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Incidence and Risk Factors of Immune Checkpoint Inhibitor-Related Pneumonitis: Retrospective Study

İmmün Kontrol Noktası İnhibitörlerine Bağlı Gelişen Pnömonitis Sıklığı ve Risk Faktörleri: Retrospektif Çalışma

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ABSTRACT Objective: This study aims to determine the frequency of pneumonitis toxicity and its potential risk factors in patients receiving immune checkpoint inhibitors (ICIs) due to various malignancies, with the goal of contributing to the reduction of mortality and morbidity. **Material and Methods:** A total of 117 patients who received at least 1 course of ICI treatment and were followed up at the medical oncology and pulmonology outpatient clinics were included in the study. The pre-treatment and post-treatment thoracic computed tomography scans taken within 2-24 months were evaluated in collaboration with a thoracic radiologist, and patterns consistent with pneumonitis were identified according to the diagnostic and staging criteria of current guidelines. Patients' medical records and laboratory findings were retrospectively reviewed; patients with respiratory symptoms, elevated C-reactive protein and sedimentation levels, but normal leukocyte levels, were considered consistent with ICI-related pneumonitis. Pneumonitis frequency and potential risk factors were analyzed. **Results:** Seventy-seven (65.8%) patients were male, and 40 (34.2%) were female, with a mean age of 57.2 years. The overall frequency of ICI-related pneumonitis was found to be 12.8%, while the frequency of high-grade pneumonitis (grade ≥3) was 1.7%, indicating it is rare but life-threatening. The most common pneumonitis was observed after nivolumab and ipilimumab combination therapy (60% of cases). Pneumonitis of all grades developed on average 5 (range 2-9) months after treatment initiation. **Conclusion:** Previous lung disease, prior thoracic radiation therapy, and nivolumab+ipilimumab combination therapy emerged as potential risk factors for the development of ICI-related pneumonitis. Identifying patients at risk for pneumonitis early in clinical practice is crucial to preventing possible complications. In this regard, our study contributes to raising awareness of pneumonitis.

Keywords: Immune checkpoint inhibitors; immunotherapy; neoplasms; pneumonia

ÖZET Amaç: Bu çalışmada, çeşitli maligniteler nedeniyle immün kontrol noktası inhibitörü [immune checkpoint inhibitors (ICI)] kullanan hastalarda pnömonit sıklığı ve buna yol açabilecek risk faktörlerini değerlendirmek, böylece mortalite ve morbiditeyi azaltmaya katkı sağlamak amaçlandı. **Gereç ve Yöntemler:** Tıbbi onkoloji ve göğüs hastalıkları polikliniklerinde takip edilen ve en az 1 kür ICI tedavisi almış 117 hasta çalışmaya dâhil edildi. Hastaların tedavi öncesi ve sonrası 2-24 ay arasında çekilen toraks bilgisayarlı tomografi görüntüleri, torasik radyolog ile birlikte değerlendirilerek pnömonit ile uyumlu paternler, güncel kılavuzlardaki tanı ve evreleme kriterlerine göre belirlendi. Hastaların epikrizleri ve laboratuvar bulguları retrospektif olarak incelendi; solunumsal semptomları olan, C-reaktif protein ve sedimantasyon düzeyleri artmış, ancak lökosit düzeyleri normal olan hastalar, ICI ile ilişkili pnömonit uyumlu kabul edildi. Pnömonit sıklığı ve olası risk faktörleri analiz edildi. **Bulgular:** Hastaların 77'si (%65,8) erkek, 40'ı (%34,2) kadındı ve ortalama yaş 57,2 yıl idi. ICI ile ilişkili pnömonit sıklığı tüm dereceler için %12,8, yüksek dereceli (derece ≥3) pnömonit için ise %1,7 olarak belirlendi. Pnömonit en sık nivolumab ve ipilimumab kombinasyonundan sonra gözlendi (%60). Tüm dereceli pnömonitlerin ortalama gelişim süresi 5 (2-9) ay idi. **Sonuç:** Önceki akciğer hastalığı, toraks bölgesine radyoterapi öyküsü ve nivolumab+ipilimumab kombinasyon tedavisi, ICI ile ilişkili pnömonit gelişimi açısından risk faktörleri olarak öne çıkmaktadır. Klinik uygulamada pnömonit gelişme riski taşıyan hastaların erken dönemde belirlenmesi, olası komplikasyonların önüne geçilmesi açısından önemlidir. Bu nedenle, çalışmamız pnömonitin farkındalığının artırmasına katkıda bulunmaktadır.

