

Prevalence of programmed death ligand-1 in patients diagnosed with non-small cell lung cancer in Lebanon

SAGE Open Medicine

Volume 9: 1–7

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DOI: 10.1177/20503121211043709

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Abstract

Introduction: Programmed death ligand-1 expression has been shown to be a good predictor of response to cancer therapy with checkpoint inhibitors. Its expression varies among different tumor types and among non-small cell lung cancer patients with different clinical and demographic characteristics. The prevalence and determinants of programmed death ligand-1 expression have been previously reported from various regions of the world, but data from Lebanon are lacking. This study examines the prevalence and the clinical, demographic and pathological predictors of programmed death ligand-1 expression in patients diagnosed with non-small cell lung cancer in Lebanon.

Methods: Medical records of 180 patients diagnosed with primary non-small cell lung cancer at our institution and tested for programmed death ligand-1 expression were reviewed. Clinical, demographic and pathological information were collected and correlated with programmed death ligand-1 expression using the chi-square test and logistic regression.

Results: One hundred eleven of the 180 non-small cell lung cancer tumor samples tested positive for programmed death ligand-1 expression (61.7%). 27.2% of those tumor samples expressed programmed death ligand-1 in 1%–49% of tumor cells, while 34.4% of tumor samples expressed programmed death ligand-1 in 50% or more of their cells. Squamous histology and advanced stage were significant predictors of programmed death ligand-1 expression (odds ratio = 2.79, 95% confidence interval [1.13–6.90], $p=0.012$ and odds ratio = 2.48, 95% confidence interval [1.23–4.99], $p=0.044$, respectively).

Conclusion: Similar to reports from other populations, our results suggest that programmed death ligand-1 expression in non-small cell lung cancer is highly prevalent in the Lebanese population, especially in patients with advanced stage at diagnosis or squamous cell carcinoma histology. Because of the small sample size, while more than 60% of the patients are Lebanese, the results of this article cannot be extrapolated to the Middle Eastern and the Levantine population.

Keywords

Programmed death ligand-1, non-small cell lung cancer, immunotherapy, immune markers, histology

Date received: 1 February 2021; accepted: 15 August 2021

Introduction

As a consequence of the ongoing tobacco epidemic, lung cancer is projected to continue being the leading cause of cancer death in both men and women.¹ The majority of lung cancer patients are diagnosed at a later stage with an associated 5-year survival currently at 18%.^{2,3} Non-small cell lung cancer (NSCLC) represents around 85% of all lung cancer cases and, up until recently, platinum-based chemotherapy had been the standard of care for treating patients with advanced NSCLC.^{4–7} Recent advances in immunotherapy using checkpoint inhibitors have drastically changed the treatment strategies for this disease, which will hopefully lead to better patient outcomes.^{8–10}

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Recent studies have shown that the tumor microenvironment may be modulated through programmed death ligand-1 (PD-L1) and its receptor programmed death-1 (PD-1).¹¹ PD-1 is a member of the CD28 family and is a key checkpoint receptor for escaping the immune response expressed mainly on activated effector T lymphocytes, such as those that infiltrate tumors.¹¹ The ligand of PD-1 (PD-L1) is overly expressed in many tumors such as lung and colorectal cancers.¹¹ Once bound to its receptor, PD-L1 induces cellular apoptosis of effector T lymphocytes, thus reducing the effectiveness of the immune response.^{11–13} Antibodies targeting PD-1 and PD-L1 such as Pembrolizumab, Nivolumab and Atezolizumab have been developed and extensively studied. These PD-1 inhibitors were granted Food and Drug Administration (FDA) approval for the treatment of NSCLC after showing better outcomes in clinical trials.^{14–16}

PD-L1 expression varies in different tumors and in different tumor microenvironments. It also varies according to clinical, demographic and pathological characteristics.^{17–19} Data regarding the prevalence of PD-L1 are emerging worldwide but are lacking in the Middle East generally and Lebanon specifically. The relation of PD-L1 expression to clinical and demographic characteristics remains controversial in some studies owing to the discrepancies in testing for PD-L1 and the different standards in assessing the cut-off for positivity.^{20–22} This study examines the prevalence of PD-L1 expression in patients diagnosed with NSCLC at a tertiary care medical center in Lebanon and determines the clinical, demographic and pathological predictors of PD-L1 expression.

