THE ROLE OF CYP17A1 IN ADENOCARCINOMA OF THE PROSTATE AT SARDJITO GENERAL HOSPITAL

[1]Dwi Prayogo, [1]Indrawarman.

[1] Department of Urology, Faculty of Medicine/Gadjah Mada University, Sardjito General Hospital, Yogyakarta.

ABSTRACT

Objective: *To determine the relationship and role of CYP17A1 gene expression to androgen biosynthesis activity in prostate cancer patients.* ***Material & Methods:*** *The samples of this study are patients diagnosed with prostate adenocarcinoma based on histopathology examination who underwent TURP surgery at Sardjito General Hospital. A total of 30 samples were examined for PCR to determine the presence and absence of CYP17A1 gene expression. CYP17A1 gene expression was analyzed with the patient's age, stage, organ metastasis, Gleason score, and PSA value.* ***Results:*** *Analysed using Chi-Square Tests, p=0.784 was obtained on expression of CYP17A1 gene with patient's age, p=0.469 on expression of CYP17A1 gene with staging tumor, p=0.855 on expression of CYP17A1 gene with presence or absence of organ metastasis, p=0.059 on expression of CYP17A1 gene expression with total Gleason score, p=0.895 on expression of CYP17A1 gene with PSA value.* ***Conclusion:*** *There was no association between CYP17A1 gene expression and intratumoral androgen biosynthesis activity based on the patient's age, patient's clinical stage, organ metastasis, Gleason score, and PSA value.*

Keywords: *Androgen, prostate cancer, CYP17A1, metastasis, Gleason score, PSA.*

ABSTRAK

Tujuan: *Mengetahui hubungan dan peran dari ekspresi gen CYP17A1 terhadap aktivitas biosintesis androgen intratumoral pada pasien kanker prostat.* ***Bahan & Cara:*** *Sampel penelitian ini adalah pasien yang didiagnosis adenokarsinoma prostat berdasarkan pemeriksaan patologi anatomi, yang menjalani operasi TURP di Rumah Sakit Dr. Sardjito. Sebanyak 30 sampel dilakukan pemeriksaan PCR untuk mengetahui ada dan tidaknya ekspresi gen CYP17A1. Dilakukan analisis hubungan ekspresi gen CYP17A1 dengan usia pasien, stadium, adanya metastasis organ, Gleason score, dan nilai PSA.* ***Hasil:*** *Analisis menggunakan uji Chi-Square didapatkan nilai p=0.784 pada hubungan ekspresi gen CYP17A1 dengan usia pasien, nilai p=0.469 pada hubungan ekspresi gen CYP17A1 dengan stadium tumor, nilai p=0.855 pada hubungan ekspresi gen CYP17A1 dengan ada tidaknya metastasis organ, nilai p=0.059 pada hubungan ekspresi gen CYP17A1 dengan jumlah Gleason score, nilai p=0.895 pada hubungan ekspresi gen CYP17A1 dengan nilai PSA.* ***Simpulan:*** *Pada penelitian ini disimpulkan bahwa tidak ada hubungan antara ekspresi gen CYP17A1 dengan aktivitas biosintesis androgen intratumoral berdasarkan usia pasien, stadium klinis pasien, metastasis organ, jumlah Gleason score, dan nilai PSA.*

Kata Kunci: *Androgen, prostate cancer, CYP17A1, metastasis, Gleason score, PSA.*

Correspondence: Dwi Prayogo; c/o: Department of Urology, Faculty of Medicine/Gadjah Mada University, Sardjito General Hospital, Yogyakarta, Indonesia. Phone: +62274587333; Fax: +62274543980. Email: justforuro@gmail.com.

