including enzalutamide and abiraterone [21]. CBC tests are routinely performed on cancer patients both before and during treatment. CBC biomarkers have been linked to prognosis and therapeutic response in CRPC according to several studies [22]. Regarding the inflammatory marker ESR, abiraterone significantly and exclusively ameliorated its level compared to baseline. In line with this study, a study conducted by Uchimoto *et al*. (2020) in Japan showed attenuation of the inflammatory marker C-reactive protein (CRP) by both enzalutamide and abiraterone after 12 months of treatment [23]. In contrast to the current finding, a study done by Hoogland *et al*. (2021) in Florida showed no significant changes in some inflammatory markers like CRP and TNF-α, while a significant increase in the level of IL-6 was observed, which could be attributed to the inhibitory effect on testosterone [24]. Additionally, after 12 months, the Abiraterone group's blood creatinine level was significantly lower than baseline, whereas the Bicalutamide and Enzalutamide groups' serum creatinine and urea levels were not significantly changed compared to the baseline; this finding was in line with a previous study [25]. In the current study, the bicalutamide group experienced a significant decrease in TSB, while the enzalutamide group did not experience any significant change. However, following six months of treatment, the T.S.B. level significantly increased. However, it returned to normal after 12 months in the abiraterone group compared to baseline. A study done by Mishra *et al*. (2024) in Texas showed that abiraterone caused elevation in serum transaminases and bilirubin levels [26]. Additionally, abiraterone inhibits cytochrome P450c17 (CYP17A1), thus inhibiting testosterone and cortisol synthesis [27]. Moreover, no remarkable effects were seen on the lipid profile except for abiraterone, which increased after 6 months of treatment and then returned to normal after 12 months when compared to the baseline value. This is comparable to a previous study done by Li *et al.* (2022) in Taiwan [13]. Prostate cancer leads to an increase in the number of LDL receptors at the cell surface, thereby elevating the uptake of LDL-derived cholesterol, altogether raising cellular cholesterol levels [28]. In the present study, a non-significant reduction of EF was noticed in the three groups after 12 months compared to baseline. A study done by Abdulfattah *et al*. (2024) in New York showed that congestive heart failure (CHF) is an extremely uncommon side effect of bicalutamide in patients with prostate cancer [29]. There is little clinical data linking the use of bicalutamide to cardiovascular problems, especially CHF. Cancer therapy-related cardiac dysfunction (CTRCD) is the term used to describe a decrease in left ventricular ejection fraction (LVEF) of more than 10% to less than 53% after the initiation of a cancer treatment agent. CTRCD is classified either as permanent and irreversible (type I) or reversible (type II). The mechanisms through which bicalutamide causes cardiac toxicity are not well understood. Bicalutamide may harm the cardiovascular system by causing hormonal imbalance, especially low testosterone levels, and the resulting metabolic effects [29]. A study done by Bretagne *et al*. (2020) in Paris showed that when compared to enzalutamide, abiraterone is linked to a

higher percentage of heart failure (HF) and atrial tachyarrhythmia (AT). Abiraterone may be riskier for AT and HF than other ADTs because it tends to cause hypermineralocorticism in addition to androgen deprivation [30]. Additionally, a significant elevation in blood pressure was seen in the abiraterone group after 6 months; however, it returned to normal level after 12 months compared to baseline, with no significant changes noticed in each of the bicalutamide and enzalutamide groups. A study was done by Betsikos *et al*. (2024) in Greece, which showed Abiraterone induced a secondary form of hypertension in a fashion resembling mineralocorticoid excess. This could be contributed by excess aldosterone and sodium retention offered by abiraterone [31]. A study done by Serrano Domingo *et al*. (2021) in Spain showed that patients' blood pressure increased as a result of taking either abiraterone or enzalutamide [32]. Another finding of the current study was the remarkable reduction of back pain incidence in the three groups compared to baseline, which was comparable to the findings of other studies [33-35]. Hormones are essential for maintaining bone homeostasis. Activated AR interacts with osteoblast precursors to promote bone formation by downregulating interleukin 6 (IL-6), which promotes osteoclastogenesis, and upregulating fibroblast growth factor (FGF), insulin-like growth factors-1 (IGF-1), and transforming growth factor (TGF)-β [35]. A great improvement in urinary symptoms was seen in the three groups compared to baseline. Studies showed the effectiveness of ADT in attenuating lower urinary tract symptoms secondary to reducing prostate size. Additionally, ADT enabled patients with acute urinary retention to regain the ability to void. Another contributing factor to the improved lower urinary tract symptoms was the changes in circulating testosterone [12,36].

Conclusions

The level of PSA, prostate size, back pain, and urinary problems declined after 12 months of therapy with bicalutamide, enzalutamide, and abiraterone; they were strongly associated with better clinical and patient-reported outcomes. Furthermore, they had no significant effects on lipid profile, Hb, EF, and metastasis. Bicalutamide was superior to Enzalutamide and Abiraterone in health-related quality-of-life outcomes, and PS. Enzalutamide was superior to bicalutamide and abiraterone in attenuating ALP, a prognostic biomarker in mCRPC, reflecting disease outcomes independent of therapy.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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