ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2023, Volume 12, Number 2: 2303-2306
P-ISSN.2089-1180, E-ISSN: 2302-2914

PD-L1 overexpression in prostate cancer: a potential targeted therapy

Gede Andi Aditya[1], Yurisal Akhmad Dany[1], Raden Danarto[1*], Indrawarman Soeroharjo[1], Ahmad Zulfan Hendri[1]

[1]Division of Urology, Department of Surgery, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada - Sardjito Hospital, Yogyakarta, Indonesia.

*Corresponding author:
Raden Danarto;
Division of Urology, Department of Surgery, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada - Sardjito Hospital, Yogyakarta, Indonesia;
dr.danarto@yahoo.co.id

Received: 2023-04-05
Accepted: 2023-06-22
Published: 2023-07-31

ABSTRACT

Background: Prostate cancer frequently presents with a non-specific clinical appearance, similar to benign prostatic hyperplasia (BPH). In many countries, early detection and treatment of prostate cancer are associated with lower mortality rates. Several prostate cancer biomarkers have been studied, one of which is programmed death ligand-1 (PD-L1), currently used as a therapeutic method. This study aimed to examine the expression of PD-L1 in prostate cancer and BPH.

Methods: This was a cross-sectional retrospective study involving subjects diagnosed with prostate cancer by histopathological examination. The expression of PD-L1 from 30 prostate tissues was analyzed using qRT-PCR. Data were then analyzed using the ANOVA test and continued with the Post Hoc test. $P < 0.05$ was considered significant.

Results: From a total of 30 prostate tissues that were examined histopathologically, ten samples were BPH (33.3%), ten samples were non-metastatic prostate cancer (non-MPCa) (33.3%), ten samples were metastatic prostate cancer (MPCa) (33.3%). The data analysis showed significant differences in PD-L1 expression between groups (p=0.000). The Post Hoc test showed significant differences between the non-MPCa group and BPH (p=0.003; 95% CI 36.1-142.8) and the MPCa group with BPH (p=0.000; 95% CI 50.9-127.3).

Conclusion: PD-L1 was overexpressed in the prostate cancer group, both in non-metastatic Pca and metastatic Pca. As a result, using PD-L1 inhibitors in the early stages of the disease may improve survival and prognosis.

Keywords: PD-L1, prostate cancer.
Cite This Article: Aditya, G.A., Dany, Y.A., Danarto, R., Soeroharjo, I., Hendri, A.Z. 2023. PD-L1 overexpression in prostate cancer: a potential targeted therapy. *Bali Medical Journal* 12(2): 2303-2306. DOI: 10.15562/bmj.v12i2.4506

INTRODUCTION

Prostate cancer is a common type of cancer. According to data from 105 countries, this form of cancer is the fourth most prevalent non-skin malignancy (7.1%), and the second most common malignancy among men. In 2018, there were 1.3 million new cases of prostate cancer and 359,000 deaths worldwide.[1] While in Indonesia, it ranks fifth as the most cancer cases in men, with 13,563 or 7.4% new cases in 2020.[2] Prostate cancer incidence in recent decades has been heavily influenced by the diagnosis of latent cancers either by PSA testing of asymptomatic individuals or by detecting latent cancer in tissue removed during prostatectomy. Early detection and treatment of prostate cancer are related to lower mortality rates in many nations, especially developing Asian countries.[1]

Prostate cancer frequently has a non-specific clinical appearance and might be mistaken for benign prostatic hyperplasia (BPH). The two diseases, however, have significantly different management and prognoses. As a result, distinguishing between the two clinical states is critical. Various markers have been studied to differentiate prostate cancer from BPH, one of which is Programmed death-ligand-1 (PD-L1).[3,4]

Programmed death-1 (PD-1) is the PD-L1 receptor. The PD-L1/PD-1 interaction is critical for regulating T-cell activation throughout the inflammatory response. The PD-1 receptor is a negative checkpoint regulator, preventing T-lymphocyte immune activation.[5] The interaction of PD-1 with its ligand, PD-L1, is the primary mediator of immunosuppression, inhibiting the proliferation of activated T cells.[6] In forming neoplasms, PD-L1 will be over-expressed, suppressing the immune system and accelerating the oncogenic process. PD-L1 can be expressed in malignancies from various organs, such as the prostate, lung, kidney, head and neck, breast, stomach, colon, cervix, and ovaries.[7] In the process of malignancy, PD-L1 is not only expressed in tumor cells but also in immune cells.[8] Previous studies showed PD-L1 expression in prostate cancer cells was found in 3.7% to 92.3% of cases, whereas expression in tumor-infiltrating lymphocytes was found in 9.9% to 14.6% of cases.[9] In BPH cases, several studies have shown negative PD-L1 expression, therefore, PD-L1 can be used to differentiate between the two conditions. This study will examine the differences in PD-L1 expression in prostate cancer and BPH.[10]

