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LITERATURE REVIEW

PD-L1 as a Potential Therapeutic Target to Immune Checkpoint Blockade in Cervical Cancer: A Review of the Literature

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Abstract: Cervical cancer (CC) is still one of the most common malignant tumors in women worldwide. Malignant tumors are known for evading immune surveillance. In cervical lesions, the mechanism has received less attention. Evasion of immune surveillance through a variety of mechanisms; one of which is the immune checkpoint pathway has attracted interest because it can be therapeutically targeted, the programmed cell death 1 (PD-1) pathway that tumor cells use to block antitumoral immune responses. Increasing the prevalence of PD-L1 expression in up to 80% of cervical malignancies, there is a significant indication using immunotherapy to maintain the immune response against malignancies. The purpose of this literature review is to examine the potential role of immune checkpoint inhibitors in the treatment of cervical neoplastic lesions, by reviewing articles on cervical intraepithelial neoplasia (CIN) and cervical cancer that carried out histopathological and immunohistochemical examination PD-L1 as well as immunotherapy treatment with anti-PD-L1. There were 10 articles were found to be associated with anti-PD-1/PD-L1 immunotherapy. In conclusion, PD-L1 is a potential therapeutic target in cervical cancer.

Keywords: PD-L1, PD-1, cervical intraepithelial neoplasia, cervical cancer, immunotherapy, immune checkpoint inhibitors

INTRODUCTION

Cervical cancer (CC) is one of the most frequent gynecological cancers, with around 570,000 new cases and more than 311,000 deaths per year. The majority of them occurred in developing countries, accounting for 85 percent of the total.[1,2] In 2013, the Indonesian Gynecological Oncology Association recorded 1474 cases of cervical cancer in the country.[3]

The increase in cancer incidence in developing countries can be attributed in part to immune-compromised disorders such as Human Immunodeficiency Virus (HIV), which are linked to a higher risk of persistent and numerous Human Papillomavirus (HPV) infections.[4,5] Human

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Papillomavirus is currently the most common sexually transmitted viral infection in the world; it is also the primary cause of cervical intraepithelial neoplasia (CIN) and CC. The most common carcinogenic strains in humans are high-risk HPV types 16 and 18.[6,7]

Human Papillomavirus integrates its Deoxyribonucleic Acid (DNA) into the cell in the basal columnar junction and produces oncoprotein E6 and E7 which changes the structure of cervical tissues into neoplastic lesions in the form of cervical intraepithelial dysplasia/neoplasia (CIN) and cancer. Theoretically, it is stated that HPV infection causes local cellular immune defects, reduces the body's ability for immunosurveillance, and triggers the development of CIN and cervical cancer. Studies explain that the avoidance of cancer cells from the immune system is one of the important mechanisms in the pathogenesis of cervical cancer.[8,9]

The increasing number of novel molecules that can be studied based on the production of viral antigens in malignant transformation and their diverse antigenicity, can be used as a reference for research on virus-induced cancer. Immunosurveillance is physiologically formed through the initiation of antigen recognition by Antigen Presenting Cells (APC) that activate naive T-cells through the T-cell receptors (TCR). The proliferation of T-cells triggers HPV-specific immune responses by differentiating into effector T-cells to eliminate virus-infected cells. This immune response is initiated via the antigen-peptide Major Histocompatibility Complex (MHC) and is regulated by immunologic checkpoints, which maintain a balance between costimulatory and inhibitory signals. Co-stimulatory antigen-dependent signal transduction between T-cells and APCs leads T-cells to be fully activated.[10,11]

Inhibition of immune checkpoint can occur if cancer cells can escape the T-cell immune response by influencing the action of cellular tumor suppressor products, such as p53, pRb (retinoblastoma protein), and Programmed Cell Death-1/Programmed Death Ligand-1 (PD-1/PD-L1). The dampening of the immune response during inflammation will result in the formation of a tumor microenvironment that favors the development of microinvasive carcinoma and Grade-3 CIN as viral inhibition of the PD-1/PD-L1 pathway attenuates the T- cell response.[12]