Materials and methods

Subjects and samples

Medical records of patients diagnosed with primary NSCLC and tested for PD-L1 expression between January 2016 and February 2018 were analyzed retrospectively at our institution. This study was approved by the Institutional Review Board and is in accordance with the Helsinki Declaration of 1975. NSCLC patients with pathology reports clearly delineating the PD-L1 status were selected. Of 200 cases identified, 20 were excluded for incomplete clinical and demographic information. A pathologist reviewed all cases to confirm the histology and select a representative area of tumor cells for PD-L1 assessment. Information was collected at the time of diagnosis and included age, sex, nationality, smoking status, family history of lung cancer, tumor stage, histology and grade, as well as the presence and extent of PD-L1 expression, and the presence of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement. All patients were treated following standard-of-care and did not previously receive anti-PD-1 or anti-PD-L1 therapy. Staging was performed according to the American Joint Committee on Cancer eighth edition manual.²³

EGFR and ALK status determination

EGFR mutation analysis was performed on paraffin-embedded tissue using ARMS and Scorpions technologies to detect 29 somatic mutations in the EGFR oncogene in real-time polymerase chain reaction (PCR) on the Rotor-Gene platform. Results classified mutations into four locations: Exon 18, 19, 20 and 21. The immunohistochemical status of ALK translocation was assessed through Ventana D5F3 using a multimer detection system.

PD-L1 status

PD-L1 expression was assessed on formalin-fixed paraffin-embedded (FFPE) tumor tissues using a qualitative immunohistochemistry (IHC) assay (PharmDx kit; Merck & Co Inc, Rahway, NJ, USA). This assay uses the primary antibody 22C3 clone anti-PD-L1 mouse monoclonal antibody to detect and visualize the PD-L1 protein in NSCLC among other cancers using the EnVision FLEX visualization system on Autostainer Link 48. Our assessment was performed using the Ventana automated immunostainer on 4 μ m-cut positively charged slides. Positive and negative controls were run along each assessment. IHC was assessed by the pathologist and PD-L1 was considered positive when membranous staining was present in 1% or more of tumor cells. Staining intensity of PD-L1 was also assessed and scored as one, two or three.

Statistical analysis

The main outcome of this study was to determine the prevalence of PD-L1 expression in NSCLC patients at a large tertiary care medical center in the Levant area. Descriptive statistics summarizing the clinical and demographic characteristics of the patients and the pathological characteristics of their tumor samples are presented. The main dependent variable was the PD-L1 status categorized as positive (more than 1% of tumor cells) or negative. The independent (exposure) variables were the various clinical and demographic characteristics of the patients and the pathological characteristics of the tumor samples.

Patient's clinical and demographic characteristics and the pathological characteristics of their tumor samples were compared between PD-L1 expression categories using Pearson's chi-square tests or Fisher's exact tests. Logistic regression was used to evaluate potential predictors of PD-L1 expression including age (\geq or $<$ 65 years), sex, smoking status (current/former smoking and never-smoking), histology (squamous and adenocarcinoma) and stage (advanced (stage IV) and early stage (stage I–III)). Regression models were adjusted for age, sex and smoking. Analysis was performed using the statistical package IBM SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA). p -value $<$ 0.05 was considered statistically significant.

Table 1. Demographic, clinical and pathological characteristics of the study population.

