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Expression of PD/PD-L1 as a prognostic bio-marker in ovarian serous carcinoma - A literature review

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SUMMARY

Ovarian cancer has the highest mortality rate of any gynecologic malignancy other. Even after optimal treatment, the prognosis remains poor. To date, no biomarker can predict the individual outcome of a patient with this disease. Two decades of studies have investigated the prognostic value of PD-1/PD-L1 in high-grade serous ovarian carcinoma; many issues remain unclear, controversial, inconsistent, and often contradictory. PD-L1 is an important immunoregulatory factor and, as a receptor for PD-1, plays an important role in inhibiting the immune response to cancer cells, thus negatively regulating T cell functions. The level of expression in PD-L1 is related to the patient's survival rate and prognosis in various types of cancers, including ovarian cancer, particularly serous ovarian carcinoma. The level of expression in PD-L1 increases the potency of tumour immunogenicity, increases the rate of an effective response to immunotherapy treatment, increases the overall survival rate, improves the most favorable prognosis of patients, and is applied in the molecular classification of high-grade serous ovarian carcinoma; therefore a high expression of PD-L1 is considered as an independent and favorable prognostic biomarker in all histological types of ovarian cancers, especially in serous ovarian carcinomas.

Key words: serous ovarian carcinoma, biomarker, PD-1/PD-L1, expression, immunotherapy, prognosis, survival rate

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INTRODUCTION

Ovarian carcinoma is one of the malignant tumors with the highest mortality rate of all gynecologic malignancies [1]. In 2012, 238,700 new cases of ovarian cancer were registered and 151,900 patients died from ovarian cancer [1]. Most patients with ovarian cancer were diagnosed at an advanced stage of the disease due to the absence of specific clinical symptoms, lack of early detection programs and late diagnosis [1]. The 5-year-survival rate in patients with advanced disease is only 20% to 30% [1]. Ovarian epithelial cancer is the most common type of ovarian cancer, accounting for more than 90% of all cases [2]. The current model of ovarian carcinogenesis classifies ovarian epithelial cancer into two types: [3].

Type I tumors are the result of benign lesions outside the ovaries that can progress to malignant lesions. Examples of type I tumors are; endometrial carcinoma, clear cell carcinoma and seromucinous carcinoma, more rarely low-grade serous carcinoma, mucinous carcinoma and Brenner tumours.

Type II tumors develop intraepithelial lesions in the Fallopian tubes and are further classified into three groups: (a) high-grade serous carcinoma, (b) carcinosarcoma and (c) undifferentiated carcinoma [3].Type II tumours account for approximately 90% of ovarian epithelial cancer deaths [3].

High-grade ovarian serous carcinoma is the most common and deadliest subtype of ovarian epithelial carcinoma. Due to the lack of symptoms, it usually only occurs at an advanced stage. Cytoreductive surgery is the most important therapy for treatment success and has survival advantages in patients without macroscopic residual tumor after primary surgery [4].

Surgery is followed by platinum-based adjuvant chemotherapy. Although most women with high-grade serous carcinoma initially respond to treatment, many women develop relapse, in which the cancer cells then develop resistance or are less sensitive to chemotherapy. The advanced stage of the tumor at the time of diagnosis and the development of recurrences are the main reasons for the poor prognosis of this disease. The use of immune checkpoint inhibitor-based antibodies targeting PD-1 and PD-L1 receptors has improved survival for many cancer patients, particularly those with advanced melanoma.

Clinical trials in lung and bladder cancer have also shown longer overall survival [5].

So far, the response rate to immune checkpoint inhibitors in patients with high-grade ovarian cancer seems to be modest [5].

However, there is hope for an increased response rate through patient selection and combination therapies. There is preclinical evidence to suggest that the population of patients responding to polymerase inhibition (PARP) and PD-1/PD-L1 antibodies may be more sensitive, and it is assumed that increased DNA damage from PARP inhibition will increase the number of tumors neoantigens, creating a more antigenic environment in which the immune microenvironment is stimulated [6]. Therefore, the development of prognostic biomarkers is needed to identify the subset of patients who will benefit from treatment. The main focus has so far been on PD-L1 expression in tumor cells, but evaluating this alone is not sufficient for patient selection in most malignant tumors. The map of PD-1/PD-L1 expression in immune cells in high-grade serous carcinoma is clinically important because, in addition to its prognostic value, it can provide important information for further investigating its potential to predict treatment response to immunotherapy.