Yang et al. reported that the expression of PD-1 and PD-L1 in cervical T-cells and dendritic cells could be associated with the presence of high-risk HPV strains and an increased degree of CIN. The binding of PD-L1 or PD-L2 ligands to PD-1 receptors on T-cells reduces proliferation and can induce apoptosis so that malignant transformation develops.[13] Recent studies have shown that cervical and vulvar squamous cell carcinoma (SCC) exhibit amplified PD-L1 expression. SCC was assessed using Fluorescence In Situ Hybridization (FISH), the genes encoding PD-L1 and PD-L2 namely CD 274 and PDCD1LG2 were amplified and could be found on multiple copies of the same chromosome.[9] In addition, the research conducted by Meng et al., reported that there was an increase in the expression of PD-L1, PD-1, and CD8+

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in cervical cancer tissue compared to normal tissue which could be associated with advanced stages of cervical cancer.[14]

Cervical cancer patients have poor survival rates with conventional chemotherapy. In recent years, better therapeutic strategies have been developed against cervical cancer, one of which is anti-PD-L1 immunotherapy. This choice of therapy has been associated with improved survival outcomes in several types of cancer, including melanoma, lung cancer, kidney, and bladder cells, but information on the clinical significance and increased expression of PD-L1 in cervical cancer are still largely lacking, especially in Indonesia. Anti-PD-L1 immunotherapy may play a role in the treatment of cervical neoplasms. The focus of this research is, therefore, to examine the role of PD-L1 as a potential therapeutic target to immune checkpoint blockade in cervical cancer.

CONTENTS

The design of this research is in the form of a systematic literature review or SLR. The study was carried out from June 2021 - September 2021. The PICO formula was used to conduct a journal review using the keywords and Medical Subject Headings (MeSH) terms were contained: Programmed Cell Death Protein 1, PD-L1, cervical intraepithelial neoplasia, cervical cancer immunotherapy, immune checkpoint inhibitors, PD-L1 immunohistochemistry, cervical cancer chemotherapy, and cervical cancer immunotherapy. Furthermore, we manually searched recommended references from systematic reviews, meta-analyses, and conference proceedings. The journals used in this systematic review were obtained through databases such as PubMed, Scopus, and ProQuest, with research options for articles from the last 5 years.

The search strategy originally generated 1359 relevant clinical studies that were retrieved via database searching. Of these 81 were removed because of repetition. Out of 1278 articles, 4 were excluded because they were non-English, and based on evaluation of the title and abstract, 1068 articles were excluded due to irrelevant research topics. The remaining 206 free full excess articles were scrutinized by a full-text review, using the exclusion and inclusion criteria. 41 studies did not meet the study design of interest, 108 articles did not discuss our outcome of interest, 31 articles studied different cancer cell types and 16 articles detected PD-L1 antigen expression using methods other than immunohistochemical staining. Of which, 10 studies were selected for this systematic review.

The selected journals or research articles were analyzed, extracted and data were synthesized using the Jadad Scale. Our assessments are arranged in table 1.

From the extraction and analysis, it is hoped that a conclusion will be found that can be used as a basis for making referrals for further research can be developed as sustainable research in the development of targeted therapies for cervical cancer patients. A characteristic of the study was made which includes the name of the researcher, year of publication, research title, country of publication, study design, number of samples or specimens, and method. After that, the extracted essence is

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then entered into a table so that the extraction results are easy to read.

Table 1. Jadad scores of the included studies

Author	Was the study described as randomized ?	Was the approach of randomization appropriate?	Was the research described as blinding?	Was the approach of blinding appropriate?	Was there a presentation of withdrawals and dropouts?	Was there a presentation of the inclusion/exclusion criteria?	Was the approach used to assess adverse effects described ?	Was the approach of statistical analysis described ?	*Total*
Reddy et.al., (2017)	1	0	0	0	1	1	1	1	5
Yang et.al., (2017)	1	1	0	0	1	1	1	1	6
Nicol et.al., (2018)	1	1	1	0	0	1	1	1	6
Saglam et.al., (2019)	0	0	0	0	1	0	1	1	3
Ngoi et.al., (2018)	0	0	0	0	1	1	0	1	3
Chen et.al., (2019)	1	0	0	0	1	1	1	1	5
JingJingChen et.al., (2020)	0	1	0	0	1	1	0	1	4
Rotman et.al., (2020)	1	1	1	0	0	1	1	1	6
Chin et.al., (2018)	1	1	1	0	0	1	1	1	6
Liang et.al., (2020)	1	1	1	0	0	1	1	1	6

