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Comparison of Testosterone and Prostate-Specific Antigen Nadir Value between Castration Resistant Prostate Cancer and Non-Castration Resistant Prostate Cancer Patients after Androgen Deprivation Therapy - A Single Center Study in Indonesia

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Abstract

BACKGROUND: Prostate cancer is the second most commonly occurring cancer in adult males worldwide. Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer. However, despite the low testosterone level (indicative of ADT success), most advanced prostate cancers progress into an androgen unresponsive or castrate resistant state; such cases are defined as castrate-resistant prostate cancer (CRPC) and were associated with worse outcomes and more rapid prostate cancer progression. This study aimed to compare the value of nadir testosterone level and nadir PSA in CRPC and non-CRPC patients who received ADT.

AIM: This study was aimed to compare value of nadir testosterone level and nadir PSA in CRPC and non-CRPC patients who received ADT.

METHODS: Prostate cancer patients receiving ADT in dr. Hasan Sadikin Bandung General Hospital in September 2018–September 2020 without previous history of CRPC and surgical castration, and prostate cancer with histopathological confirmation were included to the study. The patients prior had received complete blockade ADT with luteinizing hormone agonist (LHRH) goserelin acetate 10.8 mg injected subcutaneously per 3 months and oral anti-androgen bicalutamide 50 mg orally daily. Testosterone and PSA levels were assessed on 1st, 3rd, 6th, and 12th month. Patients then were grouped into CRPC group and non-CRPC group and further subdivided according testosterone levels (<20 and 20–500 ng/dL). Paired t-test and Chi-square test were used to analyze statistical difference ($p < 0.05$ deemed significant).

RESULTS: Significantly higher baseline PSA ($p = 0.002$) and nadir PSA ($p = 0.013$) were found on the CRPC group. Nadir testosterone in CRPC group was higher than non-CRPC group but statistically insignificant ($p = 0.849$). Time to CRPC is faster in nadir testosterone 20–50 ng/dl group than in <20 ng/dl group but statistically insignificant ($p = 0.837$).

CONCLUSION: Prostate cancer patients who had high baseline PSA and nadir PSA after ADT need a longer follow-up time and more frequent testing of the testosterone and PSA values. It can predict the incidence of CRPC and to ensure that prostate cancer patients receive adequate therapy.

Introduction

Prostate cancer is the second most prevalent cancer in males worldwide, there were approximately 1.4 million diagnosis in 2020 [1]. The mortality of prostate cancer worldwide correlates with increasing age with the average age at the time of diagnosis being 66 years [2]. Mortalities in prostate cancer cases were found in higher rates due to castration-resistant prostate cancer metastasis (mCRPC) [3]. In comparison, in dr. Hasan Sadikin General Hospital Bandung, there were 318 cases of prostate cancer; 193 organ-confined or locally advanced prostate cancer cases (60.7%) and 125 metastatic prostate cancer cases (39.3%) during 2004–2010 [4].

Androgen deprivation therapy (ADT) is a mainstay treatment for patients with advanced or recurrent prostate cancer by suppressing testicular androgen production or inhibiting androgenic effects from circulating testosterone (inhibition of androgen receptors) [5]. The therapy is administered until the circulating androgen level is reduced into similar androgen levels on castrated individuals; the low androgen level may, from a pathophysiological perspective, induce regression and arrest the growth and/or replication of cancerous androgen-sensitive prostate cells [6]. Level of circulating androgens (from a blood test) is taken to assess the therapy's efficacy [7].

Prostate-specific antigen (PSA) is a biomarker used for diagnosis, risk classification, and disease monitoring. Research by Tomika *et al.* showed that PSA assessment has many benefits, including monitoring therapy. PSA levels at diagnosis can predict response to ADT therapy [8].

Cellular growth and/or replication of cancerous prostate cells may be stopped by ADT; however, there

are other cases, despite the low testosterone level (indicative of ADT success), most advanced prostate cancers progress into an androgen unresponsive or castrate resistant state and can be recurring or metastasized to other organs; such cases are defined as castrate-resistant prostate cancer (CRPC) [5], [9] The definition of CRPC is a disease progression despite a serum testosterone below 50 ng/dL after ADT and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

As such, periodical assessment of testosterone level remains an important part of diagnosing prostate cancer recurrence. Testosterone nadir levels (< 20 ng/dl) were associated with increased cancer-specific survival rates and faster response toward ADT. Conversely, higher nadir testosterone levels (more than 20 ng/dl) were associated with worse outcomes and more rapid prostate cancer progression [7]. This study aimed to compare the value of nadir testosterone level and nadir PSA in CRPC and non-CRPC patients who received ADT.

