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Short Communication

Effects of doxazosin as adjuvant to abiraterone on viability and apoptosis of metastatic castration-resistant prostate cells cancer (mCRPC) PC3

Putu KD. Pratama[1,2], Zakaria A. Rahman[1,2], Furqan Hidayatullah[1,2], Tetuka B. Laksita[1,2] and Lukman Hakim[1,3,4*]

[1]Department of Urology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [2]Department of Urology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; [3]Department of Urology, Rumah Sakit Universitas Airlangga, Surabaya, Indonesia; [4]Faculty of Medicine and Health, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia

*Corresponding author: lukman-h@fk.unair.ac.id

Abstract

Prostate cancer is a leading cause of death among men worldwide, with limited therapeutic options for castration-resistant metastatic prostate cancer (mCRPC). The aim of this study was to investigate the potential role of doxazosin, an α1-blocker, as an adjunctive therapy for mCRPC in combination with abiraterone. Using mCRPC PC3 cells, the effects of doxazosin on cell viability and apoptosis were assessed. The experimental design was an in vitro study with post-test-only control design. Experimental groups were divided into four groups: control group, doxazosin group, abiraterone group, and combination group (doxazosin and abiraterone). Cell viability was analyzed using the cell counting kit-8 (CCK-8) assay, while apoptosis was analyzed using Fluorescence-activated cell sorting (FACS). This study found that the IC_{50} value for doxazosin was 25.42±1.42 µM (mean ± standard error). The results indicated that doxazosin significantly reduced cell viability, with effects varying based on the dose administered, and doxazosin was able to induce apoptosis in mCRPC PC3 cells. The combined treatment of doxazosin and abiraterone in mCRPC PC3 cells demonstrated a significantly higher mean apoptosis percentage compared to the control group (16.27%; 95% confidence interval (CI): 11.89–20.65; p=0.001). Furthermore, the combined treatment showed a significantly higher mean apoptosis percentage compared to abiraterone alone (4.79%; 95%CI: 0.41–9.18; p=0.029), and doxazosin alone (10.99%; 95%CI: 6.61–15.38; p=0.001). These findings suggest that doxazosin, traditionally used as an α1-blocker for lower urinary tract symptoms (LUTS), could offer a novel therapeutic approach for mCRPC patients.

Keywords: mCRPC, doxazosin, abiraterone, apoptosis, prostate cancer therapy

Introduction

Prostate cancer ranks as the primary cause of disease and death in men globally and is ranked as the fifth most common cancer, with 1.6 million new cases identified each year and 366,000 deaths attributed to this cancer in 2018 [1]. Prostate cancer ranked as the second highest cause of death in 2023 in cancer-related diseases in men in the United States [2] and the most commonly diagnosed cancer in 2020, according to GLOBOCAN data in 112 countries [3]. Prostate cancer affects men across various ethnicities and races, with higher mortality rates in lower socioeconomic groups [4]. Treatment of prostate cancer becomes more complex when the disease has metastasized and becomes resistant to castration therapy, the situation described as metastatic castration-resistant prostate cancer (mCRPC) [5].

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Recent clinical trials showed that new therapies improve survival rates in mCRPC patients. Novel hormonal therapy using abiraterone has demonstrated significant benefits in patients with mCRPC [6]. In men with locally advanced or metastatic prostate cancer, combining androgen deprivation therapy (ADT) with abiraterone and prednisolone resulted in significantly higher overall survival and longer periods without disease progression compared to ADT alone [7]. A previous study has shown that patients treated with abiraterone, following prior treatment with docetaxel chemotherapy, demonstrated an improvement in overall survival [8].However, abiraterone's high cost and side effects remain challenges [9].