DISCUSSION

PD-L1 Expression Is Associated with CIN Progression to Cervical Cancer

Persistent Human papillomavirus (HPV) infection plays a major role in the development of cervical cancer. In the study of Reddy et.al., HPV16 (59%) and HPV18 (13%) were associated with SCC cells. They investigated the expression of PD-L1 in human cervical tissue using Tissue Microarray (TMA) and immunohistochemical staining. They found that PD-L1 expression in cervical carcinoma with the highest expression in SCC cell carcinoma. This study provides a rationale for further exploring the expression of PD-L1 in SCC cells.[15]

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In another study, Yang et. al. investigated that HPV may affect the expression of PD-1 and PD-L1 in CIN and the presence of PD-1 and PD-L1 expression is associated with the progression of CIN to SCC. They found that PD-L1 expression increased with increasing CIN value. And PD-L1 expression was significantly higher in SCC, lymphatic tumor embolism, and lymph node metastases. In contrast, Nicol et.al., found that PD-L1 decreased when CIN developed into SCC, indicating that there is a possibility of an important molecular transition during the evolution of CIN to SCC. They hypothesized that over time, as tumors become highly invasive, PD-L1 expression shifts to immune cells. However, Yang et.al. found a positive correlation between PD-L1 expression.[16,17]

Anti-PD-L1 as Immunotherapy for Cervical Cancer Treatment

In terms of anti-PD-L1 as immunotherapy**,** Saglam et.al. reported that although the Food and Drug Administration (FDA) recently approved PD-L1 blockers in advanced cervical cancer, the FDA did not properly define subgroups. which patients benefit the most from the treatment. Some of the challenges in determining the effectiveness of a patient's response to therapy include (1) tumor heterogeneity (2) transient marker expression and; (3) lack of standard PD-L1 readings.[18]

Ngoi et.al. used Combined Positive Score (CPS) to analyze responders and non-responders to pembrolizumab immunotherapy in advanced cervical cancer. In this study, the micro-environment and genetic molecular profile of 4 patients were analyzed. CPS score >1 was observed in patients who achieved symptomatic progression while patients with CPS score = 0 were observed to have rapid symptoms and rapid disease progression. Ngoi et.al. concluded that CPS could help guide the selection of the optimal immunotherapy approach for women with metastatic, persistent, or recurrent cervical cancer.[19]

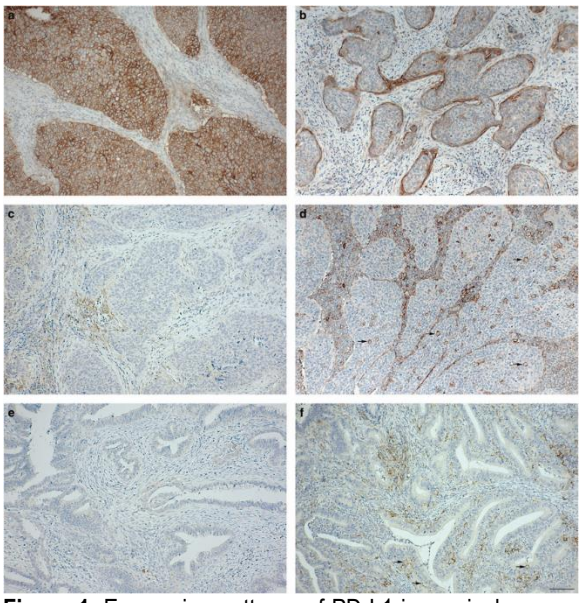

Figure 1. Expression patterns of PD-L1 in cervical cancer. Different PD-L1 expression patterns (in brown) have been detected in primary squamous cell carcinoma and adenocarcinoma. (a) Diffuse expression of PD-L1 by primary carcinoma cells. (b) Marginal expression of PD-L1 by primary carcinoma cells. (c) Primary PD-L1-negative squamous cell carcinoma. (d) Primary squamous cell carcinoma with macrophages associated with PD-L1-positive tumors. (e) Primary PD-L1-negative adenocarcinoma. (f) Primary PD-L1-negative adenocarcinoma with tumor-associated macrophages. (PD-L1 IHC, 100x).[18]

