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Methods: The study used retrospective observational cohort design upon medical record of 83 prostate cancer patients in GatotSoebroto Army Hospital, Jakarta, Indonesia. We analyzed the recorded patients' age, TNM staging, histologic grading, LHRH agonists used in therapy, along with the average baseline PSA level prior and three months following treatment. Paired T-test, Wilcoxon, ANOVA, and Kruskal-Wallis Test were used where appropriate.

Keywords: *LHRH agonist, prostate cancer, prostate-specific antigen, drug efficacy.*

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Robertus Bebet Prasetyo [α] & Andy [σ]

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Results: We found significant change in PSA levels before and three-months following the use of LHRH agonists($p < 0.001$), with the median decreasing from 56.20 (4.24-7,445.00) to 7.08 (0.01-942.00). Significant association was also found between PSA level prior to treatment and the prostate cancer groups according to stages ($p < 0.001$), histological grades ($p = 0.020$), and medications used ($p = 0.010$). However, this study found no significance of these groups in the PSA level reduction three months after therapy.

Conclusion: LHRH agonists were significant in reducing PSA level in any prior prostate cancer staging, histological grading, and medication type.

Keywords: LHRH agonist, prostate cancer, prostate-specific antigen, drug efficacy.

I. Introduction

Prostate cancer is one of the most frequently-occurring type of cancer, reported in a study from 2003 as the sixth most common cancer in the world and the third most common cancer among men.[1] There are 513,000 new cases of prostate cancer was reported globally in the 2000.[2] A data from United States in 2011 shows that this disease was diagnosed in 240 thousand men and was the cause of 33 thousand deaths.[1,3]

As prostate cancer's progression have long since been found to be dependent on hormones, androgen suppression therapy (AST) is incorporated into the standard treatment of prostate cancer.[4] Historically, AST was commonly accomplished by means of surgical procedure or estrogen therapy. Advance in AST allows pharmacologic castration using luteinizing hormone-releasing hormone (LHRH) agonist drugs as they offer wider use. LHRH agonists therapy was found to lower the number the hospital visits required, medical bill for the treatment, along with mental and physical burden that may occur from the drug injection.[5] Although current studies show that the two most common LHRH agonist used in medical setting, Leuprorelin and Goserelin, have relatively equal efficacy, Leuprorelin are comparably more expensive than the latter.

Although LHRH agonists are commonly used in the treatment regime of prostate cancer, there has yet been any study regarding the drug's influence on lowering the level of prostate-specific antigen (PSA), a prostate cancer biomarker, in Indonesia. Thus, this study aims to assess the efficacy of LHRH agonists in treating prostate cancer patients through analyzing the change of PSA levels three months following the therapy.

II. Methods

This is an observational study using retrospective cohort design that was conducted in the Urology Polyclinic of GatotSoebroto Army Hospital, Jakarta, from January of 2014 to October of 2018. The study subjects were 127 male patients older than 40 years of age who were previously diagnosed with prostate cancer and treated with LHRH agonists within the period of research. Patients that had not undergo laboratory testing for PSA prior to the treatment, developed a castrate-resistant prostate cancer, or failed to attend the follow-up care in polyclinic within three months are excluded from the study. The subjects were sampled consecutively, in which patients were selected in order of outpatient scheduling until the appropriate sample size was reached.

Data were collected from the subjects' medical record. Of the extracted data were the patient's age, cancer staging according to European Society for Medical Oncology (ESMO) classification, histological grading, treatment received, along with PSA levels

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before and after treatment. Information regarding the treatment collected for in this study were the LHRH medication type used and other therapies done for the patient.

All data were analyzed using SPSS version 23. Descriptive statistics were used to summarize the demographic characteristics of subjects according to age, TNM stage, and histologic grade. This statistics were also used to describe the usage of LHRH agonists along with average baseline and post-therapy PSA levels. Statistical analysis was used to observe the changes of PSA level three months following therapy. Paired-T test analysis was conducted with dispersed data, whereas Wilcoxon test was done for under dispersed data. Another statistical analysis used in this study is ANOVA and Kruskal Wallis, for dispersed and under dispersed data respectively, to observe the difference of PSA-lowering efficacy in different medication types, cancer stages, and histologic grades.