Issues in prostate cancer are not limited to its malignancy; symptoms related to the disease, including lower urinary tract symptoms (LUTS), are common in prostate cancer patients, with 39% experiencing moderate symptoms and 11% experiencing severe symptoms [10]. A study on benign prostatic hyperplasia (BPH) patients treated with alpha-blockers, such as doxazosin, has shown the presence of apoptosis in histopathological analyses [11]. In addition to its use in managing LUTS [12]. The ability of doxazosin to induce apoptosis in prostate cancer cells makes it a promising therapeutic option [13,14].

The combination of doxazosin and abiraterone remains relatively underexplored, yet it may offer additional therapeutic benefits in the treatment of prostate cancer. mCRPC PC3 cells, characterized as aggressive androgen-independent prostate cancer cells, are frequently used in research to study the progression of the disease [15]. These cells, originally derived from prostate cancer that metastasized to bone, contain a subpopulation of stem-like cells that play a key role in tumor growth [16,17]. The use of a combination treatment with abiraterone in this study was to observe the effect of apoptosis induced by doxazosin as a single drug and in combination with abiraterone, which is the standard ADT therapy for mCRPC. In vitro model was used in this preliminary investigation to gather initial data as a foundation before progressing to more complex investigations, including in vivo models.

The aim of this study was to evaluate the potential of doxazosin as an adjunct therapy in the management of prostate cancer. Beyond its role in alleviating LUTS symptoms and serving as an additional treatment for prostate cancer patients, this research also examines the efficacy of combining doxazosin with abiraterone to inhibit the growth of mCRPC PC3 cells.

Methods

Study design and setting

This study was an in vitro experimental study using a prostate cancer cell line, with mCRPC PC3 cells. The research was conducted at the Biomedical Laboratory, Faculty of Medicine, Brawijaya University, Malang. The experimental design employed a laboratory-based approach with a post-test-only control group design. The IC_{50} values for doxazosin and abiraterone were used to evaluate their effects on apoptosis and cell viability in mCRPC PC3 cells.

The study groups included one control group and three experimental groups, which were treated with doxazosin, abiraterone, or a combination of doxazosin and abiraterone for 72 hours. Each group was replicated six times, following the Federer formula for minimal sample size: $(n - 1)(t - 1) \geq 15$. After the 72-hour exposure period, the apoptosis rate of each group was measured using Fluorescence-activated cell sorting (FACS). The detailed research process is illustrated in **Figure 1**.

The culture of metastatic castration-resistant prostate cancer (mCRPC) PC3 cell

The prostate cancer cell cultures were purchased from the American Type Culture Collection (ATCC), USA, using mCRPC PC3 cell lines. The mCRPC PC3 cells were placed in liquid nitrogen and thawed using dry ice in a 37°C water bath for two minutes. Subsequently, the cells were placed in a centrifuge tube and centrifuged for five minutes at 125×g. The mCRPC PC3 cells were transferred to culture dishes containing complete growth medium and incubated for 15 minutes until the pH stabilized at 7.6. The culture dishes were incubated at 37°C and 5% CO_2 in an air atmosphere. Subculturing began when the cells reached 70% cell density. The complete medium consisted of F-12K medium supplemented with fetal bovine serum to a final concentration of 10%, along with additional supplements, including dimethyl sulfoxide, phosphate-buffered saline, and penicillin/streptomycin.