As a continuation of his research, Chen et.al., established an Immunocore to evaluate the prognosis of cervical cancer patients. Chen noted that the traditional method of evaluating cancer staging

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(Tumor/Node/Metastasis (TNM) system) is based solely on the density and location of cancer. Chen's study found that patients with positive TC-PD-L1 had better Overall Survival (OS) and Disease-Free Survival (DFS) compared to TC-PD-L1 negative patients ($p<0.0001$). Patients with CD8+ less tended to have worse OS than those with CD8+ more ($p<0.0025$). In conclusion, TC-PD-L1 positive and CD8+ patients had the best OS and DFS ($p<0.001$). This proves the association between the immune response and immune checkpoint inhibitors. Chen concluded that Immunocore should be a complement to TNM staging.[20]

However, in the following year, Rotman et.al., argued that the patient's response rate to anti-PD-L1 was low so it was not optimal. Rotman evaluated 3 different PD-L1 detection methods; (1) FISH; (2) RNAish; (3) IHC. FISH analysis showed that amplification of the PD-L1/PD-L2 locus was rare, ie 2%. This is because PD-L1/PD-L2 expression in cervical cancer is related to interferon induction and not gene amplification. Rotman also found that PD-L1 mRNA expression in tumor cells was detected in 56% of cases while PD-L1 protein by IHC was only detected in 41%. Rotman concluded that the RNAish method yielded the most sensitive and consistent percentage, he suggested future research to evaluate whether RNAish could serve as a better biomarker than IHC.[21]

Combining anti-PD-1/PD-L1 with Existing Cervical Cancer Chemotherapy

Although the clinical response is impressive in some patients, therapies targeting the PD-1/PD-L1 pathway are not uniformly effective for every patient. Chinn et.al., studied the expression of PD-L1 and Indoleamine dioxygenase-2,3 (IDO) in cervical and vulvar squamous intraepithelial lesions and invasive carcinoma using immunohistochemistry. Indoleamine dioxygenase-2,3 (IDO) is an immunomodulatory enzyme that has immunoinhibition effects and plays a key role in preventing several autoimmune conditions. Chinn et. al. found that cervical SCC frequently exhibits PD-L1 and IDO expression and co-expression in tumor cells and tumor-associated immune cells. Most cervical SCC patients are expected to benefit from combined PD-L1 and SSI therapy.[22]

Another combination study, from Liang et al., found that PD-L1 expression was significantly increased after cisplatin chemotherapy. PD-L1 expression was also found to be associated with CD8+ T cells. This proves that post-chemotherapy increased expression of PD-L1 is induced by adaptive immune resistance due to IFN-γ production from CD8+ T cells. With increased PD-L1 expression and lymphocyte-dominant microenvironment after cisplatin-based chemotherapy, immunotherapy with anti-PD-1/PD/L1 could be more effective in the presence of high PD/L1 expression in tumors. From these studies, it was found that the combination of neoadjuvant chemotherapy with anti-PD-1/PD-L1 immunotherapy has good potential compared to monotherapy.[23]

CONCLUSION

From 10 research literature that has been analyzed, it can be concluded that Human Papillomavirus has been shown to affect PD-L1 expression in cervical neoplastic lesions. There is a significant

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correlation between PD-L1 and the development of NIS into cervical cancer and there have been clinical trials of anti-Programmed Death Ligand 1 as immunotherapy for cervical cancer treatment. It was found that most of the research of anti-PD-L1 immunotherapy was effective for cervical cancer patients, and affected to immune checkpoint blockade in cervical cancer.

