Observational Study

Medicine®

OPEN

Prognostic significance of PD-L1 in advanced non-small cell lung carcinoma

Yanjie Zhao, MD[a,g], Feng Shi, MS[b], Quan Zhou, MD[c], Yuchen Li, PhD[d], Jiangping Wu, BS[d], Ruibin Wang, MS[e], Qingkun Song, PhD[f,*]

Abstract

This study aimed to investigate the prognostic value of PD-L1 in Chinese patients with non-small cell lung carcinoma (NSCLC).

In this retrospective study, 97 patients with NSCLC were consecutively recruited. The expression profiling of PD-1, PD-L1, p53 and Ki-67 was detected by immunohistochemistry. Median survival time was estimated by Kaplan–Meier survival curve with log-rank test. Risk factors were evaluated by Cox Proportional Hazards regression models.

The median tumor size was larger (3.5 cm) among patients with positive PD-L1 expression, compared to those with negative expression (2.0 cm; $P < .01$). Compared to those with negative PD-L1 expression, patients with positive PD-L1 expression had significantly higher rates of nerve invasion (26.3% vs 5.0%; $P < .01$), blood vessel invasion (47.4% vs 20.0%; $P < .01$) and lymph node metastasis (64.9% vs 27.5%; $P < .01$), more advanced tumor stage ($P < .01$) and Ki-67 index ($P < .01$). PD-L1 expression status was not significantly associated with disease-free (DFS) or overall survival (OS). However, for patients with advanced disease, PD-L1 positive expression was related to worse outcome (HR: 4.13; 95% CI: 1.06–16.12).

Positive PD-L1 expression is associated with more aggressive pathological features and poorer prognosis in advanced stage NSCLC.

Abbreviations: AJCC = American Joint Committee on Cancer, CFDA = China Food and Drug Administration, DFS = disease-free survival, DNA = Deoxyribonucleic acid, EGFR = epidermal growth factor receptor, FFPE = formalin fixed paraffin-embedded, HR = hazard ratio, IHC = immunohistochemistry, IRB = Institutional Review Board, NSCLC = non-small cell lung cancer, NTC = No Template Control, OS = overall survival, PBS = Phosphate buffer saline, PC = positive control, PCR = Polymerase Chain Reaction, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, P53 = p53 protein, TNM = Tumor Node Metastasis, 95% CI = 95% confidence interval.

Keywords: non-small cell lung carcinoma, PD-L1, PD-1, prognosis

1. Introduction

Lung cancer is the most common malignancy and ranks the first in cancer-related mortality in China.[1] About 0.77 million patients were diagnosed with lung cancer in China in 2018, accounting for 37% of all new cases worldwide. The mortality rate of lung cancer was higher in under-developed countries than that in developed ones.[2] Approximately 80% of lung cancers are NSCLC. Chemotherapy and targeted therapy had been standard choices for lung cancer. In recent years, with the approval of antibodies against programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1), overall survival of NSCLC patients has been greatly improved.[3–6] Patients with positive PD-L1 expression may obtain good response to immune checkpoint inhibitors.[7] Positive PD-L1 expression was associated with a

Editor: Gauri Shishodia.

QS and QZ contributed equally to this work and are co-corresponding authors.

This study was financially supported by the Organization Committee of Beijing Municipal (2018000021223TD09) and Beijing Municipal Commission of Health (Q.K.S. grant number 2015-3-057). The supporting organizations had no role in study design, data collection, analysis, and interpretation.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

[a] Department of Medical Oncology, [b] Department of Pathology, Beijing Shijitan Hospital, Capital Medical University, [c] Department of Pathology, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, [d] Beijing Key Laboratory of Therapeutic Vaccines, [e] Department of Emergency, [f] Department of Clinical Epidemiology and Evidence-based Medicine, Beijing Shijitan Hospital, Capital Medical University, Beijing, China, [g] Department of Environmental Health Sciences, Arnold School of Public Health, University of South Carolina, Columbia, SC.

[*] Correspondence: Dr. Qingkun Song, Department of Clinical Epidemiology and Evidence-based Medicine, Beijing Shijitan Hospital, Capital Medical University, Tieyi Road 10, Haidian District, Beijing 100038 China (e-mail: songqingkun@ccmu.edu.cn).

How to cite this article: Zhao Y, Shi F, Zhou Q, Li Y, Wu J, Wang R, Song Q. Prognostic significance of PD-L1 in advanced non-small cell lung carcinoma. Medicine 2020;99:45(e23172).