Anahtar Kelimeler: İmmün kontrol noktası inhibitörleri; immünoterapi; tümörler; pnömoni

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The most interesting cancer immunotherapy that has recently revolutionized the treatment of various malignancies is immune checkpoint inhibitors (ICIs), which involve antibodies against immune checkpoint molecules. These drugs, which emerged as a result of studies on tumor escape mechanisms, manipulate the immune system to revitalize the anti-tumor response and prevent the causes of escape.[1] Although ICIs have significantly progressed in the treatment of many malignancies, they may have a rare but potentially life-threatening side effect of pneumonitis, although not as much as other cytotoxic chemotherapies.[2,3] Pneumonitis is a general term used to describe inflammation of the lungs.[4] The possible risk factors and chronology of the drug-related side effects, which can cause significant morbidity and mortality, are not known. In this study, we aimed to contribute to reducing mortality and morbidity by determining the frequency of pneumonitis toxicity and possible risk factors in patients who were treated with ICIs due to various malignancy diagnoses.

MATERIAL AND METHODS

In the follow-up clinical practice at Dicle University Faculty of Medicine Hospital Medical Oncology and Pulmonary Diseases, 143 patients who were given at least 1 course of ICIs, nivolumab, pembrolizumab, ipilimumab, and atezolizumab as monotherapy or in combination between January 1, 2016-October 31, 2021 for various malignancies were evaluated.

Since 25 patients changed health centers for treatment follow-up, their data could not be accessed and they were excluded from the study. Thorax computed tomography images of the patients taken before and after treatment within 2-24 months were compared with the radiologist. Patterns compatible with pneumonitis were identified. By examining the patient's epicrisis and laboratory parameters, patients with the presence of respiratory symptoms increased C-reactive protein and sedimentation levels, normal leukocyte levels, and in selected cases, the lack of response to empirical antibiotic therapy were considered to have ICIs-related pneumonitis. Patient files were evaluated retrospectively, with the diagnosis and grading recommendations specified in the guidelines. By determining the incidence of pneumonitis, the patient's age, gender, body mass index, the immunotherapy agent they received, the presence of a history of radiotherapy RT involving the thorax region during the diagnosis of malignancy, the presence of a history or evidence of lung disease before the diagnosis and treatment of malignancy, smoking history, and the number of peripheral blood eosinophilia is evaluated. Risks have been identified. In our evaluations in univariate analyses, those with a p value of 0.05 and below and factors shown to be a significant risk in the literature were included in the multivariate regression analysis. The degree of developing pneumonitis and the month after which pneumonitis developed were examined. Patient information was accessed through patient files and the hospital information management system.

This study complies with the Declaration of Helsinki and received approval from the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee with decision number 182, dated June 9, 2022.

STATISTICAL ANALYSIS

While evaluating the data obtained in the study, SPSS version 25.0 for Windows was used for statistical analyses. Descriptive statistics were expressed as numbers, percentages, means, and standard deviations. Data were initially tested with the Kolmogorov-Smirnov test to determine whether the distribution was normal. Descriptive statistics for the sample were presented as means and standard deviations for quantitative variables, while qualitative variables were reported as absolute values and percentages. Numerical variables were given as means and standard deviations or medians (minimum-maximum). Categorical variables were given as numbers and percentages. The chi-square test was used to examine whether gender, smoking, previous RT history, presence of previous lung disease, medication used, side effect development status, and other count type data and side effect frequency changed. In addition to the statistical significance of each independent variable as a risk factor, estimated relative risk was calculated. Risk factors for the development of pneumonitis were evaluated with univariate and multivariate regression analyses. A p value of <0.05

was considered significant at a 95% confidence interval. Risk factors for the development of pneumonitis were evaluated using univariate and multivariate regression analyses. A p value <0.05 was considered statistically significant, with a 95 percent confidence interval.

RESULTS

One hundred seventeen patients were included in our study. Of these patients, 77 (65.8%) were male and 40 (34.2%) were female. The mean age was 57.2 (22-88). There were 90 (76.9%) patients who received nivolumab for the treatment of various malignancies, 8 (8.6%) patients who received ipilimumab, 7 (5.98%) patients who received atezoluzumab, 7 (5.98%) patients who received pembrolizumab, and 5 (4.27%) patients who received both nivolumab and ipilimumab treatment.