N= 180	Characteristics	N (%)
Age (years) (mean \pm SD)		65.0 \pm 10.5
Sex		
Male		122 (67.8)
Female		58 (32.2)
Nationality		
Lebanese		146 (81.1)
Iraqi		22 (12.2)
Others		12 (6.7)
Smoking status		
Never		29 (16.1)
Current		63 (35.0)
Ex-smoker		79 (43.9)
Unknown		9 (5.0)
Cancer stage at diagnosis		
I		21 (11.7)
II		16 (8.9)
III		33 (18.3)
IV		106 (58.9)
Unknown		4 (2.2)
Tumor histology		
Adenocarcinoma		132 (73.3)
Squamous		43 (23.9)
Other		5 (2.8)
Tumor grade		
Well-differentiated		6 (3.3)
Moderately differentiated		64 (35.6)
Poorly differentiated		64 (35.6)
Unknown		46 (25.5)
PD-L1 expression		
Negative		69 (38.3)
1%–49%		49 (27.2)
50% or more		62 (34.5)
EGFR mutation (N=99)		
Wild type		81 (81.9)
Mutant		18 (18.1)
ALK translocation (N= 101)		
Negative		99 (98.0)
Positive		2 (2.0)

SD: standard deviation; PD-L1: programmed death ligand-1; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

Results

Demographic data

The demographic characteristics of our sample are presented in Table 1. The mean age was 65.0 \pm 10.5 years and the majority were Lebanese (81.1%), males (67.8%), and current or previous cigarette smokers (78.9%).

Clinical characteristics

The majority of patients had stage IV disease at diagnosis (58.9%) while 11.7% and 8.9% had stage I or stage II disease

at diagnosis, respectively. The most common histological type was adenocarcinoma (73.3%), while 23.9% of the patients had squamous cell carcinoma. The majority of the tumor samples showed moderate (35.6%) or poor differentiation (35.6%). Of the patients with adenocarcinoma with adequate sample for EGFR testing ($n=99$), 18 had mutated EGFR while 2% of adenocarcinoma adequate for ALK testing ($n=101$), had ALK rearrangement (Table 1).

Pathological characteristics

One hundred eleven of the 180 NSCLC samples tested positive for PD-L1 expression (61.7%). In particular, 27.2% of the tumor samples expressed PD-L1 positivity in 1%–49% of tumor cells, while 34.5% of those samples expressed PD-L1 in 50% or more of the cells. A representative figure of the different IHC profiles is presented in Figure 1.

Association of PD-L1 expression with patient and tumor characteristics

The histologic type of NSCLC was significantly associated with PD-L1 expression, with 76.7% of tumors with squamous histology had PD-L1 expression versus 58.3% of tumors with adenocarcinoma histology ($p=0.012$). Tumor stage was also significantly associated with PD-L1 expression where 67.9% of tumors diagnosed at an advanced stage (IV) expressed PD-L1 compared with 52.9% of tumors diagnosed at a loco-regional stage (I, II and III, $p=0.044$). Other demographic, clinical or pathological characteristics that were assessed were not significantly associated with PD-L1 expression. Males were as likely to have PD-L1 expressing tumors as females (62.3% vs 60.3%, $p=0.870$). Despite having a numerically higher percentage of tumor that tested positive for PD-L1 in patients older than 65 as compared to younger patients (67.4 vs 55.7%), this did not reach statistical significance ($p=0.106$). The majority of patients in this study were either Lebanese or Iraqi without a difference in PD-L1 positivity among these two nationalities, 61.6% and 63.6%, respectively. PD-L1 was expressed in 61.3% of respective samples from current smokers and former smokers compared to a similar 62.1% in never-smokers (Table 2). The odds ratios and 95% confidence intervals for age, gender, smoking status, stage and histology were reported as 1.61 [0.81–3.17], 0.84 [0.40–1.77], 1.06 [0.42–2.62], 2.48 [1.23–4.99] and 2.79 [1.13–6.90], respectively. Adjustment for age, sex and smoking did not impact the association of PD-L1 expression with stage and tumor histologic type (odds ratio (OR)=2.48, 95% confidence interval (CI) [1.23–4.99], $p=0.044$ and OR=2.79, 95% CI [1.13–6.90], $p=0.012$, respectively). The association between PD-L1 expression and presence of EGFR mutation or ALK rearrangement could not be assessed due to the small number of patients who tested positive (Table 1).

