Available online at www.sciencedirect.com

ScienceDirect

EJSO 41 (2015) 450–456

EJSO the Journal of Cancer Surgery

www.ejso.com

Review

The prognostic value of PD-L1 expression for non-small cell lung cancer patients: A meta-analysis

A. Wang [a,f], H.Y. Wang [b,f], Y. Liu [c,f], M.C. Zhao [a], H.J. Zhang [d], Z.Y. Lu [a], Y.C. Fang [a], X.F. Chen [a,d,*], G.T. Liu [e,**]

[a] Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Shanghai, China
[b] Central Laboratory, Shanghai Pulmonary Hospital, Shanghai, China
[c] Department of Radiotherapy, Shanghai Pulmonary Hospital, Shanghai, China
[d] Department of Cardiothoracic Surgery, Huashan Hospital, Fudan University School of Medicine, Shanghai, China
[e] Center for Translational Medicine, Shanghai Pulmonary Hospital, Shanghai, China

Accepted 24 January 2015
Available online 31 January 2015

Abstract

Background: A meta-analysis was conducted to investigate the much-debated relationship between the gene expression of programmed cell death-ligand 1 (PD-L1) and cancer patient prognosis. The prognostic value of measuring PD-L1 expression in non-small cell lung cancer (NSCLC) patients was analyzed.

Methods: We searched PubMed for studies about the relationship between PD-L1 expression and NSCLC patient prognosis. Only studies with patient survival data related to PD-L1 expression in NSCLC patients with different characteristics were included. The effect size (ES) for this analysis was the hazard ratio (HR) with 95% confidence intervals (CI) for overall survival (OS).

Results: Six studies with 1157 patients were included with the defined including and excluding criteria. There is no significant heterogeneity among the studies ($I^2 = 0\%$, $p = 0.683$). PD-L1 expression was significantly associated with the differentiation of tumor (poor vs. well: OR = 1.91, 95% CI: 1.33−2.75, $p = 0.001$). High PD-L1 expression was also correlated with poor prognosis in terms of the OS of patients with NSCLC (pooled HR = 1.75, 95% CI: 140−2.20, $p < 0.001$; heterogeneity test: $I^2 = 0\%$, $p = 0.643$).

Conclusions: NSCLC patients with positive PD-L1 expression exhibited poor OS. The PD-L1 expression was higher in tumors with poor differentiation.

Keywords: Programmed cell death-ligand 1; NSCLC; Prognostic; Overall survival; Differentiation

Introduction

Lung cancer is the most common cause of cancer death, and is the most commonly diagnosed cancer in men and the fourth most commonly diagnosed cancer in women.[1] In China between 1990 and 2010, the death rate due to cancer went from the 13th to the 5th most common cause of death.[2] Approximately 85% of patients with lung cancer are diagnosed with non-small cell lung cancer (NSCLC) and 80% of lung cancer were diagnosed with late stage.[3,4] The survival rate and prognosis of patients with late stage NSCLC is extremely low.[5]

The development of cancer is a complex progress in which, T cells in the host's antitumor immune system play an important role. To evade recognition by the host's immune system, cancer cells can induce T cell non-responsiveness by expressing certain ligands which act on

* Corresponding author. Department of Cardiothoracic Surgery, Huashan Hospital, Fudan University School of Medicine, Shanghai, China. Tel.: +86 13901717039.
** Corresponding author.
E-mail addresses: Dr_chenxiaofeng@126.com (X.F. Chen), liugt@tongji.edu.cn (G.T. Liu).
[f] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejso.2015.01.020
0748-7983/

specific immune checkpoint pathways such as programmed cell death-1pathway.[6,7] In 1999, the first duplication of programmed cell death-1 (PD-1) (B7-H1) was created based on its DNA sequence.[8] PD-1, an immune checkpoint which is expressed on the surface of T, B and NK cells, is a surface-receptor member of the B7-CD28 superfamily.[6,9] The key role of the PD-1 pathway plays in blunting the T cell immune function was confirmed for the first time in PD-1 knockout mice.[10] Cells that express PD-1 evade T cell immunity via mechanisms such as exhaustion, apoptosis and anergy, and thereby defend tumor cells from cytolysis.[11] Programmed cell death-ligand 1, the major ligand for PD-1, is a cell surface protein in the B7 family which is found in tumor specimens from NSCLC patients.[6,12]