Materials and Methods

This study was an observational analytical study with a prospective case–control study design. The study aimed to observe differences in nadir testosterone level and nadir PSA on patients with prostate cancer receiving ADT; patients were then divided into two groups after a follow-up period: the CRPC group and the non-CRPC group. Patients with prostate cancer (histologically confirmed) receiving ADT in dr. Hasan Sadikin General Hospital Bandung in September 2018–September 2020 were recruited to the study. Patients with a previous history of CRPC, previous history of castration, and previous history of ADT non-compliance were excluded from the study. Patients were sampled using non-probability sampling; complete sampling was used in this study.

The ADT regiment which used in this study was complete androgen blockade (CAB) using luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate 10.8 mg) which was injected subcutaneously per 3 months, and anti-androgen (bicalutamide 50 mg orally) daily was given for 1 month to reduce the possibility of flare up. ADT was given to suppress testicular androgen production and administered until the circulating androgen level is reduced into similar androgen levels on castrated individuals.

Testosterone and prostate-specific antigen (PSA) levels were taken on the 1st, 3rd, 6th, and 12th months of the study period. Detection of testosterone levels utilized enzyme-linked immunoabsorbent assay (ELISA) kits. Variables collected in the study were baseline, nadir, time to nadir for testosterone and PSA levels, and time to CRPC. The data were presented using descriptive statistics. The data analysis was determined by the data normality (using Kolmogorov–Smirnov). The characteristics of both groups were compared using paired t-test (on normally distributed variables) and Wilcoxon test (on non-normally distributed variables). Categorical variables were compared using the McNemar test and analyzed with the Chi-square test or Fisher Exact test. Numerical data were compared using the unpaired t-test (on normally distributed variables) and the Mann–Whitney U-test (on non-normally distributed variables). $p < 0.05$ was deemed significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical number for this research was obtained from the Research Ethical Committee of Dr. Hasan Sadikin Hospital (Letter Number Approval LB.02.01/X.6.5/23/2018).

Results

Baseline characteristics are presented in Table 1. No significant differences in the baseline variables were noted. Normally and non-normally distributed data were presented with the addendum below the table ($p < 0.05$). The median age of the CRPC group was 69 years, and the median age of the non-CRPC group was 70 years. The mean body mass index (BMI) of the CRPC group was 21.43 kg/m^2, and the mean BMI of the non-CRPC group was 21.90 kg/m^2.

Table 1: Baseline Characteristics

Variables	CRPC	Non-CRPC	Normality	p value
	n = 16	n = 22		
Age (years)			0.062*	0.311**
Mean ± SD	67.69 ± 12.186	71.32 ± 9.599		
Median	69.00	70.00		
Range (min-max)	51.00–88.00	56.00–94.00		
BMI (kg/m^2)			0.001*	0.872***
Mean ± SD	21.43 ± 2.493	21.90 ± 3.717		
Median	20.93	21.40		
Range (min-max)	17.58–27.24	16.07–34.53		
ISUP score				0.999‡
1	1 (6.3%)	1 (4.5%)		
2	2 (12.5%)	2 (9.1%)		
3	1 (6.3%)	3 (13.6%)		
4	5 (31.3%)	9 (40.9%)		
5	7 (43.8%)	7 (31.8%)		
Bone metastasis				0.090‡
Non-metastasis	0 (0.0%)	9 (40.9%)		
High volume	13 (81.3%)	5 (22.7%)		
Low volume	3 (18.8%)	8 (36.4%)		
Baseline PSA			0.0001*	0.002**
Mean ± Standard	369.02 ± 448.035	205.06 ± 483.128		
Median	245.30	28.13		
Range (min-max)	21.50–1756.29	4.42–2186.27		

*Shapiro–Wilk; **Independent t-test; ***Mann–Whitney U-test; ‡Kolmogorov–Smirnov test.

No significant differences in ISUP score between both groups were noted (p = 0.999). There were no significant differences between both groups in terms of bone metastasis volume (p = 0.090). Significantly higher baseline PSA levels were noted on patients in the CRPC group (p = 0.002).

Testosterone and PSA nadir and baseline levels are described in Table 2. Significantly higher nadir PSA levels were found in the CRPC group compared to the non-CRPC group.

Table 2: Nadir Testosterone and PSA Comparison

Variables	CRPC N = 16	Non-CRPC N = 22	Normality	p value
Nadir testosterone			0.003	0.849**
Mean ± SD	22.08 ± 13.922	21.13 ± 15.472		
Median	24.25	14.50		
Range (min-max)	4.22–49.00	2.50–48.90		
Nadir testosterone				0.350‡
<20 ng/dl	7 (43.8%)	13 (59.1%)		
20–50 ng/dl	9 (56.3%)	9 (40.9%)		
PSA nadir				0.013**
Mean ± SD	13.99 ± 18.289	2.20 ± 2.629		
Median	2.08	1.26		
Range (min-max)	0.10–49.00	0.02–9.08		

*Shapiro–Wilk; **Mann–Whitney U-test; ‡Chi-square test.