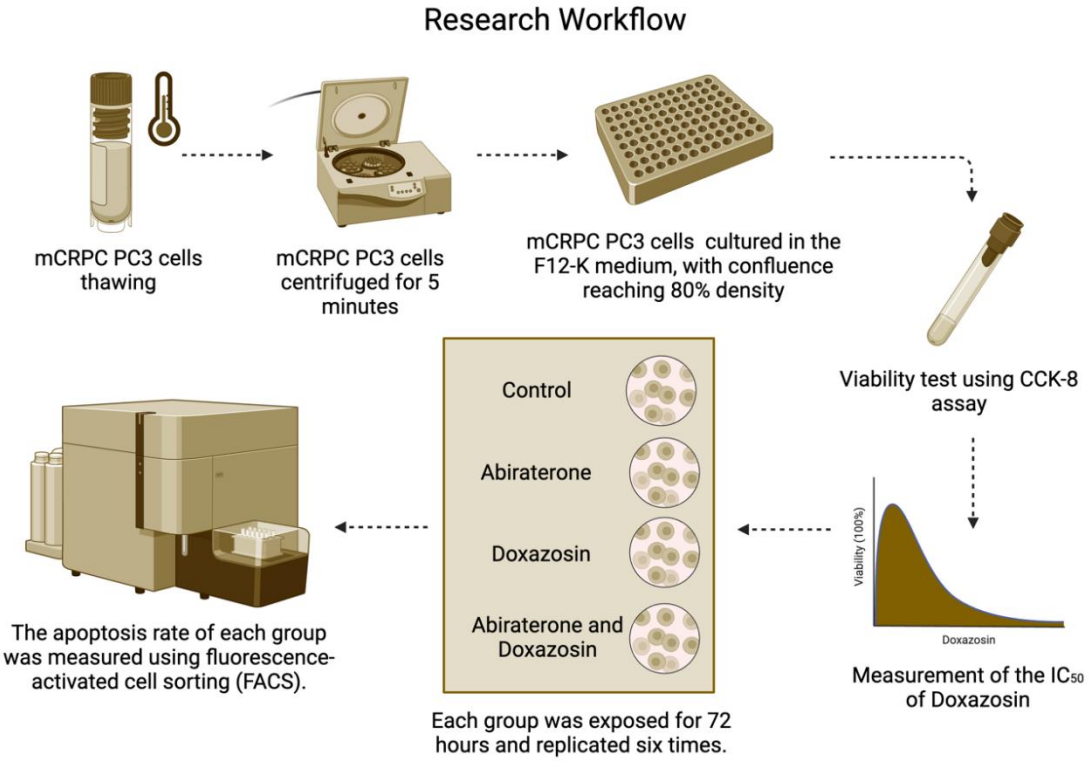

Figure 1. Research workflow, starting with the assessment of cell viability and calculation of IC_{50} values, followed by the determination of the average total apoptosis for each group.

Cell viability analysis and IC_{50} measurement

The cell viability assay was performed to evaluate the ability of doxazosin to reduce mCRPC PC3 cells proliferation and determine its IC_{50} value. Doxazosin and abiraterone were purchased from the Tokyo Chemical Industry (Tokyo, Japan). The IC_{50} value of abiraterone was 66.9 µM, obtained from a previous study with mCRPC PC3 cells from the same supplier [18]. The mCRPC PC3 cells were seeded at a density of 3,000–4,000 per well in 96-well plates and incubated at 37°C in a 5% CO_2 cell incubator for 24 hours. Doxazosin was administered to the cell plates in a complete medium for 72 hours at concentrations that varied between 0.1 to 100 µM, incubated at 37°C, 5% CO_2, and 100% humidity. The cells were subsequently incubated for two hours at 37°C and 5% CO_2 using the cell counting kit-8 (CCK-8) viability assay (50 µL of CCK-8 per mL of culture medium), the assay was done with sterility precautions. The cell relative absorbance was measured with a wavelength of 450 nm using an RT-2100C microplate reader (Rayto Life and Analytical Sciences Co., Ltd Shenzen, China). The cell viability analysis and IC_{50} measurement were replicated six times.

Cell apoptosis analysis

Apoptosis analysis was performed on four groups: one control group and three experimental groups (doxazosin, abiraterone, and the combination of doxazosin and abiraterone). The mCRPC PC3 cells underwent two washes with BioLegend Cell Dye Buffer (Elabsciences, Houston, TX, USA) before being resuspended in Annexin V binding buffer (Elabsciences, Houston, TX, USA) at a concentration of 1.0×10^6 cells/mL. A 100 µL sample of the cell suspension was transferred to a 5 mL test tube, followed by the addition of 5 µL of fluorescein isothiocyanate (FITC) Annexin V (Elabsciences, Houston, TX, USA) and 10 µL of propidium iodide (Elabsciences, Houston, TX, USA) solution. Incubation of the tubes was done in the dark at room temperature (25°C) for 15 minutes, followed by the addition of 400 µL of Annexin V binding buffer to each tube.