In recent years, PD-L1 expression has been studied in several cancers, including breast, gastric, pancreatic, ovarian cancer, renal cell carcinoma, melanoma and glioblastoma.[13–19] And the overexpression of PD-L1 indicated better prognosis in glioblastoma patients, yet the opposite result of PD-L1 was reported in gastric cancer.[15,19] In addition, the predictive role of PD-L1 for anti-PD-1/PD-L1 immunotherapy in cancer patients has raised people's attention.[20,21] The association between abnormal PD-L1 expression and NSCLC survival has also been investigated. The prognostic value of PD-L1 expression remains controversial.[6,22–26] Because some studies of PD-L1 expression have relied on relatively small sample sizes with limited statistical power, it is necessary to assess the possible association between PD-L1 and the prognosis for NSCLC patients using an up-to-date meta-analysis.

Materials and methods

Search strategy

Relevant studies in English were searched in the database of PubMed with the following terms: "Programmed cell death-ligand 1", "PD-L1", "B7-H1" and "lung cancer". The last search was conducted on August 26, 2014. If necessary we also searched the Cochrane Library. When the same patients were included in different publications, the most recent study was used for analysis.

Inclusion and exclusion criteria

Qualified studies were gathered in accordance with the following inclusion criteria: (1) the histology type of cancer was NSCLC; (2) valid TNM stage and cancer differentiation data, as well as sufficient survival data, such as hazard ratio (HR) or relative ratio (RR) with 95% confidence intervals (CI), overall survival (OS) was estimated using the Kaplan–Meier method; (3) published in English; (4) evaluated the association between PD-L1 expression and prognosis or pathological features; (5) patients' prognosis were assessed by OS; (6) similar research experimental design and methods; (7) PD-L1 expression was divided into high (positive) and low (negative) categories; and (8) relevant information could be extracted from the full-text study. Exclusion criteria included: (1) duplicate reports, ongoing studies, letters, conference papers and reviews; (2) studies about lung cancer cell lines, animal models and other types of cancer; (3) studies with insufficient survival data for which HR and CI could not be determined; (4) papers not in English; (5) methods and experimental design distinct different from those of the selected studies; and (6) the sample size is fewer than 100 patients.

Data extraction

To find all eligible research, two investigators independently searched the databases used in this paper for potential records on the basis of the inclusion criteria. The following information was extracted from the eligible studies: first author surname, publication year, geographic region, lung cancer histology, cancer stage, PD-L1 detection method, sample size, and expression-related survival. Table 1 shows the included studies' specific clinical characteristics. Disagreements were settled by the discussion among the authors.

Statistical analysis

The effective value used in this meta-analysis to evaluate the relationship between PD-L1 expression and NSCLC prognosis was the HR. Meanwhile, pooled odds ratio (OR) with 95% CI were appropriate for the association between PD-L1 expression and clinical characteristics. When the HR > 1, a poor prognosis for NSCLC patients was indicated by positive PD-L1 expression. If the article provided the HR or RR with 95% CI, we used the data. If the study did not provide the HR or RR with 95% CI, we calculated the HR and 95% CI using Kaplan–Meier survival curves and the software Engauge Digitizer Version 4.1 (http://digitizer.sourceforge.net/). The data were used following the method proposed by Tierney et al.[27] The multivariate analysis based results were collected when both multivariate and univariate analysis were conducted in the studies. Cochrane's Q test (Chi-squared test; Chi^2) and I^2 metric were used to evaluate the statistical heterogeneity of the pooled HR with 95% CI.[28] When $I^2 = 0\%–25\%$, it indicates there is no heterogeneity, $I^2 = 25\%–50\%$ indicates there is a moderate heterogeneity, $I^2 = 50\%–75\%$ indicates there is a medium heterogeneity and $I^2 = 75\%–100\%$ indicates there is an extreme heterogeneity. If $I^2 < 50\%$ or $p \geq 0.10$ in a Q test, a fixed-effect model (the Mantel–Haenszel method) was applied in the following meta-analysis. Otherwise, a random-effect model was appropriate for the analysis.[29] If $I^2 > 50\%$, a subgroup analysis or the method that pick one study out created by Patsopoulos et al.[30] was used to settle the question of heterogeneity. We used odds ratios (OR) with 95% CI to analyze the connection between PD-L1 expression and clinical characteristic containing the stage,