The programmed death receptor 1 (PD-1) was first described in the early 1990s, highlighting its role in expression [7]. Programmed Death 1 (PD-1, CD-28) is an immune checkpoint receptor of the CD-28 family and is expressed on the surface of activated T cells, B cells and other immune cells, particularly dendritic (DCs) cells, [8]. The major ligand of PD-1 is PD-L1, [9]. PD-1 is a receptor that binds to PD-L1. PD-L1 is expressed on the surface of tumor cells [8].

Programmed Death Ligand-1 (PD-L1) is a surface glycoprotein belonging to the B7/CD-28 co-stimulatory factor family and is constitutively expressed in specific tumor cells and immune cells (macrophages). The interaction of PD-1 and PD-L1 inactivates T cells by reducing or impairing the function of immune cells that infiltrate the tumor and weaken tumor immunogenicity. Therefore, tumor immunogenicity and expression in PD-1/PD-L1 are essential features for the molecular classification of high-grade serous ovarian carcinoma.

Physiologically, the programmed death receptor 1 (PD-1) is clearly expressed on the surface of activated T cells. Its ligands PD-L1 and PD-L2 are extensively expressed on the surface of dendritic cells, macrophages, activated vascular endothelial cells and mesenchymal stem cells [8]. Antigen-presenting dendritic cells can increase tumour immunogenicity by identifying, taking up, processing, and presenting tumour-related antigens that activate T cells. Since dendritic cells can enhance immunogenicity, the dendritic cell infiltration rate and the potency of immunogenicity can be indicated by the expression level in PD-1/PD-L1 [8].

The PD-1/PD-L1 expression level can also be considered a predictor of the infiltration rate of antigen-presenting cells, which benefit greatly from anti-PD-1/PD-L1 immunotherapy [8]. Although protein expression can be detected on the surface of PD-1 cells within 24 hours after stimulation, the functional effects of PD-1 binding are observed within a few hours after T cell activation [9-11].

PD-1 and its ligands, PD-L1 and PD-L2 expressed within the tumor microenvironment, may modulate the balance between T cell activation, tolerance, and immunopathology during long-term exposure to the antigen, [12]. To avoid monitoring of the immune system, tumor cells in the tumor microenvironment can regulate PD-L1 expression through a variety of mechanisms and bind to the PD-1 negative immune control point on the surface of T cells, thus inhibiting T cell function, and losing its lethal effect on tumor cells [13].

The expression of PD-L1 in cancer cells is believed to represent the classic resistance of adaptive immunity in cancer. It was found that IFN as a promoter of PD-L1 in tumor cells plays an essential role in tumor adaptive immune resistance [13, 14].

PD-L1 is expressed in several types of tumors such as melanoma, glioblastoma, lung cancer, kidney cancer, head and neck cancer, gastric, colon, pancreatic, breast, cervical and ovarian cancer [14,15]. Monoclonal antibodies (mAbs) that inhibit or block the PD-1/PD-L1 pathway have been developed to treat cancer by enhancing T-cell functions. By targeting PD-1 and PD-L1, immune checkpoint inhibitors can reactivate cytotoxic T cells to act against cancer cells. Attempts to use monoclonal antibodies (mobs) to inhibit PD1/PD-L1 interactions have ushered in a new era of immunotherapy-based cancer treatments. This therapy aims to increase tumor immunogenicity and antitumor immunity [16-18].

Immunotherapy for cancer treatment focuses on shifting the balance from a tumor-promoting microenvironment to an anti-tumour environment; As a result, it allows the immune system to maximize an effective anti-tumour response. PD-L1 is expressed by tumor cells [19] to inactivate T cells through binding to PD-1 [20, 21] and to escape from the immune system, [19].

PD-L1 inhibitors pharmacological block the PD-1/PD-L1 interaction, thus enhancing the body's immune response to the destruction of cancer cells, [22,23]. The evolution of immune checkpoint inhibitors as a new option in cancer treatment represents one of the most successful approaches to the detection of cancer drugs in recent years [24]. Indeed, immune checkpoint inhibitors have emerged as a first-line treatment for multiple cancers, such as; metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, breast cancer, head and neck cancer, ovarian cancer, and some advanced hematologic tumours [21]. Examples of PD-L1-targeting immunosuppressive inhibitors include atezolizumab, avelumab, pembrolizumab, and durvalumab, [22, 25]

CORRELATION BETWEEN PD-L1 EXPRESSION AND CLINICOPATHOLOGICAL FACTORS OF SEROUS OVARIAN CARCINOMA

It is now known that tumor cells can express PD-L1. Furthermore, it has been reported that the expression level in PD-L1 is associated with patient survival and prognosis in

various cancer types including ovarian cancer, especially serous ovarian carcinoma [26, 27].