Received: 4 June 2020 / Received in final form: 25 September 2020 / Accepted: 7 October 2020

http://dx.doi.org/10.1097/MD.0000000000023172

poor prognosis,[8–10] if the patients received therapies other than inhibitors of PD-1 or PD-L1. Though a PD-1 inhibitor was approved for NSCLC therapy, PD-L1 inhibitors have not been approved in China.[8] In this study, we aimed to investigate the association between PD-1/PD-L1 protein expression in NSCLC tumor tissues and pathological features, analyze potentially prognostic effects of PD-1/PD-L1 levels on relapse and overall survival, as well as explore supporting evidence for immunotherapy using PD-1/PD-L1 inhibitors for Chinese patients with NSCLC.

2. Materials and methods

All procedures involving human participants were performed in accordance with ethical standards of the Institutional Review Board (IRB) of Beijing Shijitan Hospital, Capital Medical University, as well as 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study, informed consent was waivered by IRB.

To explore the association between PD-L1 expression and prognosis, 97 NSCLC patients were retrospectively recruited consecutively from January 1, 2016, to December 31, 2016. All patients received surgical treatment at the Department of Thoracic Surgery, Beijing Shijitan Hospital, Capital Medical University and were confirmed with histopathology diagnosis.

Expression of PD-1, PD-L1, P53 (p53 Protein) and Ki-67 were detected by immunohistochemistry (IHC) on 4 μm-thick formalin fixed paraffin-embedded (FFPE) sections. Monoclonal antibodies against PD-1 (mouse anti-human, #UMAB199), PD-L1 (rabbit anti-human, #SP142), P53 (rabbit anti-human, #EP9), and Ki-67 (mouse anti-human, #MIB1) were purchased from Beijing Zhong Shan Golden Bridge Biotechnology Co. Ltd. Sections were baked for dehydration at 60°C in an oven for 60 minutes, dewaxed for 20 minutes, and washed in 100%, 100%, 95%, and 75% alcohol for 2 minutes, respectively; and then washed with PBS (Phosphate buffer saline) by 5 times, 2 minutes each time. Antigen was retrieved using the EnVision FLEX Target Retrieval Solutions for 2 minutes 30 seconds. The sample was cooled to room temperature for 20 minutes; washed with PBS by 5 times, 2 minutes each time; incubated with 3% H_2O_2 at room temperature for 15 minutes; washed with PBS by 5 times, 2 minutes each time; sealed with 5% serum at 37°C for 15 minutes; discarded and added a moderate primary antibody at 4°C for a night; washed with PBS by 5 times, 2 minutes each time; and then added DAB for 5 to 10 minutes and AP-red for 10 to 15 minutes. Slides were counterstained with hematoxylin.

Hot-spot area was determined under low-power field for Ki-67 assessment. Then 1000 cells were counted under high-power field and the percentage of nuclear-positive cells was calculated. The P53 mutant was defined as >70% nuclear-positive cells. More than 1% lymphocytes with positive staining on cytoplasm/membrane was diagnosed as positive expression of PD-1. More than 1% tumor cells with brown staining on cytoplasm/membrane was determined as positive expression of PD-L1.

2.1. EGFR mutation test

Tumor DNA was extracted from FFPE tissue according to the instructions of DNA extraction kit. EGFR (epidermal growth factor receptor) Master Mix containing EGFR Enzyme Mix and Reaction Mix was prepared in separate sterile centrifuge tube, pipetted gently more than 10 times and centrifuged briefly. 35.3 μl of each EGFR Master Mix and 4.7 μl NTC (No Template Control), PC (positive control) or sample DNA were added in PCR (Polymerase Chain Reaction) tube respectively and centrifuged to the bottom of the tube. PCR protocol was setup according to the cycling parameters recommended by the manufacture. TNM (Tumor Node Metastasis) stage is performed in accordance with eighth edition of the TNM classification of Lung Cancer.[11]

2.2. Statistical analysis

All data were analyzed by SPSS software (version 19.0). Age, tumor size, Ki-67 index, P53 status, and AJCC (American Joint Committee on Cancer) stage were analyzed by Wilcoxon ran-sum tests. Pathological type, nerve invasion, blood vessel invasion, EGFR mutation status, and lymph node metastasis were analyzed by Chi-Squared tests. PD-1 expression status was analyzed by McNemar test based on PD-L1 expression status. Kaplan–Meier survival curves with log-rank tests were used to estimate the effects of PD-L1 expression on disease-free survival (DFS) and overall survival (OS). The hazard ratio (HR) and 95% confidence interval (CI) were estimated by Cox-Hazard Proportion Models with adjustment of age, sex, histopathology type, clinical stage, blood vessel invasion, and nerve invasion. All analyses were two-sided tests with a significant level at $P < .05$.