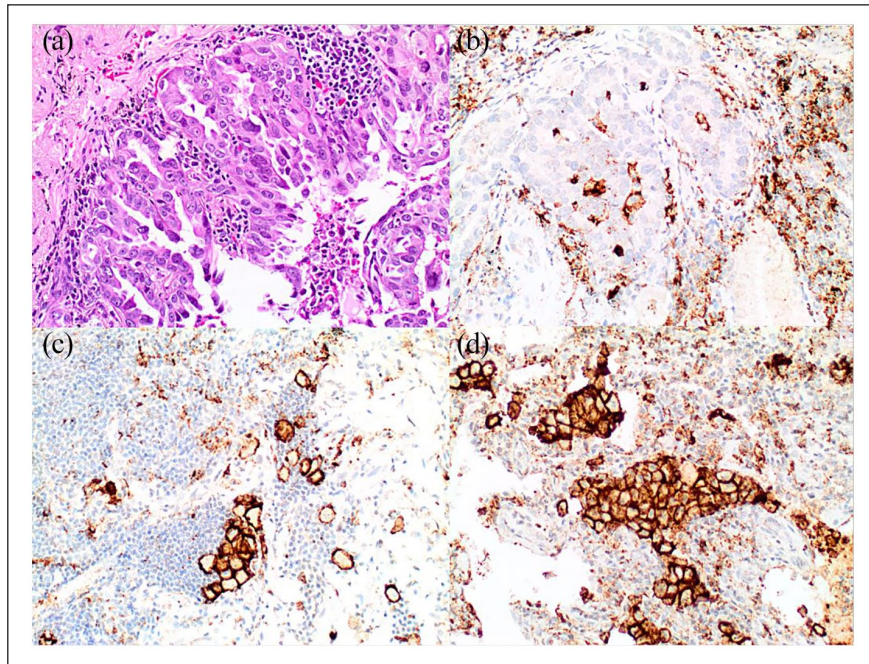


Figure 1. (a) Adenocarcinoma specimen. H&E stain. Power: 20 \times . (b) Adenocarcinoma specimen. PD-L1 stain: negative. Power 20 \times . (c) Adenocarcinoma specimen. PD-L1 stain: positive, 1%–49% of tumor cells. (d) Adenocarcinoma specimen. PD-L1 stain: positive, more than 50% of tumor cells.

Table 2. Demographic, clinical and pathological characteristics stratified by PDL-I expression status.

Variable	Categories	PD-L1 positive, N (%)	PD-L1 negative, N (%)	p-value
Age (years)	>65	62 (67.4)	30 (32.6)	0.106
	\leq 65	49 (55.7)	39 (44.3)	
Gender	Male	76 (62.3)	46 (37.7)	0.801
	Female	35 (60.3)	23 (39.7)	
Nationality	Lebanese	90 (61.6)	56 (38.4)	1.000
	Iraqi	14 (63.6)	8 (36.4)	
	Other*	7 (58.3)	5 (41.7)	
Smoking status	Current or former	87 (61.3)	55 (38.7)	0.936
	Never	18 (62.1)	11 (37.9)	
TNM staging	Advanced	72 (67.9)	34 (32.1)	0.044*
	Local/regional	37 (52.9)	33 (47.1)	
Histology	Adenocarcinoma	77 (58.3)	55 (41.7)	0.012*
	Squamous	33 (76.7)	10 (23.3)	
	Other	1 (20.0)	4 (80.0)	
Grade	I	3 (50.0)	3 (50.0)	0.594
	II	37 (57.8)	27 (42.2)	
	III	42 (65.6)	22 (34.4)	

PD-L1: programmed death ligand-1.

*Indicates statistical significance.

Discussion

This study shows that the majority of NSCLC tumors sampled at a tertiary care oncology center in Lebanon expressed PD-L1 and that squamous cell carcinoma and advanced

stage tumors were significant predictors of PD-L1 expression, both twice as likely to express PD-L1.