FACS analysis, using the 488 nm line of argon-ion laser and detection through the PE/Texas Red® channel with a 610/10 bandpass filter, was employed to quantify apoptotic cells. A total of 10,000 cells were analyzed per replicate. Subsequently, gating was applied to differentiate cells and exclude debris. Forward scatter (FSC) was used to represent cell size, while side scatter (SSC) represented cellular granularity. The cell apoptosis analysis was replicated six times.

In the analysis, the gating quadrant was classified into four criteria: first, Annexin V negative and propidium iodide negative cells represent the normal cell population. Second, Annexin V positive and propidium iodide negative cells represent the mCRPC PC3 cells in the early stage of apoptosis. Third, Annexin V positive and propidium iodide positive cells represent the mCRPC PC3 cells in the late apoptosis cells. Fourth, Annexin V negative and propidium iodide positive cells represent the mCRPC PC3 cells undergoing necrosis. The total mean in early and late apoptosis was counted in this study. The emitted fluorescence of cells was measured using Becton Dickinson (BD) FACSCalibur (BD Bioscience, Franklin Lakes, NJ, USA).

Statistical analysis

Optical density (OD) values for cell viability obtained from CCK-8 assays and the apoptosis percentages from gating analysis were subjected to statistical analysis. Cell viability analysis and IC_{50} were measured using GraphPad Prism software version 8. Normality tests using the Saphiro-Wilk test and homogeneity tests using Levene's test were performed. The one-way ANOVA statistical test was selected for normal distribution data, and Tukey's HSD post-hoc test was applied to assess significant differences between the groups. Statistical analysis using SPSS version 20 (IBM, New York, USA) was performed.

Results

Effect of doxazosin on cell viability and IC_{50} values in mCRPC PC3 cells

Treating mCRPC PC3 cells with escalating doses of doxazosin (1 µM, 2 µM, 4 µM, 8 µM, 15 µM, and 31 µM) produced absorbance values between 0.335 a.u. and 0.403 a.u. The IC_{50} for viability was determined by dividing the relative absorbance value of each treatment by the absorbance value of the control group. The viability analysis is plotted in **Figure 2**. The results showed that doxazosin reduced the viability of mCRPC PC3 cells depending on the dosage, with an R^2 value of 0.9853. The IC_{50} value of doxazosin for mCRPC PC3 cells was determined to be 25.42±1.42 µM (mean ± standard error).