III. Results

From January of 2014 to October of 2018, there were 83 prostate cancer patients that underwent LHRH agonist therapy with the median age of 70 years. The youngest of the subjects was 51 years old, whereas the oldest was 80 years old. The median of baseline PSA level was 5.40 ng/ml, with maximum and minimum value 4.24 and 7,445.00 ng/ml, respectively. The demographic characteristic of this study is further described in Table 1.

Wilcoxon analysis shows significant difference between circulating PSA level before and three months following prostate cancer treatment with LHRH agonists ($p < 0.001$), with median value of decrease from 54.00 (4.24-7,445.00) to 7.08 (0.01-942.00). Significant difference was also found using Kruskal-Wallis analysis upon baseline PSA levels between prostate cancer stages, histologic grades, and LHRH medication used (stage, $p < 0.001$; histologic grade, $p = 0.020$; LHRH medication, $p = 0.009$). However, there were no significant distinction of PSA levels three months following therapy between there groups. (stage, $p = 0.135$; histologic grade, $p = 0.067$; LHRH medication, $p = 0.139$) (Table 2)

Table 1: Patients' Characteristic

	Total (n = 83)	Precentage (%)
Stage		
T1-T2a, N0M0	23	27.7
• IIA	• 6	• 7.2
• IIC	• 2	• 2.4
• IIIA	• 5	• 6.0
• IIIC	• 10	• 12.0
T2bN0M0	7	8.4
• IIA	• 1	• 1.2
• IIIA	• 4	• 4.8
• IIIC	• 2	• 2.4
T2c-T4 orN1 orM1	53	63.9
• IVA	• 2	• 2.4
• IVB	• 51	• 61.4
Histologic grading		
1	10	12.0
2	4	48
3	21	25.3
4	20	24.1
5	28	33.7
LHRH Medication		
Goserelin	47	56.6
Leuprorelin	28	33.7
Goserelin and Leuprorelin	8	9.6

Table 2: Changes in PSA levels according to cancer stage, histologic grade, and LHRH medication used in treatment

	PSA prior to treatment	PSA 3 months following treatment
Stage		
T1-T2a, N0M0	13.10 (4.24-134.00)	6.70 (0.44-80.80)
T2bN0M0	26.00 (14.00-64.54)	0.30 (0.01-22.40)
T2c-T4 or N1 or M1	80.00 (4.70-7,445.00)	10.23 (0.07-647.00)
P-value	< 0.001	0.135

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Histologic grade 1 2 3 4 5	 20.00 (9.40-115.79) 84.12 (4.24-236.70) 48.60 (7.89-7,445.00) 108.25 (4.70-889.00) 60.37 (11.68-596.64)	 3.30 (0.01-80.80) 9.65 (1.88-392.60) 3.30 (0.07-647.00) 6.20 (0.10-76.90) 13.27 (0.40-147.00)
P-value	0.020	0.067
LHRH Medication Goserelin Leuprorelin Both	 68.00 (4.24-596.64) 40.00 (9.40-7,445.00) 889.00 (26.00-889.00)	 9.00 (0.01-392.60) 13.10 (0.07-647.00) 6.20 (0.30-6.20)
P-value	0.009	0.139

IV. Discussion

In this study, there were 83 out of 172 prostate cancer patients administered with LHRH agonists as androgen suppression therapy. The median age of the subjects was 70 years, ranging from 51 to 80 years. These result are supported by a study conducted in 2013 to 2015 in Prof. Dr. R. D. Kandou Central General Hospital in Manado, where it was found the age profile of prostate cancer patients ranges from 51 to 90 years, with 61-70 years as the largest age group.[6] A majority of the patients that received LHRH agonists were also found with high-risk prostate cancer, with 63.9% in the staging of T2c-T4 or N1 or M1 (61.4% in the IVB prognostic group) and 33.7% with the histologic grade of 5.

