Journal of Biosciences and Medicines, 2023, 11, 1-8
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

A Review of the Impact of PD-L1 Expression on the Prognosis of Small Cell Lung Cancer

Pan Zhu, Yanhua Xu*

Department of Oncology, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: *1773293648@qq.com

How to cite this paper: Zhu, P. and Xu, Y.H. (2023) A Review of the Impact of PD-L1 Expression on the Prognosis of Small Cell Lung Cancer. *Journal of Biosciences and Medicines*, **11**, 1-8.
https://doi.org/10.4236/jbm.2023.117001

Received: June 4, 2023
Accepted: July 4, 2023
Published: July 7, 2023

Abstract

Small cell lung cancer is an invasive neuroendocrine carcinoma with early metastasis potential. It tends to grow rapidly and metastasize early, with the majority of patients diagnosed as advanced stage small cell lung cancer (ES-SCLC). Systemic treatment consisting of platinum drugs and etoposide chemotherapy is the main treatment method, although the objective effective rate of this combination is 60% - 80%. However, most SCLC patients experience disease progression shortly after initial treatment, with a median overall survival of 10 months. There are few second-line treatment drugs available, and immunotherapy using checkpoint inhibitors has completely changed the treatment of many cancer types. Adding immune checkpoint inhibitors (ICI) to conventional chemotherapy as first-line treatment can improve the survival rate of widespread small cell lung cancer (ES-SCLC), but so far, there are no definitive factors to determine patients who are more likely to benefit from immunotherapy. This review summarizes the results of immunotherapy trials for small cell lung cancer. And a review was conducted on the predictive factors of these trials, with special emphasis on the expression of PD-L1 in small cell lung cancer to determine its clinical value.

Keywords

Small Cell Lung Cancer, PD-L1, PD-1, Immunotherapy

1. Introduction

Lung cancer is the number one killer affecting national health. Both the incidence rate and mortality rate rank first in malignant tumors. Small cell lung cancer (SCLC) accounts for 10% - 15% of the total number of lung cancer. SCLC is closely related to smoking. Lung cancer causes about 150,000 deaths worldwide every year: almost all deaths are related to smoking. The number of muta-

tions found shows that SCLC cells have a very high number of somatic cell non synonymous mutations (tumor mutation burden, TMB), which are reported to be 7.4 - 8.62 mutations per million bases [1] [2] [3]; The high mutation load characteristic of SCLC promotes the development of immune checkpoint inhibitors as single drugs or in combination with chemotherapy. The IMPower133 [4] Ctrial is the first clinical trial to demonstrate that immunotherapy combined with chemotherapy can prolong patient PFS and OS compared to current standard chemotherapy in first-line treatment of ES-SCLC. The combination of chemotherapy and immunotherapy can bring significant benefits to the treatment of small cell lung cancer. Future strategies to improve first-line treatment outcomes for patients should explore biomarkers to predict treatment efficacy and explore new combination therapy strategies.

2. PD-1 and PD-L1

PD-1 receptor (also called CD279) is a transmembrane protein and a co inhibitory receptor, which exists on the surface of T cells, B cells, monocytes and activated natural killer cell [5] [6]. Naturally, it interacts with two ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273) expressed in antigen presenting cells (APCs) [7] [8], PD-L1 is considered as the main effector of PD-1 dependent immunosuppression [9]. Programmed cell death ligands (PD-L) 1 and 2 are ligands for the programmed cell death 1 (PD-1) receptor. PD-L1 is mainly expressed on T cells, B cells, macrophages, and dendritic cells, while PD-L2 is expressed on APC (antigen presenting cells) and T helper cells [10] [11] [12]. They are members of the B7/CD28 ligand receptor family and are currently the most studied inhibitory immune checkpoint. A retrospective study showed that a comprehensive analysis of subgroups of first-line ICIs patients, second-line or later treatment ICIs patients, patients aged ≥ 62 years and <62 years who received ICIs, patients with bone metastasis and patients without bone metastasis who received ICIs showed that PD-1 and PD-L1 inhibitors may achieve significant survival benefits and safety in ES-SCLC patients [13].

3. Tumor Immune Escape Mechanism

When the programmed death ligand 1 (PD-L1) on the surface of cancer cells binds to the receptor (PD-1) on cytotoxic t cells, it inhibits T cell activation and cytotoxicity, leading to one of the mechanisms of tumor immune escape [8]. Immunotherapy means that PD-1 and CTLA-4 on T cells combine with PD-L1 on cancer cells to activate the immune activity of T cells. The activation of t cells ensures the upregulation of PD-1 and the production of cytokines, which also upregulate the expression of PD-L1, creating a positive feedback mechanism, which plays an important role in preventing tissue destruction and the development of autoimmunity. The understanding of ICI is based on the PD-1/PD-L1 axis, and in some studies, PD-L1 expression has been evaluated as a potential predictive biomarker for the efficacy of ICI in small cell lung cancer [14] [15].

However, despite some correlations observed, there is a lack of specific evidence to support the use of PD-L1 expression levels as a predictive biomarker for immunotherapy responses in SCLC.