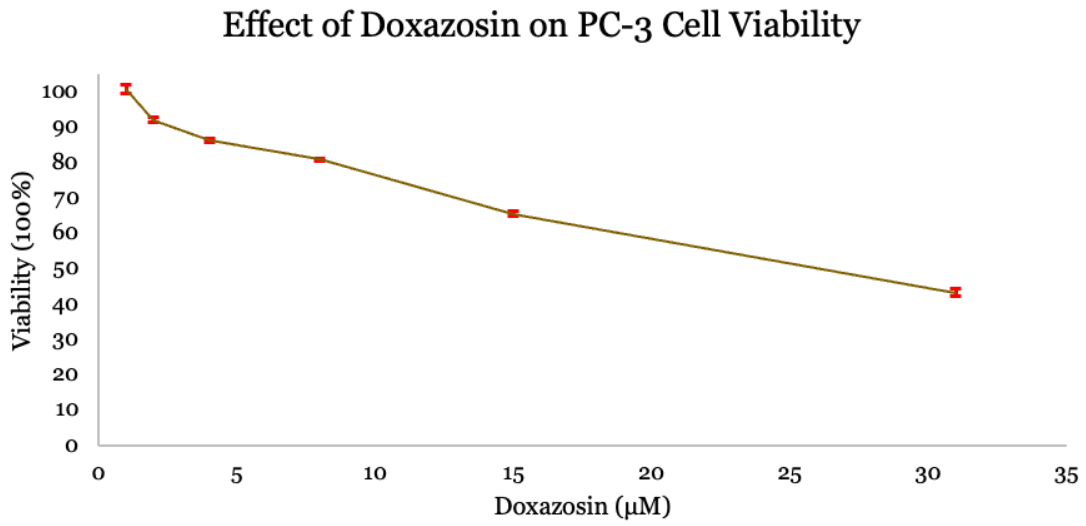

Figure 2. Relationship between doxazosin dose and corresponding cell viability for each dose. The estimated IC50 was calculated using a variable slope equation by the GraphPad Prism statistical application.

Effect of doxazosin on apoptosis in mCRPC PC3 cells

This study used FACS to assess the percentage of cells undergoing apoptosis after treatment. mCRPC PC3 cells were then classified into four quadrants based on the cell emission signals presented in **Figure 3**. Early apoptosis was identified in the lower right quadrant, and late apoptosis in the upper right quadrant.

