Bosphorus Medical Journal
Boğaziçi Tıp Dergisi

Original Article

DOI: 10.14744/bmj.2023.24572

Bosphorus Med J 2023;10(4):237–241

Prognostic Significance of PD-L1 Expression in Stage 4 Non-Small-Cell Lung Cancer

Evre 4 Küçük Hücreli Dışı Akciğer Kanserinde PD-L1 Ekspresyonunun Prognostik Önemi

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Cite this article as:
Korkmaz P, Özden Ş, Kıyık M. Prognostic Significance of PD-L1 Expression in Stage 4 Non-Small-Cell Lung Cancer. Bosphorus Med J 2023;10(4):237–241.

Received: 15.10.2022
Revision: 03.07.2023
Accepted: 10.07.2023

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ABSTRACT

Objectives: Since lung cancer is the most deadly cancer in the world, developments regarding immune control points and molecules affecting these points have increased. The positive effects of immunotherapy treatments affecting the PD-1/programmed death receptor ligand-1(PD-L1) immune checkpoint on prognosis have drawn attention to these immunocheckpoints. While immunotherapy studies developed for the PD-1 pathway continue rapidly, the aim of this study is to investigate whether PD-L1 level can be used as a prognostic marker in non-small-cell lung cancer independent of immunotherapy.

Methods: 115 patients admitted to our center between January 01, 2016, and January 01, 2018 and diagnosed with non-small-cell lung cancer were retrospectively analyzed. The files of all patients were scanned in detail and their pathological data were confirmed. Demographic data of the patients included in the study, pathological diagnosis methods, treatment information about the disease, and past medical histories of the patients were recorded with reference to the hospital database.

Results: The patients with PD-L1 <50% were considered the negative group (NG), and the group with a PD-L1 value of 50% or more was considered the positive group (PG). There were 27 patients in the NG and 11 patients in the PG. It was determined that 21 (67.8%) of 27 NG patients and 3 (21.3%) of 11 PG patients died. In total, 24 (73.2%) of 38 patients were found to have died. While the mean survival in the NG was 10.81 months, the mean survival in the PG was 28.54 months. Mean survival in the PG was statistically significant (p=0.046).

Conclusion: PD-L1 expression was found to be a positive predictive value in Stage 4 non-small-cell lung cancer. Our study differs from other studies in that it excluded epidermal growth factor receptor, anaplastic lymphoma kinase, and ROS mutations. To determine the relationship of PD-L1 with prognosis more clearly, there is a need for randomized, prospective studies with larger patient groups that exclude target mutations and are independent of immunotherapy and targeted therapies.

Keywords: Immunotherapy; lung cancer; programmed death receptor ligand-1.

ÖZET

Amaç: Akciğer kanserinin dünyadaki en ölümcül kanser olması nedeniyle immün kontrol noktaları ve bu noktaları etkileyen moleküllerle ilgili gelişmeler artmıştır. PD-1/PD-L1 immün kontrol noktasını etkileyen immünoterapi tedavilerinin prognoz üzerindeki olumlu etkileri bu immün kontrol noktalarına dikkat çekmiştir. PD-1 yolu için geliştirilen immünoterapi çalışmaları hızla devam ederken, bu çalışmanın amacı PD-L1 düzeyi, immünoterapiden bağımsız olarak küçük hücreli dışı akciğer kanserinde prognostik bir belirteç olarak kullanılıp kullanılamayacağını öngörmektir.

Yöntem: 01 Ocak 2016-01 Ocak 2018 tarihleri arasında merkezimize başvuran ve küçük hücreli dışı akciğer kanseri tanısı konulan 115 hasta retrospektif olarak incelendi. Tüm hastaların dosyaları detaylı bir şekilde tarandı ve pa-

tolojik verileri doğrulandı. Çalışmaya dahil edilen hastaların demografik verileri, patolojik tanı yöntemleri, hastalığa ilişkin tedavi bilgileri ve hastaların geçmiş tıbbi öyküleri hastane veri tabanı referans alınarak kaydedildi.

Bulgular: PD-L1 <%50 olan hastalar negatif grup, PD-L1 değeri %50 ve üstü olan grup pozitif grup olarak kabul edildi. Negatif grupta 27, pozitif grupta 11 hasta vardı. Yirmi yedi negatif grup hastasının 21'inin (%67,8) ve 11 pozitif grup hastasının 3'ünün (%21,3) öldüğü belirlendi. Toplam 38 hastanın 24'ünün (%73,2) öldüğü belirlendi. Negatif grupta ortalama sağkalım 10,81 ay iken, pozitif grupta ortalama sağkalım 28,54 aydı. Pozitif grupta ortalama sağkalım istatistiksel olarak anlamlıydı (p=0,046).