INTRODUCTION

Prostate cancer is the second most common cancer in male, which covers about 15% of all diagnosed cancer. In 2012, there are approximately 1.1 million people with prostate cancer worldwide.[1] Prostate cancer is the most common non-skin malignancy in male in United States (US), accounting for 1 out of 6 males in the US. The incidence rate shows that prostate cancer is the most malignancy worldwide and the second most in male.[2]

Androgen has an important role in prostate cancer development. Some studies reported that there is a relationship between prostate atrophy and androgen withdrawal.[3] In animal research, the castration procedure significantly decreases prostate tumor growth.[4] There is an androgen molecular action mechanism in the cell regulation cycle and prostate cancer growth in vitro.[5] Nowadays, androgen deprivation therapy (ADT) is the most common and efficient prostate cancer treatment with metastasis.[6]

There is some preventive therapy for prostate cancer. Some of them have the same mechanism such as finasteride, dutasteride, selenium, and Vitamin E. Various genes in the synthesis and metabolism of androgens have been studied in relation to the predisposition and progression of prostate cancer, such as several members of the steroid 5α-reductase (SRD5A), 3β-hydroxysteroid dehydrogenase (HSD3B), and 17β-hydroxysteroid dehydrogenase (HSD17B) families, androgen receptor (AR), cytochrome P450 17 (CYP17), and cytochrome P450 19A1 (CYP19A1).[7]

Cytochrome p450 17A1 (CYP17A1) is a monooxygenase which acts on steroid hormone synthesis. CYP17A1 turns pregnenolone into dehydroepiandrosterone and progesterone into androstenedione through two reactions: 17α-hydroxylase and 17,20-lyase reaction. Hydroxylase reaction acts on glucocorticoid biosynthesis while the rest (hydroxylase and lyase reaction) are needed in androgen and estrogen biosynthesis.[8]

OBJECTIVE

The purpose of this study is to determine the relationship and role of CYP17A1 gene expression to androgen biosynthesis activity inside the tumor. We also look for the relationship of intratumor androgen biosynthesis and prostate specific antigen (PSA) score, Gleason score, and prostate cancer stage. If the prostate cancer progressivity mechanism is known, the prevention strategy and management of prostate cancer will be better.

MATERIAL & METHODS

This is a cross-sectional study to determine the relationship of CYP17A1 gene expression and intratumor androgen biosynthesis in prostate cancer. The study population was adenocarcinoma of prostate patients, based on its histopathology, who underwent Transurethral Resection of Prostate (TURP). The sample size was 30 subjects. Subjects who are included in this study were: adenocarcinoma of prostate patients (stage 1-4) who underwent TURP. The patients who refused to take a part in this study were excluded. This study was conducted in Sardjito general hospital and Molecular Biology Laboratorium FKKMK UGM, on April-November 2018. We examined CYP17A1 gene expression on prostate tissue specimen. The prostate tissue specimens were sent to Anatomy Pathology and Histology Cell Biology Departement FKKMK UGM to carried out histopathology examination with Hematoxylin-Eosin for adenocarcinoma of prostate diagnosis and CYP17A1 gene expression examination. Electrophoresis was conducted after PCR with agarose 2% and seen under ultraviolet ray. Analysis of the result used SPSS software version 15.0.

RESULTS

Having samples taken from patients with prostate cancer (adenocarcinoma of the prostate), 30 samples were obtained with the youngest was 52 years, the oldest was 88 years, and the mean prostate cancer patients age was 72.03 years.

Table 1. Age of adenocarcinoma of prostate patients.

Information	Age (Year)
Lowest age	52
Highest age	88
Mean	72.03

From the collected samples, there was no patient diagnosed with T1a stage, there was a patient with T1b stage, 4 patients with T1c stage, 2 patients with T2a stage, a patient with T2b stage, 12 patients with T2c stage, no patient with T3a and T3b stage, and 10 patients with T4 stage.

Table 2. Adenocarcinoma of prostate stage

Tumor stage	Number (%)
T1a	0
T1b	1 (3.3)
T1c	4 (13.3)
T2a	2 (6.7)
T2b	1 (3.3)
T2c	12 (40)
T3a	0
T3b	0
T4	10 (33.3)

Based on metastatic status there were 16 patients (35.3%) with distant organ metastasis (M1) and 14 patients (46.7%) without metastasis.

Table 3. Metastasis status.