The time to CRPC and the difference of nadir testosterone regarding time to CRPC is described in Tables 3 and 4, respectively. The mean time of CRPC in the study was 15.81 months, with a median time of 14 months. No significant differences in time to CRPC in both low (<20 mg/dl) and high (20–50 mg/dl) testosterone groups. The low nadir testosterone group had a longer time to CRPC compared to the high nadir testosterone group; the difference was not significant (p = 0.837).

Table 3: Time to CRPC

Variables	n = 16
Time to CRPC (months)	
Mean ± SD	15.81 ± 4.708
Median	14.00
Range (min-max)	10.00–24.00

Table 4: Time to CRPC comparison between testosterone concentration

Variable	Time to CRPC (months)			Nilai P
	Mean ± Std	Median	Range (min-max)	
Nadir testosteron				0.837**
<20 ng/dl	16.71 ± 5.678	13.00	10.00–23.00	
20–50 ng/dl	15.11 ± 4.014	15.00	10.00–24.00	

**Mann–Whitney U-test.

Discussion

Prostate cancer is an androgen-sensitive malignancy; thus, it provides the rationale of ADT as the mainstay treatment for prostate cancer. The function of ADT is not a guaranteed cure to prostate cancer; there are several instances of growth of prostate cancer cells that will eventually cease to be dependent on androgen hormones. The condition was aptly defined as CRPC [9]. The previous studies on the PSA and testosterone levels to nadir had been noted; they had concluded that higher nadir PSA and testosterone on ADT were associated with a worse prognosis. Lower PSA had been associated with a lower risk of progression in patients with prostate cancer [10]. Time to- and levels of nadir PSA were associated with the risk of developing CRPC [11]. The present study results were concurrent with previous studies; higher nadir PSA was found on significantly higher rates in the CRPC group compared to the non-CRPC group. As such, the study confirmed that PSA is a possible prognostic indicator of progression to CRPC in patients with prostate cancer receiving ADT.

In this study, in the CRPC group, there were significantly higher baseline PSA (p = 0.002) and nadir PSA (0 = 0.013) compared with non-CRPC group. Another study by Hamano *et al.* also concluded that PSA nadir and time to PSA nadir during initial ADT were significantly associated with overall survival in CRPC patients [12]. According to those results, patients who had high baseline PSA and nadir PSA after ADT treatment had more risk to develop into CRPC. So that, in prostate cancer patients who received ADT, a longer follow-up time of testing the testosterone and frequent PSA testing every 3 months can be used to predict the incidence of CRPC and to ensure that prostate cancer patients receive adequate therapy. Because when prostate cancer (PC) treated with castration evolves into a castration-resistant phase, it was previously considered as the point where survival could not be prolonged.

Testosterone on castration level is an important indicator of progression to CRPC in patients with prostate cancer. In this study, time to CRPC is faster in nadir testosterone 20–50 ng/dl group than in < 20 ng/dl group but statistically insignificant (p = 0.837). Morote *et al.* had noted that patients with breakthrough increases level of testosterone > 32 ng dl had a lower survival rate, free of androgen-independent progression, than patients without these increases [13]. Study by Shore *et al.* showed that achieving testosterone < 20 ng/mL improves outcomes and delays CRPC emergence. Regular testosterone assessments will evaluate whether testosterone is adequately suppressed in the setting of potential progression to CRPC. Based on those findings, we suggest that if testosterone levels can be driven lower with adjunctive therapies, patient overall outcome might be improved [14].

Treatment options which can be used to suppressed testosterone level, such as abiraterone, may be able to help decrease testosterone to ≤ 25 ng dl among patients who do not achieve this level within 1 month on regular ADT. Another alternative is LHRH antagonists which appear to offer an effective option in the management of prostate cancer by suppressing testosterone levels and reducing PSA. In contrast to the agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. In theory, if the testosterone level is more quickly decreased to castrate levels, patients could achieve greater benefits [15].

The study was one of the few studies to provide additional information regarding the association between testosterone and PSA levels on progression to CRPC. The limitation of the study was the relatively small sample size, limited time for follow-up (in this study was 24 months), and many patients lost to follow-up due to the current situation of the COVID-19 pandemic.

Conclusion

Nadir PSA was significantly higher in the CRPC group after receiving ADT. Nadir testosterone was not significantly higher in the CRPC group. The nadir PSA value was significantly higher in the CRPC group after receiving ADT. The nadir value of testosterone was not significantly higher in the CRPC group. In prostate cancer patients who received ADT, a longer follow-up time of testing the testosterone and PSA values every 3 months can be used to predict the incidence of CRPC and to ensure that prostate cancer patients receive adequate therapy.

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