4. Comparison of PDL1 Expression in SCLC and NSCLC for Survival Rate and Response to Inhibitors

A meta-analysis [16] included 50 articles published between 2011 and 2017 related to immunohistochemical (IHC) detection of PD-L1 expression and prognosis in cancer patients. Including 11,383 patients, out of 50 studies, 24 focused on the expression of PD-L1 in non-small cell lung cancer (NSCLC), 12 focused on adenocarcinoma (ADC), 5 focused on squamous cell carcinoma (SCC), 3 focused on small cell lung cancer (SCLC), 2 focused on pulmonary lymphoepithelial tumor like carcinoma (LELC), 1 focused on lung sarcomatoid carcinoma, 1 focused on high-grade neuroendocrine tumor (HGNET), and 1 focused on pulmonary pleomorphic carcinoma (PPC), and 1 focus on pleomorphism, spindle cell, and giant cell lung cancer (PSCHCC). PD-L1 expression was found in 4293 participants (37.7%), although the definition of PD-L1 positive expression varies in the study. The combined overall survival rate (OS) was used to evaluate the relationship between PD-L1 expression and prognosis, while the combined odds ratio (OR) was used to investigate the correlation between PD-L1 expression and clinical pathological features. The results showed that all 50 studies, including 11,383 patients, evaluated the correlation between PD-L1 expression and OS. The comprehensive results (HR = 1.45, 95% CI: 1.24 - 1.68) indicate that overexpression of PD-L1 exhibits a shorter OS and a 45% increase in mortality in cancer. Subgroup analysis was performed on OS based on histology, TNM staging, sample type, threshold, ethnicity, and PD-L1 IHC determination. According to histological subgroup analysis, high PD-L1 expression significantly reduced OS in non-small cell lung cancer patients (HR = 1.35, 95% CI: 1.13 - 1.61), ADC patients (HR = 1.79, 95% CI: 1.22 - 2.64), SCC patients (HR = 7.79, 95% CI: 1.39 - 2.32), and LELC patients (HR = 3.04, 95% CI: 1.19 - 7.77), but PD-L1 expression was not associated with survival in small cell lung cancer patients (HR = 1.05, 95% CI: 0.39 - 2.78).

The expression of PD-L1 in SCLC showed highly variable results of 0 - 71.6% [17] [18] [19], The study of 71.6% PD-L1 expression used commercial rabbit monoclonal antibodies (Abcam, Cambridge, UK) [18]. A study [20] compared the levels of biomarkers, including PD-L1, B7-H3, B7-H4, CD3, CD8, CD20, and whole cell keratin, with those obtained in a retrospective cohort of lung adenocarcinoma (LADC) and lung squamous cell carcinoma (LSCC) using the same QIF (multiple quantitative immunofluorescence) assay method and analysis platform. The results showed that all TIL markers of SCLC were significantly lower in water on average than LADC and LSCC ($P = 0.01$, $P < 0.0001$). This study tested a total of 90 SCLC samples, with a positive rate of 7.3% for PD-L1 protein, and there was no significant correlation between high PD-L protein le-

vels and 5-year overall survival. Non small cell lung cancer (NSCLC) patients who exhibit high expression levels tend to have more favorable responses to PD-1 and PD-L1 inhibitors [21] [22] [23]. KEYNOTE-001 and KEYNOTE-010 studies have shown that patients with advanced NSCLC with PD-L1 expression ≥ 50% are more likely to respond to treatment with the pd-1 immune checkpoint inhibitor pembrolizumab [24]. According to reports, the expression frequency of PD-L1 in SCLC cells is lower than that in NSCLC (10% - 40% vs 66%) [25] [26] [27]. In summary, the expression of PD-L1 in SCLC is lower than that in NSCLC, and the proportion of PD-L1 protein expression in SCLC varies greatly. The biological determinants of this difference are still unknown, and these differences can be explained using different IHC analysis, analysis platforms, and hierarchical entry points. High PD-L1 expression significantly reduces the survival rate of NSCLC, but there is no significant correlation between PD-L1 expression and survival rate in small cell lung cancer patients. NSCLC with high PD-L1 expression rate is more favorable for the response to inhibitors, but the predictive value of tumor PD-L1 expression in SCLC is still unclear.

5. The Effect of PD-L1 Expression Rate on the Treatment of Small Cell Lung Cancer

A phase II experiment: the results of the KEYNOTE-158 [27] cohort study of SCLC were presented at the 2018 ASCO annual meeting. In this Phase II trial, 107 patients with recurrent SCLC received pembrolizumab 200 mg every three weeks, regardless of PD-L1 status. The primary endpoint of this study was ORR, while DOR, PFS, and OS were secondary endpoints. In the study population, 85 patients (79%) received more than 2 previous treatments, 42 patients (39%) were PD-L1 positive SCLC, and 50 patients (47%) were PD-L1 negative SCLC. Evaluate PD-L1 positivity in the pharmDx test by cloning 22C3 with anti PD-L1 antibody. According to the PD-L1 status, the ORR of PD-L1 positive patients (35.7%) is significantly higher than that of PD-L1 negative patients (6.0%). In addition, the median OS of patients with PD-L1 positive and PD-L1 negative tumors was 14.6 (95% CI 5.6 inexplicable) and 7.7 months (95% CI 3.9 - 10.4), respectively.