METHOD

This cross-sectional retrospective study involved 30 subjects diagnosed with prostate cancer by histopathological examination in RSUP Dr. Sardjito Yogyakarta from 2015 until 2020. The sample is a Formalin-Fixed Paraffin-Embedded (FFPE) tissue from a patient at the time of study with exclusion criteria:

1) damaged or unreadable FFPE tissue isolated using Favor Prep™ Total RNA Minikit and 2) the subject has received chemotherapy and/or immunotherapy. All the patients who met these criteria were included in this study (total sampling). Then, the expression of PD-L1 from PPFE tissues was analyzed using KAPA SYBR® FAST qPCR Kit. Data analysis used SPSS software version 25, which included univariate and bivariate analysis. The research was carried out with ethical clearance from the Universitas Gadjah Mada/RSDS Medical and Health Research Ethics Committee, number KE/FK/0109/EC/2022.

RESULTS

As presented in Table 1, the prostate tissue histopathological samples were divided into three equal groups (33%, respectively). The sample's mean age was 69.60±7.76 years, with the highest in the non-MPCa group. The mean PD-L1 level in the non-MPCa and MPCa groups was 90.91 ± 60.38 and 90.59 ± 43.25, respectively, while in BPH, it was only 1.41 ± 0.32. This result shows that PD-L1 expression in the group with prostate cancer is higher than in the BPH group. As much as 65% of samples with a GST score > 7 and 70% with an ISUP grade > 2 (Table 2).

The results of the PD-L1 analysis (Table 3) showed that there were significant differences (p=0.000) between groups. A post hoc test was then carried out, and the results showed that there was a significant difference between the non-MPCa group and BPH (p=0.003) and the MPCa group and BPH (p=0.000), while there was no difference between the non-MPCa group and the MPCa group (p=1.000). A comparison of PD-L1 data distribution in each group is described in the box plot (Figure 1).

Table 1. Sample characteristics

Characteristic	Value
Age (years ± SD)	
BPH	69.50 ± 7.76
Non-MPCa	71.00 ± 5.64
MPCa	67.20 ± 7.96
PD-L1 expression (total ± SD)	
BPH	1.41 ± 0.32
Non-MPCa	90.91 ± 60.38
MPCa	90.59 ± 43.25
Histopathology (total)	30 (100%)
BPH (%)	10 (33%)
Non-MPCa (%)	10 (33%)
MPCa (%)	10 (33%)

PD-L1: Programmed death-ligand-1; MPCa: Metastatic Prostate Cancer; SD: Standard Deviation; BPH: Benign Prostate Hyperplasia

Table 2. Prostate cancer degrees

Grade	Frequency	
	n	%
GS		
≤7	7	35
>7	13	65
ISUP Grade		
≤2	6	30
>2	14	70

GS: Gleason Scoring; ISUP: International Society of Urology Pathology

Table 3. Programmed Death-Ligand-1 (PD-L1) expression

Histology	PD-L1 expression (±SD)	*P*
BPH	1.41 ± 0.32	0.000
Non-MPCa	90.91 ± 60.38	
MPCa	90.59 ± 43.25	

PD-L1: Programmed death-ligand-1; MPCa: Metastatic Prostate Cancer; SD: Standard Deviation; BPH: Benign Prostate Hyperplasia

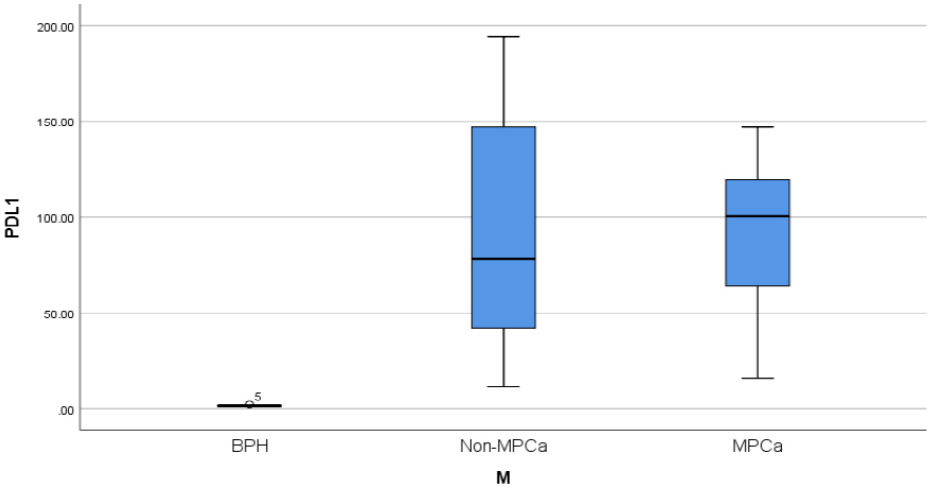

Figure 1. Box plot PD-L1 distribution in BPH, Non-MPCa, and MPCa group.