3. Results

58.8% (N = 57) of NSCLC patients had positive PD-L1 expression (Table 1). Compared to those with negative expression, NSCLC patients with positive PD-L1 expression were more likely to be diagnosed as squamous cell carcinoma (38.6% vs 12.5%), larger tumor size (3.5 cm vs 2.0 cm), more frequently nerve invasion (26.3% vs 5.0%), blood vessel invasion

Table 1

The association between PD-L1 status and clinical-pathological characteristics.

	PD-L1		
	Positive (N = 57)	Negative (N = 40)	*P*
Age, median (IQR)*	61.0 (14.0)	63.0 (15.0)	.531
Sex, N (%)			.116
Male	44 (77.2)	25 (62.5)	
Female	13 (22.8)	15 (37.5)	
Pathological type, n (%)			.005
Adenocarcinoma	35 (61.4)	35 (87.5)	
Squamous cell carcinoma	22 (38.6)	5 (12.5)	
Tumor size, median (IQR)*	3.5 (4.0)	2.0 (1.9)	<.001
Nerve invasion			.007
No	42 (73.7)	38 (95.0)	
Yes	15 (26.3)	2 (5.0)	
Blood vessel invasion			.006
No	30 (52.6)	32 (80.0)	
Yes	27 (47.4)	8 (20.0)	
Lymph node metastasis			<.001
No	20 (35.1)	29 (72.5)	
Yes	37 (64.9)	11 (27.5)	
Stage*			<.001
I	14 (24.6)	22 (55.0)	
II	8 (14.0)	10 (25.0)	
III + IV	35 (61.4)	8 (20.0)	

* Wilcoxon rank-sum test.

Table 2

Association between PD-L1 expression and other markers.

	PD-L1		*P*
	Positive (n = 57)	Negative (n = 40)	
PD-1 status, n (%)*			<.001
Negative	36 (63.2)	31 (77.5)	
Positive	21 (36.8)	9 (22.5)	
Ki-67 index, median (IQR)**	50% (35%)	20% (48%)	.001
P53 status, n (%)**			.078
Negative	8 (14.0)	7 (17.5)	
Week	5 (8.0)	8 (20.0)	
Normal	38 (66.7)	24 (60.0)	
Strong	6 (10.5)	1 (2.5)	
EGFR mutation, n (%)			.395
Negative	10 (55.6)	7 (41.2)	
Positive	8 (44.4)	10 (58.8)	

* McNemar test.
** Wilcoxon rank-sum test.

(47.4% vs 20.0%), and lymph node metastasis (64.9% vs 27.5%), as well as more likely to be in advanced stages (61.4% vs 20%) (Table 1).

As shown in Table 2, PD-L1 expression was significantly associated with PD-1 expression. The median Ki-67 index was higher among patients with positive PD-L1 expression. The P53 status or EGFR mutation status had no significant correlation with PD-L1 expression ($P = .078$ and .395, respectively).

Median follow-up time was 32 months. Loss of follow-up rate was 9.3%. PD-L1 expression status was not significantly associated with DFS or OS (Fig. 1). Three-year DFS rate was 54.7% vs 65.8% among patients with positive vs negative PD-L1 expression, respectively. Three-year OS rate was 60.8% vs 78.9% among patients with positive vs. negative PD-L1 expression, respectively. In advanced stages of patients, PD-L1 expression was significantly associated with OS (HR 4.13; 95CI, 1.06–16.12), but there is no association between PD-L1 and early stage NSCLC (HR 0.48; 95CI, 0.09–2.56) (Table 3).