REFERENCES

1. WHO. Comprehensive Cervical Cancer Control. Geneva. 2014;366–78.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Rachmadi L, Siregar NC, Kanoko M, Andrijono A, Bardosono S, Suryandari DA, et al. Role of cancer stem cell, apoptotic factor, DNA repair, and telomerase toward radiation therapy response in stage IIIB cervical cancer. Oman Med J. 2019;34(3):224–30.
4. Clifford GM, Tully S, Franceschi S. Carcinogenicity of human papillomavirus (HPV) types in HIV-positive women: A meta-analysis from HPV infection to cervical cancer. Clin Infect Dis. 2017;64(9):1228–35.
5. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Heal. 2020;8(2):e191–203.
6. Fang J, Zhang H, Jin S. Epigenetics and cervical cancer: From pathogenesis to therapy. Tumor Biol. 2014;35(6):5083–93.
7. Bhat P. Human papillomavirus E7 oncoprotein expression by keratinocytes alters the cytotoxic mechanisms used by CD8 T cells. Oncotarget [Internet]. 2018;9(5):6015–27. Available from: https://www.scopus.com/inward/record.uri?partnerID=HzOxMe3b&scp=85040674414&origin=inward
8. Cervical Intraepithelial Squamous Cell Lesion - PubMed.
9. Liu Z, Shi H. Prognostic role of squamous cell carcinoma antigen in cervical cancer: A meta-analysis. Dis Markers. 2019;2019.
10. Qin Y, Ekmekcioglu S, Forget MA, Szekvolgyi L, Hwu P, Grimm EA, et al. Cervical cancer neoantigen landscape and immune activity is associated with human papillomavirus master regulators. Front Immunol. 2017;8(JUN):1–8.
11. Wang RF, Wang HY. Immune targets and neoantigens for cancer immunotherapy and precision medicine. Cell Res [Internet]. 2017;27(1):11–37. Available from: http://dx.doi.org/10.1038/cr.2016.155
12. Sales KJ. Human Papillomavirus and Cervical Cancer. Cancer Inflamm Mech Chem Biol Clin Asp. 2014;40(5):165–80.
13. Yang W, Song Y, Lu YL, Sun JZ, Wang HW. Increased expression of programmed death (PD)-1 and its

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ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia. Immunology. 2013;139(4):513–22.
14. Meng Y. PD-L1 expression correlates with tumor infiltrating lymphocytes and response to neoadjuvant chemotherapy in cervical cancer. J Cancer [Internet]. 2018;9(16):2938–45.
15. Reddy OL, Shintaku PI, Moatamed NA. Programmed death-ligand 1 (PD-L1) is expressed in a significant number of the uterine cervical carcinomas. Diagn Pathol. 2017;12(1):1–11.
16. Nicol AF, de Andrade CV, Gomes SC, Brusadelli MG, Lodin HM, Wells SI, et al. The distribution of novel biomarkers in carcinoma-in-situ, microinvasive, and squamous cell carcinoma of the uterine cervix. Ann Diagn Pathol [Internet]. 2019;38:115–22.
17. Yang W, Lu YP, Yang YZ, Kang JR, Jin YD, Wang HW. Expressions of programmed death (PD)-1 and PD-1 ligand (PD-L1) in cervical intraepithelial neoplasia and cervical squamous cell carcinomas are of prognostic value and associated with human papillomavirus status. J Obstet Gynaecol Res. 2017;43(10):1602–12.
18. Saglam O, Zhou J, Wang X, Conejo-Garcia JR. PD-L1 expression correlates with young age and CD8+ TiL density in poorly differentiated cervical squamous cell carcinoma. Int J Gynecol Pathol. 2020;39(5):428–35.
19. Ngoi NYL, Heong V, Lee XW, Huang YQ, Thian YL, Choo BA, et al. Tumor molecular profiling of responders and non-responders following pembrolizumab monotherapy in chemotherapy resistant advanced cervical cancer. Gynecol Oncol Reports. 2018;24(January):1–5.
20. Chen H, Xia B, Zheng T, Lou G. Immunoscore system combining CD8 and PD-1/PD-L1: A novel approach that predicts the clinical outcomes for cervical cancer. Int J Biol Markers [Internet]. 2020;35(1):65–73.
21. Rotman J. PD-L1 and PD-L2 Expression in Cervical Cancer: Regulation and Biomarker Potential. Front Immunol [Internet]. 2020;11.
22. Chinn Z, Stoler MH, Mills AM. PD-L1 and IDO expression in cervical and vulvar invasive and intraepithelial squamous neoplasias: implications for combination immunotherapy. Histopathology. 2019;74(2):256–68.
23. Liang Y, Yu M, Zhou C, Zhu X. Variation of PD-L1 expression in locally advanced cervical cancer following neoadjuvant chemotherapy. Diagn Pathol. 2020 Jun 3;15(1).