A randomized, double-blind, phase I/III study IMpower133 [6], In this study, untreated ES-SCLC patients were randomly assigned 1:1 to receive 4 cycles of CP (5 mg/mL/min intravenous injection [IV], day 1) + ET (100 mg/m^2 IV, days 1 - 3) and atezolizumab (1200 mg IV, day 1) or placebo, Then maintain atezolizumab or placebo until unacceptable toxicity, disease progression, or loss of clinical benefits.PD-L1 testing is not required when collecting tumor specimens for registration. The two main endpoints, PFS and OS, were evaluated by the researchers. The results showed that patients received atezolizumab plus CP/ET treatment (5201 cases) or placebo plus CP/ET treatment (5202 cases).The median OS of atezolizumab plus CP/ET group and placebo plus CP/ET group were 12.3 and 10.3 months, respectively (hazard ratio 0.76; 95% CI, 0.60 - 0.95; P =

0.05154). At 18 months, the survival rates of patients in the atezolizumab + CP/ET group and placebo + CP/ET group were 34.0% and 21.0%. PD-L1 detection was performed using the PD-L1 immunohistochemistry (SP263) method on the Ventana Bench Mark ULTRA automated staining platform, A study [28] showed that the only clone with expression levels higher than the low range in SCLC cases was SP263 (44.9% [29]). Given these findings, SP263 seems to be a feasible antibody clone that can be used to detect the expression of PD-L1 in patient tissues and has high therapeutic efficacy. If the percentage of TC expressing PD-L1 at any intensity is 1%, or if the proportion of IC expressing PD-L1 in the tumor area at any intensity is 1%, the sample is considered PD-L1 expression positive; Due to the absence of PD-L1 immunohistochemistry (IHC) validated thresholds in SCLC, the prevalence of PD-L1 was gradually evaluated based on non SCLC (NSCLC) PD-L1 immunohistochemistry thresholds: 1%, 5%, 25%, and 50% TC or IC. The results showed that regardless of PD-L1 immunohistochemistry or bTMB status, patients could benefit from the addition of atezolizumab, and the expression of PD-L1 did not predict the degree of benefit of this experiment.

A study [30] comprehensively analyzed data from the SCLC cohort in KEYNOTE-028 and KEYNOTE-158 studies, Among the 131 SCLC patients included in these two studies, this comprehensive efficacy and safety analysis included 83 patients with recurrent or metastatic SCLC (19 from KEYNOTE-028 and 64 from KEYNOTE-158); Patients receiving pembrolizumab treatment (KEYNOTE-028 group 10 mg/kg every 2 weeks or KEYNOTE-158 group 200 mg every 3 weeks); The primary endpoint of both studies was ORR; Secondary endpoints include response duration, progression free survival (PFS), overall survival (OS), as well as safety and tolerability. In these two studies, the status of tumor PD-L1 was centrally evaluated. In KEYNOTE-028, tumor samples were evaluated using laboratory developed prototype immunohistochemistry analysis and 22C3 antibody clones. If the sample exhibits membrane PD-L1 expression in at least 1% of tumors and related inflammatory cells or positive staining in the matrix, it is considered PD-L1 positive. In KEYNOTE-158, PD-L1 expression was evaluated using the PD-L1 IHC 22C3 pharmDx method, and samples with a PD-L1 combined positive score of at least 1 were considered positive. The combined positive score is the ratio of PD-L1 positive cells (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells multiplied by 100. The results showed that the combined analysis had an ORR of 19.3%, while the overall ORR of KEYNOTE-158 was 18.7%. Patients were enrolled regardless of their PD-L1 status, while KEYNOTE-028 had an ORR of 33.3%, and only PD-L1 positive tumor patients were enrolled. The median OS and PFS (7.7 and 2.0 months, respectively) observed in this combined analysis were similar to the overall population (9.7 and 8.7 months, respectively, for KEYNOTE-028 and KEYNOTE-158, with a median PFS of 1.9 and 2.0 months, respectively). 51 patients (61.4%) experienced any level of treatment related adverse events; Eight

patients (9.6%) experienced level 3 or higher events. The final results indicate that Pembrolizumab exhibits persistent anti-tumor activity in patients with recurrent or metastatic SCLC who have previously received two or more treatments, regardless of PD-L1 expression. The KEYNOTE-158 study (including patients from the SCLC cohort) showed that patients with high tumor mutation burden had a higher response rate than those without high tumor mutation burden.

6. Conclusion

In summary, the impact of PD-L1 expression level on the treatment of small cell lung cancer is not clear. Immunotherapy combined with chemotherapy significantly improves the survival rate of small cell lung cancer, but for patients with the greatest benefit, exploration is still needed to maximize treatment efficiency, explore biomarkers for predicting treatment response, and explore multi-drug combination therapy such as chemotherapy combined with immunotherapy combined with anti-vascular therapy, Extending the survival period and improving the quality of life of small cell lung cancer patients to the greatest extent possible may become an inevitable trend in future research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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