Sonuç: PD-L1 ekspresyonunun evre 4 küçük hücreli dışı akciğer kanserinde pozitif bir prediktif değer olduğu bulundu. Çalışmamız EGFR, ALK ve ROS mutasyonlarını dışlaması ile diğer çalışmalardan ayrılmaktadır. PD-L1'in prognoz ile ilişkisini daha net belirleyebilmek için daha geniş hasta grupları ile hedef mutasyonları dışlayan, immünoterapi ve hedefe yönelik tedavilerden bağımsız randomize, prospektif çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Akciğer kanseri; immünoterapi; PD-L1.

Lung cancer continues to rank first among the most lethal cancers worldwide.[1] Non-small-cell lung cancer is the most common cancer group among all lung cancer types. According to the recent studies, 5-year survival is around 25%.[2]

In recent years, molecular factors that are especially effective in tumor growth and spread have started to be identified and studies have been published. Following the identification of target molecules, immunotherapy studies and targeted therapies have started to attract attention. In metastatic non-small-cell lung cancer, 5-year survival rates ranging from 15% to 50% depending on biomarkers have been reported with immunotherapy and targeted treatment options.[3,4] New treatment models targeting epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) rearrangements have been shown to favorably affect prognosis in non-squamous non-small-cell lung cancer.[5-7] The fact that targeted therapies can only be used in certain groups of patients has led to the investigation of the links between cancer and the immune system. The best-defined immune checkpoints are cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death receptor 1 (PD-1), and its receptor ligands programmed death receptor ligand-1 (PD-L1) and PD-L2. CTLA-4 and PD-L1 inhibit T-cell activation through different mechanisms.[8] The PD-1 receptor is expressed on CD-4 and CD-8 T-cells, regulatory T-cells (Treg), and B-lymphocytes.[9] Once the PD-1 receptor binds to PD-L1 and PD-L2, the production of inflammatory cytokines is inhibited. Increased PD-1 and ligand expression in some tumor types causes tumor cells to escape the immune system, creating a favorable environment for tumor growth.[10] PD-1 and PD-L1 inhibitors activate the T-cell response in the opposite direction, resulting in recognition and shrinkage of the tumor cell by the immune system.[11]

While immunotherapy studies developed for the PD-1 pathway continue rapidly, the aim of this study is to investigate whether PD-L1 level can be used as a prognostic marker in non-small-cell lung cancer independent of immunotherapy.

Methods

All procedures related to this study were prepared in accordance with the 1964 Declaration of Helsinki. The study was approved by the ethics committee of our hospital (approval date: March 03, 2019, approval code: 2019/1734).

Between January 1, 2016 and January 01, 2018, 115 patients who were admitted to our center and diagnosed with non-small-cell lung cancer were retrospectively reviewed. The files of all patients were reviewed in detail, and pathological data were confirmed. Demographic data, pathological diagnostic methods, disease-related treatment information, and past medical history of the patients included in the study were recorded with reference to the hospital database. 115 patients diagnosed with non-small-cell lung cancer were analyzed according to surgical status, PD-L1 status, target mutation status (EGFR, ALK, and ROS-1 positivity), chemotherapy and/or immunotherapy status, presence of other organ malignancies, stage status according to TNM 8th edition staging system, Eastern cooperative oncology group (ECOG) performance scores and whether they had myocardial infarction and cerebrovascular events in the past 6 months. All patient samples were analyzed to check whether PD-L1 ratio had been previously checked. Patients without PD-L1 ratio in pathological samples were excluded from the study. Patients operated for lung cancer, patients with positive EGFR, ALK, and ROS-1 mutations, and patients receiving immunotherapy were excluded from the study. However, patients with other organ malignancies, Stage 1, 2, and 3 patients according to TNM 8th edition staging system, ECOG

3 and 4 patients, and patients with a history of myocardial infarction and cerebrovascular events in the past 6 months were excluded from the study because it would affect life expectancy. When the exclusion criteria were applied, 38 patients were included in the study. 38 patients' age, gender, pathological subtype, TNM (M1a, M1c, and M1c) stage, PD-L1 ratio, chemotherapy regimens, and radiotherapy status were analyzed.