Metastasis Status	Number
Metastasis	16 (53.3)
Non-metastasis	14 (46.7)

The Gleason total score was divided into 4 groups: 9 patients score couldn't be counted, a patient with 6 Gleason score (good differentiation), 2 patients with 7 Gleason score (moderate differentiation), and 18 patients with 8-10 Gleason score (poor differentiation).

Table 4. Gleason score.

Gleason score	Number (%)
Can't be counted	9 (30)
6	1 (3.3)
7	2 (6.7)
8-10	18 (60)

PSA score was divided into: <4 (5 patients), 4-10 (1 patient), 11-50 (7 patients), 51-100 (3 patients), 101-150 (1 patient), and >150 (13 patients).

Table 5. PSA score.

PSA Score	Number (%)
<4	5 (16.7)
4-10	1 (3.3)
11-50	7 (23.3)
51-100	3 (10)
101-150	1 (3.3)
>150	13 (43.3)

Table 6. CYP17A1 gene expression.

CYP17A1 gene expression	Number (%)
Positive	24 (80)
Negative	6 (20)

From the CYP17A1 gene examination, there were 24 patients (80%) with positive gene expression and 6 patients (20%) with negative gene expression.

DISCUSSION

The relationship of CYP17A1 gene expression and patient age, prostate cancer stage, metastasis status, Gleason score, and PSA score were analyzed using the Chi-Square test. The p value of CYP17A1 gene expression and patient age was 0.784, CYP17A1 and cancer stage was 0.469, CYP17A1 and metastasis status was 0.855, CYP17A1 with Gleason score was 0.059, CYP17A1 and PSA score was 0.895.

Table 7. The p value.

Variable	p value
Patient age	0.784
Prostate cancer stage	0.469
Metastasis status	0.855
Gleason score	0.059
PSA score	0.895

P value from 5 variables was above 0.05 which means there is no relationship between CYP17A1 gene expression and patient age, prostate cancer stage, metastasis status, Gleason score, and PSA score.

Cytochrome p450 17A1, also called 17α-monooxygenase steroid, 17α-hydroxylase, 17,20-lyase, or 17,20-desmolase, is a hydroxylase enzyme in the human which encoded by CYP17A1 gene in the chromosome 10. Many cells and tissue express this enzyme, including the reticular zone of the adrenal cortex, fasciculate zone, and gonad tissue.

Cytochrome p450 17A1 (CYP17A1) is a monooxygenase which acts on steroid hormone synthesis. CYP17A1 turns pregnenolone into dehydroepiandrosterone and progesterone into androstenedione through two reactions: 17α-hydroxylase and 17,20-lyase reaction. Hydroxylase reaction acts on glucocorticoid biosynthesis while the rest (hydroxylase and lyase reaction) are needed in androgen and estrogen biosynthesis.[8]

Generally, CYP17A1 inhibition is an important target for prostate cancer treatment because it results in androgen which promotes tumor cell growth.[9]

Study about CYP17A1 gene expression and its relation to prostate cancer prognostic factors (age, clinical stage, metastasis status, Gleason score, and PSA score) is limited. This study wants to determine the CYP17A1 in prostate cancer treatment.

From this study, we found that there was a high CYP17A1 gene expression; 80% from all adenocarcinoma of prostate patients. But it was still unknown whether there was any patient who included in CRPC (castration-resistant of prostate cancer) criteria or not.

All variables, prostate specific antigen (PSA) score, Gleason score, prostate cancer stage, metastasis status, and patient age, were not related to CYP17A1 (p value >0.05). But if we compared

among them, Gleason score had the lowest p value (p value = 0.059).

This study had some limitations, such as limited number and variation of the sample. So, we need more study with a bigger sample and controlled variation to develop the role of CYP17A1 on prostate cancer treatment and management.

CONCLUSION

From this study, we concluded that there is no relationship between CYP17A1 gene expression and intratumor androgen biosynthesis based on prostate cancer patient age, prostate cancer stage, metastasis status, Gleason score, and prostate specific antigen (PSA) score.

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