The 2016 global treatment pattern of prostate cancer have shown androgen-suppression therapy as the treatment of choice of men with late stage prostate cancer. This treatment was chosen with the patient's disease status as the primary driver in 29% of the cases, while patient's age was deemed the most important factor in only 7% of the case.[7] This pattern supports the findings of this study, as the major age group of patients sampled resembles the general age profile of prostate cancer patients, while in contrast, the majority were in pathologically advanced stage of disease. Androgen suppression therapy are indicated after the failure of definitive therapy and local salvage, thus most patients received the treatment at a later progression.[8]

LHRH agonist therapy were efficacious in suppressing PSA level during three-month follow-up. Current evidence have shown that LHRH monotherapyis an equal alternative of surgical castration in terms of efficacy and adverse effects. However, patients usually experience a transient flare-up of prostate cancer and PSA level. In theory, LHRH agonists act by modulating the action of hypothalamus and overtaking the control imposed by gonadotropin-releasing hormone (GnRH). Initially, the secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone will surge, leading to transient surge of PSA. Then, after 2-4 weeks of treatment, this drug will inhibit the expression of LHRH in pituitary cells, thus restricting the secretion of gonadal steroids by desensitization. The inhibition of sex steroid secretion will interfere with tumor's mitogenic stimuli, eventually leading to the decline of circulating PSA.[9-10]

The median value of PSA 3 months after LHRH agonists treatment found in this study was 7,08 (0,01-942,00). Similarly, Ishizuka showed that both 1-month and 3-months depot of LHRH agonist drugs caused a drop of PSA levels from baseline since 4-weeks after treatment, and gradually decreased until most of the samples reached <4.0 ng/mL of PSA after week-12.[5]

PSA and its derivatives are well known as an indicator of prostate cancer progression for the use of screening and post-therapy observation.[11-2] Prior to LHRH agonists therapy, PSA levels between prostate cancer stages in this study were largely variable. However, 3-months after therapy, no significance difference was found. The same phenomenon was observed with PSA levels between histologic grades prior and after therapy. This can be attributed to the initial PSA levels before therapy, as Choueiri also observed invariable PSA levels after reaching nadir with the time of 6 months. His study also reported that prostate cancer patients with higher PSA levels (median of 146) who received AST have significantly faster rate of PSA decline (>52 ng/mL/year) and higher PSA nadir. Crucially, fasted PSA decline rate are associated with higher mortality.[13]Another study has reported that PSA level can predict the outcome of prostate cancer LHRH medication, as a level below 0,3 ng/ml shown better response toward LHRH agonist therapy.[14]

Neither Goserelin, Leuprorelin, or the use of both drugs have any significance towards the outcome of LHRH therapy, as the PSA levels 3 months following the treatment was insignificant. This finding is supported by other studies that also found no difference between LHRH medication types and the response of AST.[15-6]

The limitations of this study are due to the nature of the data collected, as the accuracy depends on correct documentation in the medical records. Also, androgen suppression therapy is given for patients in late stage or failed definitive therapy. Thus, each patients have a unique clinical scenario and treatment plan prior to study. These variables, coupled with small samples, might interfere with our result. However, PSA

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level is reduce significantly in any prostate cancer patients following 3 months of LHRH agonist therapy.

V. Conclusion

This study shows that within three months following therapy, LHRH agonists were significant in reducing PSA level in any prior cancer status (stage, histologic grade, and medication). However, neither cancer stage, histology grade, nor medication type were significantly associated with the decline of PSA level prior and after therapy. Due to the limitation of the retrospective nature used in this study, the author recommends further research of LHRH agonists and other yet-to-be approved AST drugs in Indonesia, such as GnRH antagonist, using larger and better-controlled cohort.

Conflict of interest
There are no conflicts of interest

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