PD-L1 Analysis

From commercial PD-L1 antibodies, 22C3 pharmDx (Dako, Carpinteria, CA), Dako Autostainer Link48 semi-automatic immunohistochemistry device and Dako PT link device were used. PD-L1 was evaluated with the immunohistochemical method under the light microscope with H and E slides. The PD-L1 (+) tumor cells were proportioned to all tumor cells to obtain the PD-L1 score (tPD-L1) for the tumor. Cases similar to PD-L1 antibody 22C3 pharmDx evaluation in lung carcinomas; tumor cells were divided into four groups as those staining less than 1%, those with >1% staining <50%, and those with 50% or more staining.

Statistical Analysis

Statistical Package for the Social Sciences (Inc., Chicago, IL, USA) program, version 20.0 was used for statistical analysis. While evaluating the study data, mean and standard deviation values of central tendency measures were given for numerical variables, and frequency distributions (number and percentage) were given for categorical variables. Whether there was a difference between the two groups was checked with the independent sample t-test for the variables conforming to the normal distribution, and the Mann–Whitney U-test for the variables not conforming to the normal distribution. The survey analysis of the patients was analyzed by the Kaplan–Meier method.

Results

Of the 38 patients included in the study, 33 (86.8%) were male and 5 (13.2%) were female. Median age was 63 years. When pathological subtypes were examined, 28 (73.7%) adenocarcinoma, 6 (15.8%) non-small-cell lung cancer undefined type, and 4 (10.5%) squamous cell carcinoma were found. When the patient files were analyzed retrospectively, it was seen that all patients were grouped as ECOG-1. It was determined that all patients received chemotherapy and 25 patients received radiotherapy.

According to the literature studies on PD-L1, the range of values was calculated in two ways. In the first analysis, patients with a PD-L1 of 0% were considered a negative group (NG), while all values above 0% were considered a positive group (PG). When the analysis was examined, the PD-L1 value of 16 (42.1%) patients was found to be 0% and PD-L1 value of 1% and higher in 22 (57.9%) patients. In the analysis performed, the mean and median survival were not found to be statistically significant (p=0.128).

In the second analysis, the patients with PD-L1 <50% were considered the NG, and the group with a PD-L1 value of 50% or more was considered the PG. There were 27 patients in the NG and 11 patients in the PG. It was determined that 21 (67.8%) of 27 NG patients and 3 (21.3%) of 11 PG patients died. In total, 24 (73.2%) of 38 patients were found to have died. While the mean survival in the NG was 10.81 months, the mean survival in the PG was 28.54 months. Mean survival in the PG was statistically significant (Fig. 1, p=0.046).

Discussion

Lung cancer remains the leading cause of death for both sexes worldwide.[1] With the discovery of targeted therapies and immune checkpoints, immunotherapy studies have accelerated. Treatment models including pembrolizumab monotherapy, pembrolizumab and chemotherapy combi-

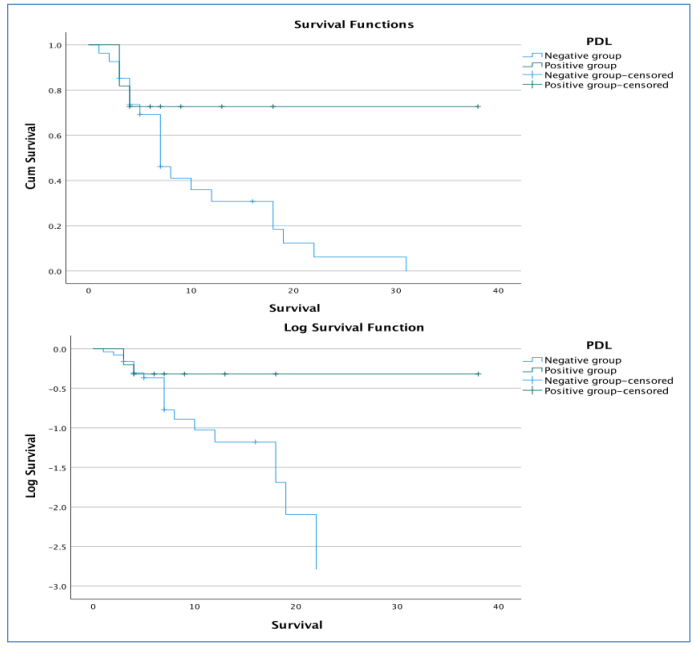

Figure 1. Prognostic effect of PD-L1 expression on survival of Stage 4 NSCLC.