In serous ovarian carcinoma, high expression of PD-L1 in tumor-infiltrating stromal lymphocytes, tumor cells and tumor-infiltrating intraepithelial lymphocytes was observed at 20.7% to 63.2% [28].

The stromal expression of PD-L1 is an independent prognostic factor in all histological types of ovarian cell carcinoma, including serous ovarian carcinoma [28]. In the analysis of patients with serous ovarian carcinoma, only high stromal PD-L1 expression was associated with an increased overall survival rate and acted as an independent prognostic factor for residual tumour and tumour stage [28].

Hamanishi et al. [29] Performed immunostaining of PD-L1 with their clone and reported the clinical significance of PD-L1 expression in ovarian cancer. They only assessed PD-L1 expression in tumour cells and classified patients with high and low PD-L1 expression solely based on their intensity. They showed that high PD-L1 expression was associated with increased progression-free overall survival and that PD-L1 was an independent and poor prognostic factor.

Kunze CA et al. [30] Performed immunostaining for PD-L1 using clone EPR1161 and interpreted PD-L1 expression in both tumor cells and tumour-infiltrating lymphocytes according to a semi-quantitative result of immunoreactivity in high grade serous ovarian carcinoma. The result showed that both PD-L1 and PD-L1-positive membrane tumour-positive groups of tumor-infiltrating lymphocytes were associated with increased progression-free survival. However, only the PD-L1 membrane tumor was an independent prognostic factor.

Webb et al. [31] performed PD-L1 immunostaining in ovarian cancer using two PD-L1 clones, SP142 and E1L3N. They classified patients with PD-L1 expression in more than one cell as a PD-L1 positive group and showed that PD-L1 positivity in high-grade serous carcinoma was an independent prognostic factor conducive to disease-specific survival.

Although all of the above studies have shown that PD-L1 expression is associated with ovarian cancer prognosis, it is unclear whether PD-L1 expression is associated with prognosis in any part of the tumour. The results showed that only PD-L1 expression in tumour-infiltrating stromal lymphocytes was significantly associated with overall survival and was favorable as an independent prognostic factor for all histological types of ovarian cancer, especially serous ovarian cancer [28].

Theoretically, PD-L1 plays a role in inhibiting tumor-specific T cells, whether they are expressed in tumor cells or in immune cells. Thus, the beneficial prognostic effect of tumor-infiltrating stromal lymphocytes expressing PD-L1 contrasts with the role of PD-L1. Studies have shown that T cells expressing PD-L1 can directly overcome the immunosuppressive tumor microenvironment, which explains the favorable prognostic effect of stromal PD-L1 expression. Therefore, it is necessary to further study the more detailed components of tumor-infiltrating stromal lymphocytes and to identify which subtype of stromal tumor-infiltrating lymphocytes expressing PD-L1 has clinical importance, especially a favorable prognostic effect on ovarian cancer [28].

The results of these studies show that PD-L1 expression in tumour-associated lymphocytes is also important for the therapeutic effect of immune checkpoint inhibitors. Therefore, the level of PD-L1 expression of tumour-infiltrating lymphocytes can be a predictor of the response to immunotherapy in serous ovarian carcinoma [28]. This indicates that the expression of PD-L1 in tumour-infiltrating stromal lymphocytes can be a very important factor in the prognosis of patients with serous ovarian carcinoma [28].

Furthermore, high expression of PD-L1 in infiltrating tumour intraepithelial lymphocytes was associated with increased overall survival and could be a prognostic factor for response to immunotherapy, but these data require additional research to confirm [28].

PROGNOSTIC ROLE OF PD/PD-L1

Ovarian cancer has the highest mortality rate of any gynecologic malignancy. Even after optimal treatment, the prognosis remains poor. To date, no biomarker can predict the individual outcome of a patient.

Numerous studies have investigated the prognostic value of PD-L1 and PD-1 in high-grade serous ovarian carcinoma, where many issues remain unclear, controversial, inconsistent, and often contradictory. Initially, it was assumed that PD-L1 is expressed only in tumour cells, but today it has been proven that; the main cells that express PD-L1 are macrophages and that PD-1 is expressed almost exclusively by lymphocytes.Therefore, the assessment of PD-L1 expression in immune infiltrates, in addition to tumour cells, can provide a clearer picture in terms of prognosis [31].