4. Discussion

Lung cancer is the most common malignancy worldwide. The crude mortality rate was 43.41 per 100,000 persons (57.64 per 100, 000 males and 28.45 per 100, 000 females), while the cumulative incidence rate (0–74 years old) was 3.34% in 2013.[1] Immunotherapy is an alternative approach to treat patients with NSCLC.[12] With the widespread use of immune checkpoint inhibitors, the prognosis of cancer has been significantly improved. On June 15, 2018, China Food and Drug Administration (CFDA) approved Opdivo anti-PD-1 for the second line treatment of NSCLC. On September 12 and October 22, CFDA approved Keytruda anti-PD-1 for the first line treatment of

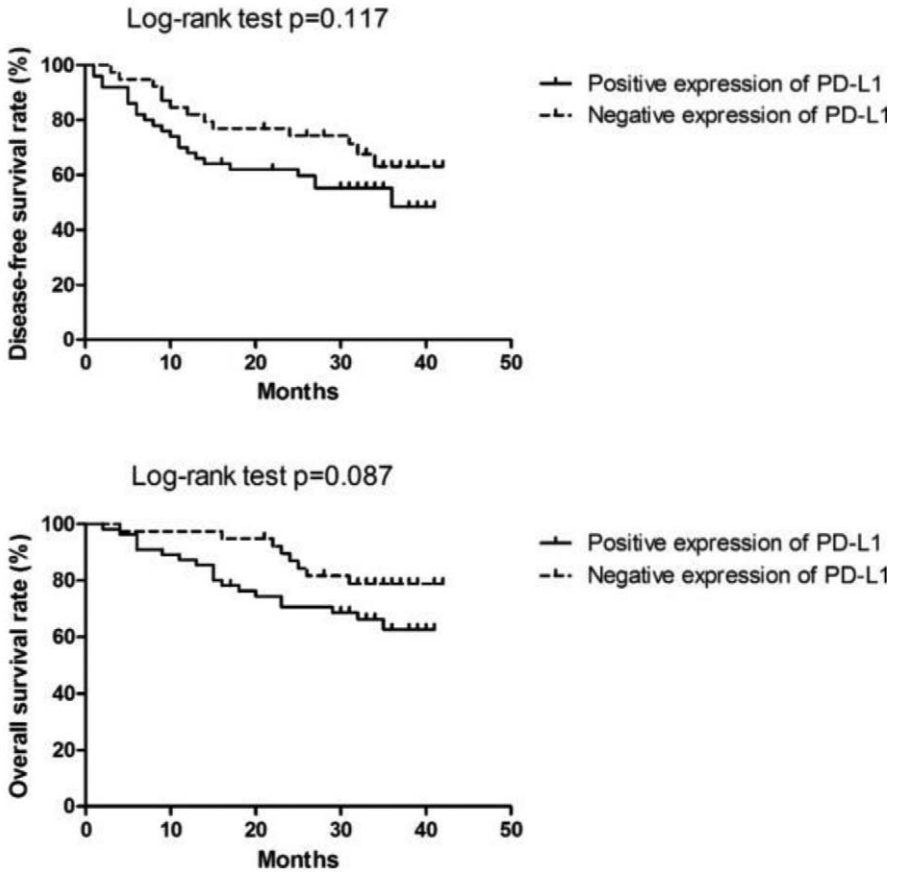

Figure 1. Prognostic effects of PD-L1 expression on disease-free survival and overall survival of NSCLC patients.

Table 3

HR and 95%CI of PD-L1 expression on prognosis.

	Disease-free survival		Overall survival	
	HR	95% CI	HR	95% CI
Univariate analysis	1.70	0.86, 3.35	2.01	0.89, 4.58
Multivariate analysis*	1.04	0.48, 2.24	1.60	0.66, 3.91
Multivariate analysis in stage I + II*	1.53	0.41, 5.78	0.48	0.09, 2.56
Multivariate in advanced stage (III + IV)*	1.45	0.43, 4.88	4.13	1.06, 16.12

* adjusted with age, sex, stage, pathology type, blood vessel invasion, and nerve invasion.

NSCLC. PD-L1 expression, as a negative prognostic factor of malignancy, may predict the efficacy of checkpoint inhibitors.

PD-1, a receptor on T lymphocytes, limits adaptive immune response and prevents auto-inflammatory and autoimmune reaction.[13] In cancer patients, PD-1 expression is higher on tumor-infiltrating T lymphocytes, PD-1 transmits inhibitory signals into T cells after ligation with PD-1 ligands, PD-L1[14] and PD-L2 [15] expressed on neoplastic cells. The PD-L1 is variably expressed on the surface of cancer cells and antigen-presenting cells within tumors tissues, providing a potent inhibitory signal within tumor microenvironment.[16] Our study reveals that PD-L1 expression on NSCLC cells is significantly associated with PD-1 expression on T cells. This is consistent with a previous report on positive correlation between PD-1 expression on TILs and PD-L1 expression on tumor cells.[17]

Positive expression of PD-L1 leads to poor prognosis in cancer patients.[18] Compared to PD-L1 (-), patients with PD-L1 (+) had a larger tumor size, higher risk of nerve invasion, higher risk of blood vessel invasion and higher risk of lymph node metastasis. NSCLC patients with positive expression of PD-L1 were more likely to be in advanced stages. A meta-analysis[19] indicated that PD-L1 expression was associated with gender, histology, tumor size, lymph nodal metastasis, TNM stage, and EGFR mutation.