nation therapy, and a combination of atezolizumab, bevacizumab, and chemotherapy have been included in the first-line immunotherapy treatment in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC.[12-14] PD-1 ligand limits the adaptive immune response through T-cells.[15] In cancer patients, the rate of PD-1 is high on tumor-infiltrating T-lymphocytes, thus providing a strong inhibitory signal in the tumor microenvironment by connecting with PD-1 ligands PD-L1 and PD-L2.[16,17]

When studies on PD-1 and its ligand PD-L1 are analyzed, the results show differences. In our study, PD-L1 progression was found to be associated with better prognosis in Stage 4 non-small-cell lung cancer patients. Our study differs from other studies in that target mutations were excluded, only Stage 4 patients were included and not all patients received immunotherapy.

In a study on PD-L1, positive expression of PD-L1 was reported to be associated with poor prognosis.[18] Similarly, in studies on other tumor types, PD-L1 expression on tumor cells was reported to be correlated with poor clinical prognosis in many cancers such as kidney cancer, ovarian cancer, lung cancer, and breast cancer.[19-22] However, the effect of PD-L1 on prognosis has become more controversial with the publication of other studies contradicting the results of these studies. For example, in an early-stage study conducted with 289 patients in 2019, although there was a significant relationship between tumor size increase and PD-L1, no significant relationship was found between PD-L1 and prognosis. In this study, EGFR, ALK, and ROS mutations were not excluded from the study.[23] Similarly, when the results of a study conducted with 225 patients in 2019 were examined; all of the patients were found to have early stage disease. The PD-L1 cutoff value was accepted as 50%, and the results of the study were examined. In this study, EGFR, ALK, and ROS mutations were not excluded. In the study, no significant relationship was found between the increase in PD-L1 value and prognosis, and it was concluded that PD-L1 is not a prognostic factor.[24]

Contrary to these studies, in a large and comprehensive study conducted in recent years, PD-L1 expression and tumor infiltration did not reveal any significant effect on overall survival; however, a favorable prognosis was found for PD-L1 expression in tumor cells in patients with pulmonary squamous cell carcinomas, higher T descriptors, or lymph node metastases who received adjuvant therapy. In this study, tumors were considered PD-L1 positive if >5% of tumor cells showed at least moderate staining. If >5% of lymphocytes showed PD-1 staining, the tumor was considered PD-1 positive. In addition to in this study, borderline prognostic effects were found in some multivariate subgroup analyses for infiltration of PD1-positive lymphocytes.[25]

Our study is a single-center study. Therefore, the patient population was selected from a limited environment. Since the patient information was analyzed considering the available data in the patient files, the smoking histories of the patients could not be obtained exactly, and therefore the relationship between PD-L1 and smoking could not be evaluated. This is one of the limitations of our study. The biggest difference of our study from other studies is that we excluded patients with positive EGFR, ALK, and ROS mutations. Patients with positive mutations were excluded from the study because mutations have different effects on surveillance and may change the prognosis analysis of patients receiving targeted therapy. When both early and late studies are analyzed, it is noteworthy that this distinction was not made. In addition to the studies, in which PD-L1 was found to be an unfavorable prognostic factor, there are also a number of studies indicating that PD-L1 is prognostically insignificant. Therefore, it is thought that randomized prospective studies with larger patient groups in early stage disease and advanced stage disease are needed.

Conclusion

PD-L1 expression was found to be a positive predictive value in Stage 4 non-small-cell lung cancer. Patients with a PD-L1 value of 50% and above have a longer mean survival in the follow-ups performed under standard chemotherapy, although they did not receive immunotherapy, and this was statistically significant. Our study differs from other studies by excluding EGFR, ALK, and ROS mutations. Randomized, prospective studies with larger patient groups, excluding target mutations, independent of immunotherapy and targeted therapies, and randomized, prospective studies with larger patient groups are needed to reveal the relationship between PD-L1 and prognosis more clearly.

Disclosures

Ethics Committee Approval: The study was approved by the ethics committee of our hospital (approval date: March 03, 2019, approval code: 2019/1734).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.K., P.K., Ş.Ö.; Supervision – M.K., Ş.Ö.; Materials – M.K., P.K.; Data collection &/or processing – M.K., P.K., Ş.Ö.; Literature search – P.K., Ş.Ö.; Writing – M.K., P.K., Ş.Ö.; Critical review – Ş.Ö., M.K., P.K.

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