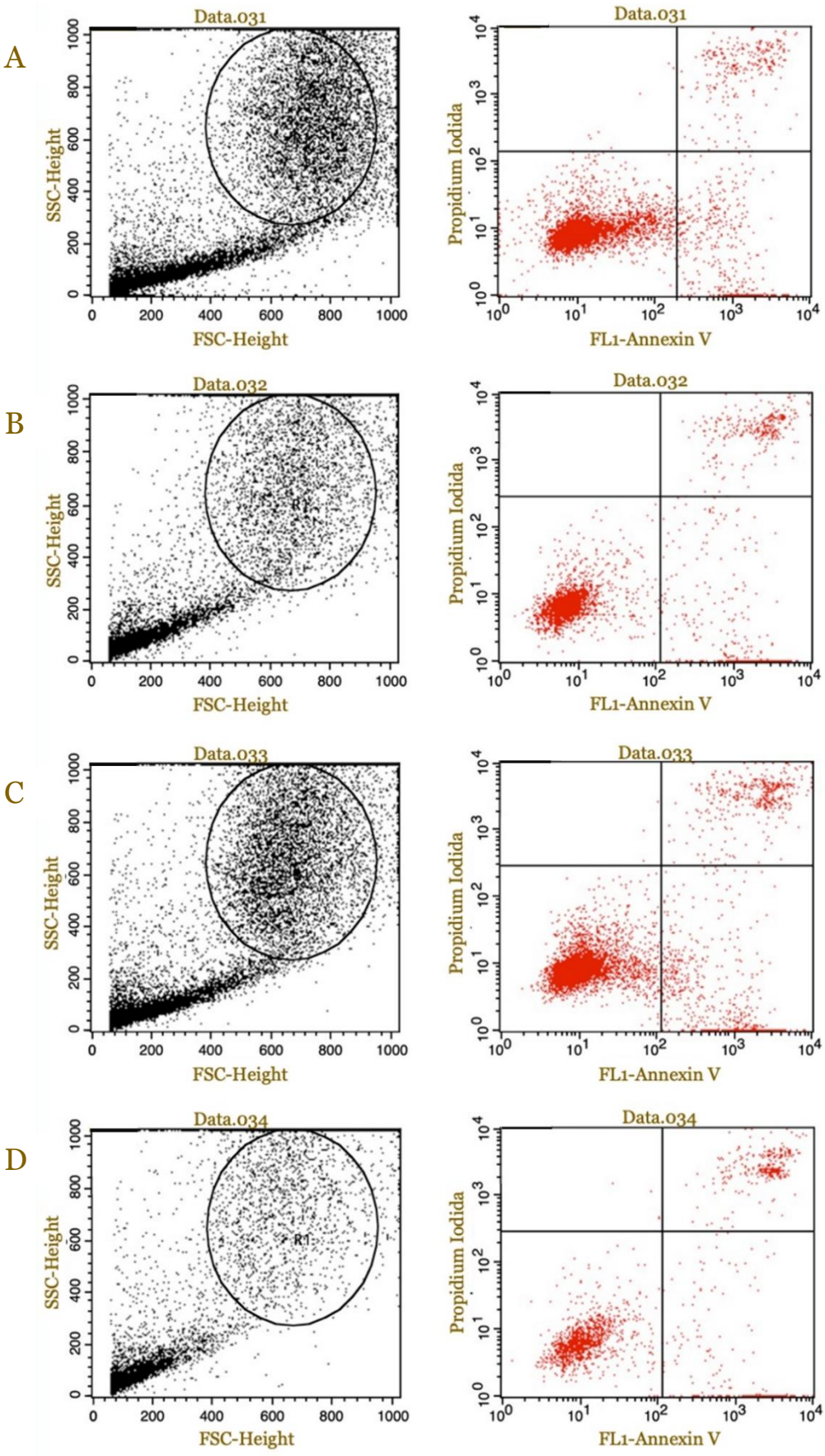

Figure 3. Fluorescence-activated cell sorting (FACS) analysis. Gating and quadrant distribution of metastatic castration-resistant prostate cancer (mCRPC) PC3 cells in the control group (A). Gating and quadrant distribution of mCRPC PC3 cells treated with abiraterone (B). Gating and quadrant distribution of mCRPC PC3 cells exposed to doxazosin (C). Gating and quadrant distribution of mCRPC PC3 cells treated with the combination of doxazosin and abiraterone (D).

Data in this study demonstrated a normal distribution, and one-way ANOVA analysis demonstrated a significant difference in total mean apoptosis between the groups (p=0.001). The bar chart shows the differences in total mean apoptosis between the groups presented in **Figure 4**. Post-hoc analysis using Tukey's HSD showed that all three groups, abiraterone, doxazosin, and the combination of doxazosin and abiraterone, exhibited higher total apoptosis compared to the control group. Interestingly, the combination of doxazosin and abiraterone resulted in greater total mean apoptosis than abiraterone as a single drug (p=0.029). Consequently, when the combination of doxazosin and abiraterone was compared to doxazosin alone, the combination showed higher total apoptosis (p=0.001). The post hoc analysis is presented in **Table 1**. These findings emphasize notable variations in apoptotic activity across the treatment groups, with the abiraterone and doxazosin combination consistently demonstrating the strongest effect.

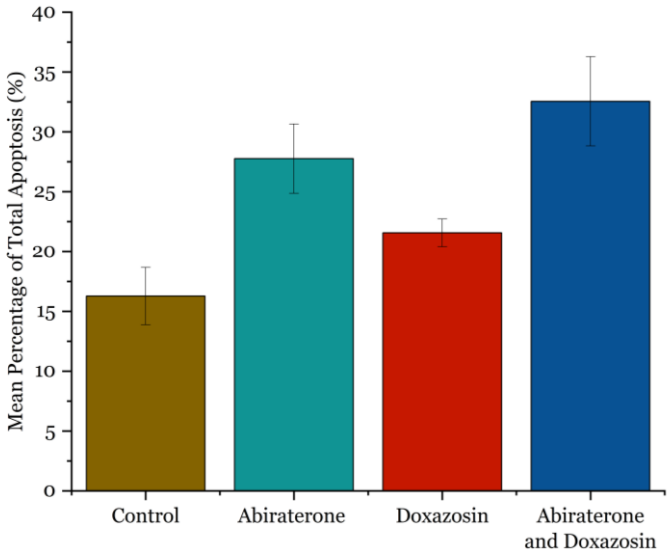

Figure 4. Comparison of the mean percentage of total apoptosis in metastatic castration-resistant prostate cancer (mCRPC) PC3 cells following treatment with doxazosin, abiraterone, or a combination of doxazosin and abiraterone.