DISCUSSION

The Gleason Score is fundamental in determining the prognosis of prostate malignancy.[11-14] Study by Egevad *et al.* in 305 prostate cancer patients gets as much as 22% with a Gleason score of 4-5, 29% with a score of 6, 18% with a score of 7, and 32% with a score of 8-10.[15] Likewise, other studies by Swanson et al. also show that most samples with a score of ≤7.[16] The results obtained in this study were inversely proportional to the previous studies, mainly with a Gleason score > 7. This difference may be due to differences in demographic factors, including awareness of early examination and screening programs.

The role of interaction between PD-1/PD-L1 has been widely studied in

various types of cancer, including prostate cancer.[4,10,14] PD-1/PD-L1 pathway induces apoptosis of effector T-cells, inhibits T-cell activation, and suppresses the anti-tumor immune response.[15-19] Sharma *et al.* showed that the expression of PD-1 and PD-L1 in tumors was detected in 78.2% and 15.0% of cases, respectively.[9,17] Other studies also found positive PD-1 expression (7.7 %-8.0%) and PD-L1 expression (3.7% -92.3%) levels in tumor cells.[9,10,16-19] In healthy prostate tissue or BPH, none showed positive PD-L1 results. PD-L1 expression was significantly more prevalent in the higher T stage and positive lymph nodes.[9] A study by He J *et al.*, who compared carcinoma with benign tissue, found PD-L1 positive expression significantly higher in cancer cases compared with benign tissue.[19] The same results were obtained in this study; PD-L1 expression was significantly higher in prostate cancer compared to BPH. Gevensleben *et al.* also reported that 52.2% of prostate cancer cases post radical prostatectomy had moderate to high PD-L1 expression and were positively associated with proliferation rate (ki-67 expression), Gleason score and androgen receptor expression. These results also indicate that high PD-L1 expression is associated with a more aggressive type of prostate cancer.[20]

The relationship between PD-L1 expression in prostate cancer cells is also associated with a worse prognosis. PD-L1 expression was associated with a significantly higher risk of biochemical recurrence after radical prostatectomy with a hazard ratio (HR) of 1.49-2.37 (p=0.004-0.011).[4] This expression was also associated with a higher risk of metastases (p = .00774).[20] Other data yield opposite results; PD-L1 expression in tumor cells or lymphocytes is only associated with a higher Gleason score but not with clinical T stage and metastasis.[19,21] Our study found no significant differences in PD-L1 expression between non-MPCa and MPCa. The difference in the results of some previous studies may be due to differences in the distribution of cell types. A study by Haffner et al. on metastatic castrate-resistant prostate cancer (mCRPC) showed that in adenocarcinoma, only 7.7% had positive PD-L1 expression. In contrast, in small-cell carcinoma, as many as 42.9% showed positive expression.[14]

The limitations of this study are; first, this study was performed in a retrospective and single institution with a relatively small number of samples, contributing to a low research power. Second, this study only evaluated the differences in PD-L1 expression between prostate cancer and benign form (BPH). However, its role as a risk or predictor factor of prostate cancer outcomes is still questionable and become an exciting topic for further research.

CONCLUSION

PD-L1 expression was significantly higher in prostate carcinoma compared to BPH. However, there was no difference in PD-L1 expression between non-MPCa and MPCa. Using PD-L1 inhibitors in early-stage disease can potentially improve survival and better prognosis.

ETHICAL CONSIDERATIONS

The research was carried out with ethical clearance from the Universitas Gadjah Mada/RSDS Medical and Health Research Ethics Committee, number KE/FK/0109/EC/2022. The identity of the research subjects was kept confidential.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

FUNDING

This research was conducted without grants, sponsors, or other funding sources.

AUTHOR CONTRIBUTION

All authors have made the same contribution in writing the report on the results of this study, from the stage of proposal preparation, data search, and data analysis to the interpretation of research data and presentation of the final report.

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