PD-L1 is an important immunoregulatory factor and, as a receptor for PD-1, plays an important role in inhibiting the immune response to cancer cells, thereby negatively regulating T cell functions. The binding of PD-1 to its ligand PD-L1 impairs the activation and differentiation of T cells [31].

Although the PD-1/PD-L1 pathway is a negative regulator of T-cell activation, women with tumours; with high PD-1 expression in intraepithelial lymphocytes and with high PD-L1 expression in macrophages survive longer [31].

In patients with high-grade ovarian carcinoma, high expression of PD-1 in intraepithelial lymphocytes (CD3) and PD-L1 in macrophages is a predictor of a significant reduction in the risk for death in patients with this pathology, despite age when it was diagnosed, stage of the tumour, and residual tumour after primary surgery [31].

The expression of PD-1 in lymphocytes and PD-L1 in macrophages within the tumor epithelium offers a significant survival advantage in high-grade serous ovarian carcinoma [31].

Buderath P et al. [32]. found that the presence of PD-1-positive tumour-infiltrating immune cells was significantly associated with prolonged overall survival. This favourable prognosis

supports the hypothesis that the expression of PD-1 and PD-L1 in tumour-infiltrating immune cells represents a strong immune response.

PD-L1 expression has the potential to be a prognostic biomarker, guiding physicians in selecting individuals who might clinically benefit f rom a nti-PD-1/PD-L1 immunotherapy. Therefore, accurate and possible prognostic factors must be verified to better guide personalized treatment and improve treatment outcomes, both in terms of overall survival and survival without progression of ovarian cancer patients. PD-1 / PD-L1 have a prognostic and predictive role, helping to classify the molecular subtypes of high-grade serous ovarian carcinoma.

The PD-1/PD-L1 expression level can be considered a predictor of the infiltration rate of the antigen-presenting cells. Patients with high antigen-presenting cell infiltration may have high immunogenicity and a satisfactory prognosis (since a highly immunogenic tumor may benefit greatly from anti-PD-1/PD-L1 immunotherapy). Strong immunogenicity can contribute to an effective response to immunotherapy.

CONCLUSION

Programmable Death-1 (PD-1) is an immune checkpoint receptor of the CD-28 family and is expressed on the surface of activated T cells, B cells and other immune cells, particularly dendritic cells and lymphocytes. PD-1 is a receptor that binds to the programmed cell death ligand 1 (PD-L1) expressed on the surface of tumor cells and immune cells (e.g., macrophages, stromal lymphocytic infiltration associated with tumors, activation of endothelial cells). The interaction of PD-1 and PD-L1 can prevent T cell activation by reducing or impairing the function of tumor-infiltrating immune cells and weakening tumor immunogenicity. Many studies indicate that PD-1 and PD-L1 molecules are biologically important regulators of the immune response in serous ovarian carcinoma and that the introduction of immunosuppressive inhibitory drugs may be valuable in this type of cancer with a prognosis of weak. PD-L1 is an important factor as an immune regulator, and as a receptor for PD-1, it plays an important role in inhibiting the immune response to cancer cells. PD-L1 inhibitors pharmacological block the PD-1 / PD-L1 interaction, thus enhancing the body's immune response to the destruction of cancer cells. The map of PD-1/PD-L1 expression in immune cells in serous ovarian carcinoma is clinically important because, in addition to its prognostic value, it can provide important information to predict treatment response to immunotherapy. The level of expression in PD-L1 is related to the patient's survival rate and prognosis in various types of cancers, including ovarian cancer, particularly serous ovarian carcinoma. The level of expression in PD-L1 increases the potency of tumour immunogenicity, increases the rate of an effective response to immunotherapy treatment, increases the overall survival rate, improves the most favorable prognosis of patients, and is applied in the molecular classification of high-grade serous ovarian carcinoma; therefore a high expression of PD-L1 is considered as an independent and favorable prognostic biomarker in all histological types of ovarian cancers, especially in serous ovarian carcinomas, and is widely explored.

AUTHOR'S CONTRIBUTIONS

All authors read and approved the final version of the manuscript.

INFORMED CONSENT

Informed consent was not needed.

CONFLICT OF INTEREST

The authors declare that there is no financial interest or conflict of interest

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