Ki-67 was identified as a nuclear non-histone protein.[20] Because it is expressed during all phases of the cell cycle except the resting stage (G0), it has been used as a marker to evaluate proliferation in NSCLC,[21] lymphoma,[22] oral carcinoma,[23] and breast cancer.[24] Our previous study indicated that Ki-67 as a negative prognostic marker for BC patients, and a high Ki-67 index implied an exhausted status of tumor microenvironment.[25] Nonetheless, the relationship between Ki-67 expression and NSCLC prognosis was debated.[26–28] We found that the median Ki-67 index was higher among patients with high expression of PD-L1.

PD-L1 expression on tumor cells correlates with poor clinical prognosis in many cancers, such as renal cancer, ovarian cancer, lung cancer, and breast cancer.[29–32] It was reported that high PD-L1 expression in NSCLC was an independent predictor for poor prognosis.[33] Although PD-L1 expression in tumors has been linked to a shorter survival in advanced NSCLC, its use as a prognostic factor requires more investigation. The prognostic value of PD-L1 still remains controversial. Cooper identified high PD-L1 expression independently associated with longer OS.[34] Our study showed that PD-L1 expression status was not significantly associated with DFS or OS. However, hierarchical analysis revealed that among advanced NSCLC patients, high expression of PD-L1 increased the risk of death. We did not find an association between PD-L1 and early stage NSCLC. This finding is similar to Yu study.[35] One theory is heterogeneity selection. It is believed that in early stage disease, tumor cells without PD-L1 expression will be eliminated by T cells, and tumor cells with PD-L1 will escape from the immune response. As the tumor stage progresses, more tumor cells express PD-L1 and have the ability of escaping immune elimination.[35] A small sample size was 1 limitation. In addition, this was a retrospective design and further prospective studies are necessary to validate current findings.

5. Conclusions

Positive PD-L1 expression was associated with larger tumor size, lymph node metastasis, positive nerve, and blood vessel invasion and later stage in NSCLC patients. PD-L1 expression may increase the risk of death among advanced NSCLC patients. Further prospective studies are warranted.

Author contributions

Study design: QS and QZ. Data collection: YZ, FS, YL and JW. Data analysis: QS and YZ. Manuscript writing and modification: QS, YZ, FS, QZ, YL, RW and JW. Submission approval: QS, FS, QZ, YZ, YL, RW and JW.

Conceptualization: Yanjie Zhao, Quan Zhou, Qingkun Song.
Data curation: Yanjie Zhao, Feng Shi, Yuchen Li, Jiangping Wu.
Funding acquisition: Qingkun Song.
Investigation: Yanjie Zhao, Quan Zhou.
Methodology: Yanjie Zhao, Qingkun Song.
Project administration: Qingkun Song.
Writing – original draft: Yanjie Zhao, Feng Shi, Quan Zhou, Yuchen Li, Jiangping Wu, Ruibin Wang, Qingkun Song.
Writing – review & editing: Yanjie Zhao, Qingkun Song.

References

[1] Chen WQ, Zuo TT, Zheng RS, et al. Lung cancer incidence and mortality in China in 2013. Zhonghua Zhong Liu Za Zhi 2017;39:795–800.
[2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[3] Gandhi L1 RD1, Gadgeel S1 EE1, Felip E1 DAF1, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–92.
[4] West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924–37.
[5] Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase iii trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017;35:3924–33.
[6] Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040–51.