Table 1. Results from Post hoc analysis using Tukey's HSD on metastatic castration-resistant prostate cancer (mCRPC) PC3 cells apoptosis

Groups	Mean difference	95% confidence interval		p-value
		Minimum	Maximum	
Abiraterone vs control	11.48	7.09	15.86	0.001*
Doxazosin vs control	5.28	0.89	9.66	0.015*
Abiraterone and doxazosin vs control	16.27	11.89	20.65	0.001*
Abiraterone vs doxazosin	6.2	1.81	10.58	0.004*
Abiraterone and doxazosin vs abiraterone	4.79	0.41	9.18	0.029*
Abiraterone and doxazosin vs doxazosin	10.99	6.61	15.38	0.001*

* Statistically significant at $p<0.05$

Discussion

The present study found that the IC_{50} of doxazosin for mCRPC PC3 cells was determined to be 25.42±1.42 µM (mean ± standard error), confirming its ability to reduce mCRPC PC3 cell viability. However, reported IC_{50} values for doxazosin vary. Research on doxazosin's IC_{50} in PC3 cells reported a value of 23.3 µM, while in LNCaP cells, a value of 17.2 µM was observed [19]. Previous studies on doxazosin using the MTT assay reported IC_{50} values of 38.60 µM in PC3 cells, 37.44 µM in DU-145 cells, and 28.11 µM in LNCaP cells [20].These variations are likely attributable to differences in cell characteristics, treatment durations, incubation times, and measurement techniques.

This study also evaluated apoptosis in mCRPC PC3 cells treated with doxazosin, abiraterone, and their combination using FACS. Doxazosin exhibited a significantly higher mean percentage of total apoptotic effect compared to the control group. Observations through FACS showed that doxazosin induced apoptotic activity, which was visible in the upper right quadrant of the plot as

late apoptosis and in the lower right quadrant as early apoptosis. These results were consistent with a previous study that also used Annexin V and PI staining, which showed a significant increase in apoptosis at a doxazosin concentration of 25 μM [21]. Furthermore, the cytotoxicity induced by doxazosin in mCRPC PC3 cells is primarily mediated through apoptosis rather than necrosis [21].Further evidence of doxazosin's apoptotic mechanism was obtained through terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining, observed under a fluorescent microscope with green fluorescence (FITC) in the nuclei, indicating apoptotic activity [22]. Another TUNEL staining was performed to confirm the presence of apoptosis in mCRPC PC3 cells, accompanied by additional evidence from the increased expression of clusterin mRNA following treatment with doxazosin, a protein produced to protect cells from apoptosis [23].

A notable finding from this study was the enhanced apoptosis observed with the combination of doxazosin and abiraterone, compared to abiraterone alone. This indicates that the combination of doxazosin, which targets apoptosis through the TGF-β1 pathway, and abiraterone, which suppresses androgen signaling, may exert a synergistic effect in promoting cancer cell death. The apoptotic activity of mCRPC PC3 cells with abiraterone has also been previously studied in combination with silodosin and metformin [18] and decursinol angelat [24]. Abiraterone inhibits the CYP17A1 enzyme, which is essential for steroid production, thereby reducing androgen levels in both adrenal and prostate tumor tissues [25]. Abiraterone also modulates apoptosis molecular pathways by increasing pro-apoptotic protein activity, such as caspase-3, while decreasing anti-apoptotic proteins like BCL-2 [26]. Furthermore, abiraterone can inhibit autophagy, leading to decreased cell viability and arrest of the cell cycle at the G2/M phase [25].