This study represents the first attempt to examine the prevalence of PD-L1 expression in adults diagnosed with NSCLC in the Lebanese population and attempt to correlate

it with demographic, clinical and pathological characteristics. According to the most recent cancer registry in Lebanon, a total of 1212 cases of lung cancer are diagnosed every year with the majority of them having NSCLC.²⁴ The association of sustained clinical benefits and improved progression-free survival after treatment with PD-1 blockers has been established in several clinical trials.^{15,16,25} Yet, studies in Lebanon and the Middle East, generally, are lacking regarding expression of the PD-L1.

Therefore, the finding of high prevalence of PD-L1 expression in our sample is important as it highlights the need to test for PD-L1 and for considering immunotherapy in the therapeutic strategies in our NSCLC patient population. However, in Lebanon, data on the prevalence of PD-L1 expression in patients diagnosed with NSCLC are non-existent. This study is the first to report this prevalence in 180 patients with histologically confirmed NSCLC and who have not received prior systematic treatment for their disease.

While there are no prior reports regarding PD-L1 expression in the Middle Eastern countries to compare our findings to, several studies have assessed PD-L1 prevalence worldwide.^{24,26,27} The mean age of our cohort was 65 years with the majority being Lebanese males who are either current or prior smokers. Most of the cases had adenocarcinoma and were diagnosed at a late-stage, very similar to those reported in the Lebanese National Cancer Registry.^{26–29}

Our reported prevalence of PD-L1 expression (61.7%) is comparable to other reports from other parts of the world, which ranged between 50% and 70%.^{18,21,22,30,31} The prevalence of PD-L1 expression was 68% in the Keynote-001, 010 and 024 clinical trials participants in whom PD-L1 expression was assessed using methods similar to this study (22C3 PharmDx).^{15,32–34} Other studies have reported a prevalence of PD-L1 expression ranging from 7.4% to 82%, and this variability can be explained by the use of different PD-L1 expression cut-offs (1 vs 10% of tumor cells) and different antibodies to detect PD-L1 expression (28-8 vs SP142).^{19,20–22,34–44} Similar to prior reports, we also found that advanced stage IV and squamous cell carcinoma histology are significantly predictors of PD-L1 expression.^{19,21,31} It is noteworthy to mention that this study's participants had not received systemic treatment prior to PD-L1 testing, an important consideration since PD-L1 expression is a dynamic marker that might change in response to therapy.^{14,45}

Limitations

One obvious limitation of this article is its retrospective nature in a single center which could lead to selection bias. The number of patients from neighboring countries is not sufficient enough to warrant a representative sample from countries of the Middle East. In addition to that, follow-up data for these patients are not available and as such no survival analysis could be performed. For the same reason, the

data about the treatment given to the patient could not be collected and the treatment response could not be determined. Also, for the purpose of this study, the power analysis was not done. Despite the fact that this is the first paper to study PD-L1 expression from the population in Lebanon, a larger sample size is warranted.

Conclusion

The prevalence of PD-L1 expression in NSCLC samples from patients assessed in a tertiary care center in Lebanon is similar to other populations around the world such as the Western or the Asian. This article sheds the light on the importance of evaluating immune markers expression in patients with NSCLC in view of the high prevalence of PD-L1 in our sample cohort and their established link to optimal targeted therapy. Our knowledge about the microenvironment of lung tumors is changing and more studies regarding PD-L1 expression as well as other immune markers are needed to improve the choice of therapy and prognosis of NSCLC.

Author contributions

Substantial contributions to the conception or design of the work, data acquisition and/or interpretation. Drafting and/or critical revision of the final manuscript. Approval of the final version to be submitted. This manuscript has been read and approved by all the authors, the requirements for authorship as stated above have been met, and each author believes that the manuscript represents honest work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the American University of Beirut Institutional Review Board (approval no. BIO-2018-0048).

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent

It is not applicable. Obtaining a written consent was waived by the institutional review board.

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Data availability

The raw data used to support the findings of this study are available from the corresponding author upon request.

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