[7] Steve Lu, Stein Julie E, Rimm David L, et al. Comparison of biomarker modalities for predicting response to PD-1/PD-L1 checkpoint blockade: a systematic review and meta-analysis. JAMA Oncol 2019;5:1195–204.
[8] Okita R, Maeda A, Shimizu K, et al. PD-L1 overexpression is partially regulated by EGFR/HER2 signaling and associated with poor prognosis in patients with non-small-cell lung cancer. Cancer Immunol Immunother 2017;66:865–76.
[9] Jung HI, Jeong D, Ji S, et al. Overexpression of PD-L1 and PD-L2 Is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res Treat 2017;49:246–54.
[10] Zhang M, Sun H, Zhao S, et al. Expression of PD-L1 and prognosis in breast cancer: a meta-analysis. Oncotarget 2017;8:31347–54.
[11] Chansky K, Detterbeck FC, Nicholson AG, et al. The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2017;12:1109–21.
[12] Anagnostou VK, Brahmer JR. Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res 2015;21:976–84.
[13] Annibali O, Crescenzi A, Tomarchio V, et al. PD-1/PD-L1 checkpoint in hematological malignancies. Leuk Res 2018;67:45–55.
[14] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027–34.
[15] Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2:261–8.
[16] Balar AV, Weber JS. PD-1 and PD-L1 antibodies in cancer: current status and future directions. Cancer Immunol Immunother 2017;66:551–64.
[17] He Y, Rozeboom L, Rivard CJ, et al. PD-1, PD-L1 protein expression in non-small cell lung cancer and their relationship with tumor-infiltrating lymphocytes. Med Sci Monit 2017;23:1208–16.
[18] Yeo MK, Choi SY, Seong IO, et al. Association of PD-L1 expression and PD-L1 gene polymorphism with poor prognosis in lung adenocarcinoma and squamous cell carcinoma. Hum Pathol 2017;68:103–11.
[19] Zhang M, Li G, Wang Y, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. Sci Rep 2017;7:10255.
[20] Martin B, Paesmans M, Mascaux C, et al. Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis. Br J Cancer 2004;91:2018–25.
[21] Wen S, Zhou W, Li CM, et al. Ki-67 as a prognostic marker in early-stage non-small cell lung cancer in Asian patients: a meta-analysis of published studies involving 32 studies. BMC Cancer 2015;15:520.
[22] Jeong TD, Chi HS, Kim MS, et al. Prognostic relevance of the Ki-67 proliferation index in patients with mantle cell lymphoma. Blood Res 2016;51:127–32.
[23] Gissi DB, Gabusi A, Tarsitano A, et al. Ki67 Overexpression in mucosa distant from oral carcinoma: a poor prognostic factor in patients with long-term follow-up. J Craniomaxillofac Surg 2016;44:1430–5.
[24] Yerushalmi R, Woods R, Ravdin PM, et al. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 2010;11:174–83.
[25] Zhao YJ, Zhang J, Shi F, et al. Expression of PD-1 on CD4+ tumor-infiltrating lymphocytes in tumor microenvironment associated with pathological characteristics of breast cancer. J Immunol Res 2018;2018: 5690258.
[26] Minami K, Saito Y, Imamura H, et al. Prognostic significance of p53, Ki-67, VEGF and Glut-1 in resected stage I adenocarcinoma of the lung. Lung Cancer 2002;38:51–7.
[27] Yoo J, Jung JH, Lee MA, et al. Immunohistochemical analysis of non-small cell lung cancer: correlation with clinical parameters and prognosis. J Korean Med Sci 2007;22:318–25.
[28] Yamashita S, Moroga T, Tokuishi K, et al. Ki-67 labeling index is associated with recurrence after segmentectomy under video-assisted thoracoscopic surgery in stage I non-small cell lung cancer. Ann Thorac Cardiovasc Surg 2011;17:341–6.
[29] Ghebeh H, Mohammed S, Al-Omair A, et al. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia 2006;8:190–8.
[30] Yang CY, Lin MW, Chang YL, et al. Programmed cell death-ligand 1 expression is associated with a favourable immune microenvironment and better overall survival in stage I pulmonary squamous cell carcinoma. Eur J Cancer 2016;57:91–103.
[31] Nakano O, Sato M, Naito Y, et al. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. Cancer Res 2001;61:5132–6.
[32] Abiko K, Mandai M, Hamanishi J, et al. PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. Clin Cancer Res 2013;19:1363–74.
[33] Mu CY, Huang JA, Chen Y, et al. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol 2011;28:682–8.
[34] Cooper WA, Tran T, Vilain RE, et al. PD-L1 expression is a favorable prognostic factor in early stage non-small cell carcinoma. Lung Cancer 2015;89:181–8.
[35] Hui Yu, Zhengming Chen, Karla Ballman, et al. Correlation of PD-L1 expression with tumor mutation burden and gene signatures for prognosis in early stage squamous cell lung carcinoma. J Thorac Oncol 2019;14:25–36.