A previous study on quinazoline-based drugs, including doxazosin and terazosin, revealed significant reductions in the viability of prostate cancer cell lines, specifically mCRPC PC3 and DU-145, as well as in primary cultures of human prostate smooth muscle cells (SMC-1) when doxazosin and terazosin were used at concentrations exceeding 10 μM [27]. This reduction in viability was not observed with alpha-blockers with the absence of the quinazoline ring structure, including tamsulosin [27].Furthermore, an experiment with mCRPC PC3 and LNCaP cells treated with varying concentrations (0.01–100 μM) of alpha-blockers (prazosin, doxazosin, tamsulosin, and alfuzosin) demonstrated a reduction in cell viability with prazosin and doxazosin, both of which contain the quinazoline ring structure [19].

Further exploration of the anticancer properties of quinazoline derivatives has included the effects of doxazosin on various cancer cell lines, such as MCF-7 breast cancer cells, SW-480 colon cancer cells, and HTB bladder cancer cells, all of which showed reduced viability [27]. Doxazosin has also demonstrated anticancer activity in renal cell carcinoma, pancreatic cancer, and glioblastoma [14], as well as in HeLa cervical cancer cells, HepG-2 hepatocellular carcinoma cells, and MCF-7 cells [28].

The potential of alpha-blockers has been extensively explored as an alternative treatment for CRPC [21]. The quinazoline structure in doxazosin offers benefits in inducing apoptosis in prostate cancer cells [29]. However, epidemiological data on the chemopreventive role of quinazoline-based alpha-blockers in prostate cancer remain limited and inconsistent [26]. Doxazosin induces apoptosis by activating the transforming growth factor- β1 (TGF-β1) signaling pathway, which subsequently triggers caspase-3 activation to promote apoptosis [26]. Doxazosin also regulates the intracellular effectors SMAD4 and SMAD7, further enhancing apoptosis via the TGF-β1 pathway. Additionally, the TGF-β1 pathway increases IkBα expression, which inhibits nuclear factor-kappa B (NF-κB) signaling, consequently reducing angiogenesis, invasion, and metastasis in prostate cancer cells [30]. Doxazosin also reduces cancer cell proliferation by decreasing vascular endothelial growth factor (VEGF) levels in human prostate cancer cells and endothelial cells [31].

The study has several limitations. First, the study design is based on an in vitro model that lacks the ability to substitute for complexity and cannot fully replicate the physiological conditions of an in vivo model. Second, the researchers were unable to thoroughly explore the pathways involved in the apoptosis underlying the findings of this study. Third, the study utilized only a single cell line, which does not adequately represent real physiological conditions, limiting the direct applicability of the findings. These limitations will be addressed in future research.

This research highlights the potential of doxazosin as a complementary treatment for mCRPC by showing its apoptosis-inducing effects in mCRPC PC3 cells. It becomes an adjuvant treatment that can be given to prostate cancer patients in addition to chemotherapy drugs. The combination of doxazosin with abiraterone was more effective in inducing apoptosis than abiraterone alone. While these in vitro results are promising, further in vivo studies and long-term evaluations are necessary to confirm doxazosin's safety and efficacy in treating mCRPC. This research lays the groundwork for future studies on doxazosin as an effective supplemental therapy to improve outcomes for mCRPC patients.

Conclusion

This study supports doxazosin as an adjunctive therapy for mCRPC, as evidenced by its ability to reduce cell viability and induce apoptosis in mCRPC PC3 cells compared to the control. The combination of doxazosin and abiraterone demonstrated increased apoptosis in mCRPC PC3 cells compared to treatment with abiraterone or doxazosin alone. Although the in vitro results are promising, further in vivo studies are necessary to validate doxazosin's anticancer effects, confirm its long-term safety, and evaluate its potential in combination therapies. This study lays a foundation for future research into doxazosin's role in enhancing CRPC therapy effectiveness.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

The use of artificial intelligence is intended for language refinement purposes.

How to cite

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