It was determined that 15 (12.8%) patients developed pneumonitis of varying degrees, which was thought to be related to ICIs. Of these, 11 (12.2%) were patients who received nivolumab, 3 (60%) were patients who received nivolumab and ipilimumab, and 1 (14.3%) were patients who received atezoluzumab. No clinical, radiological, or laboratory findings suggesting pneumonitis were observed in those who received pembrolizumab and ipilimumab monotherapy. In high grades (grade ≥3), it was found to be rare but life-threatening at 1.7%. The most common ICI-related checkpoint inhibitor pneumonitis (CIP) was found to develop after nivolumab and ipilimumab combined treatment [n=3 (60%) of 5 patients] (Table 1). Among the types of malignancy, patients diagnosed with non-small cell lung cancer (NSCLC) were the most common for all grade CIP [n=4 (17.3%) of 23 patients]. Three (13.3%) patients with malignant melanoma, 3 (11.1%) patients with renal cell cancer (RCC), and 1 (20%) patient with laryngeal carcinoma developed pneumonitis after receiving nivolumab (Table 2). Three (60%) of 5 patients with malignant melanoma who received ipilimumab and nivolumab combined treatment developed pneumonitis. One (50%) patient who received atezolizumab due to bladder carcinoma developed pneumonitis. All grades of pneumonitis were observed to develop in an average of 5 (2-9) months (Figure 1). According to the results of multivariate regression analysis, it was determined that the presence of a history of RT involving the thorax before ICI treatment, the presence of a history or finding of pre-existing lung disease, and the combined use of nivolumab and ipilimumab significantly increased the risk of developing CIP in patients (Table 3).

DISCUSSION

In this study, we found that the frequency of CIP was 12.8% overall, with 1.7% of cases being high-grade (grade ≥3), which is rare but life-threatening. Pneumonitis was most commonly observed after nivolumab and ipilimumab combination therapy, and the average onset of pneumonitis was 5 months after treatment initiation. Additionally, prior lung disease, previous thoracic radiation therapy, and nivolumab+ipilimumab combination therapy were identified as potential risk factors for the development of ICI-related pneumonitis.

While ICIs have revolutionized the treatment of various malignancies, they can also have a rare but life-threatening side effect of pneumonitis, although not as much as other cytotoxic chemotherapy. Since the possible risk factors and chronology of this significant side effect, which can cause significant morbidity and mortality, are unknown, it is impossible to predict when and to whom it may occur. Since respi-

TABLE 1: Occurrence of CIP according to types of ICIs used as monotherapy or in combination

Pneumonitis	Nivo	Ipili	Atezo	Pemb	Nivo+ipili	Total
Yes	11	0	1	0	3	15
No	79	8	6	7	2	102
Total	**90**	**8**	7	7	5	**117**

Nivo: Nivolumab; Ipili: Ipilimumab; Pemb: Pembrolizumab; Atezo: Atezoluzumab

TABLE 2: Types of malignancies and corresponding ICIs in patients who developed CIP

Malignancy	Nivo	Atezo*	Nivo+ipili	Total
NSCLC	4	0	0	4
Malignant melanoma	3	0	3	6
RCC	3	0	0	3
Laryngeal carcinoma	1	0	0	1
Bladder cancer	0	1	0	1
Total	11	1	3	15

Nivo: Nivolumab; Ipili: Ipilimumab; Atezo: Atezoluzumab;
NSCLC: Non-small-cell lung cancer; RCC: Renal cell cancer

ratory symptoms observed as a result of ICI-related pulmonary toxicity are not specific, a differential diagnosis is necessary. Clinicians should carefully evaluate newly developed respiratory symptoms. A multidisciplinary board, including chest disease specialists, should discuss the case if necessary.

In our study, the frequency of CIP was 12.8% for all grades and 1.7% for high grades (grade ≥3). This frequency was 17.3% for all grades among patients with NSCLC, 13.3% among patients with melanoma, and 11.1% among patients with RCC.

According to a meta-analysis compiled by Nishino M. et al. in 2016, the frequency of CIP is 0.8% for the highest grades (grade ≥3) and 2.7% for all grades.[2] In NSCLC studies, the frequency for all grades was between 1.4-5.8%, in RCC studies it was between 2.7-4.8%, and in melanoma studies, it was between 1-4.8%.

In a meta-analysis compiled by Ma et al. in 2018, the incidence of all-grade and high-grade pneumonia in non-small cell lung cancer was found to be significantly higher compared with other tumor types such as melanoma, RCC, and head and neck squamous cell carcinoma (3.1% vs. 2.0%; p=0.02, 1.4% vs. 0.6%; p=0.03).[5]

One of the most recent and comprehensive meta-analyses, involving 142,703 patients, reported an overall CIP incidence of 16% for all grades and 6% for grade ≥3 pneumonitis.[6] However, meta-analyses and retrospective studies suggest that the frequency of CIP ranges from <2% to 19%. This extensive range is likely related to the recent increase in the frequency of ICI use, patient selection for ICIs, presence of known previous lung disease, and type of primary cancer.[7-9]

In our study, some parameters we evaluated regarding the risk of developing CIP were age, gender, body mass index, type of malignancy, and peripheral blood eosinophil count. In some articles in the literature, it was stated as a potential risk factor for CIP, but in some articles, it was seen that these parameters were not significant in terms of risk factors.[10-15] In our study, it was seen that these parameters were not significant in terms of risk factors.

One of the parameters we evaluated as a potential risk factor for CIP was the presence of previous or current smoking habit, and in our study, a significant relationship was found in the univariate regres-

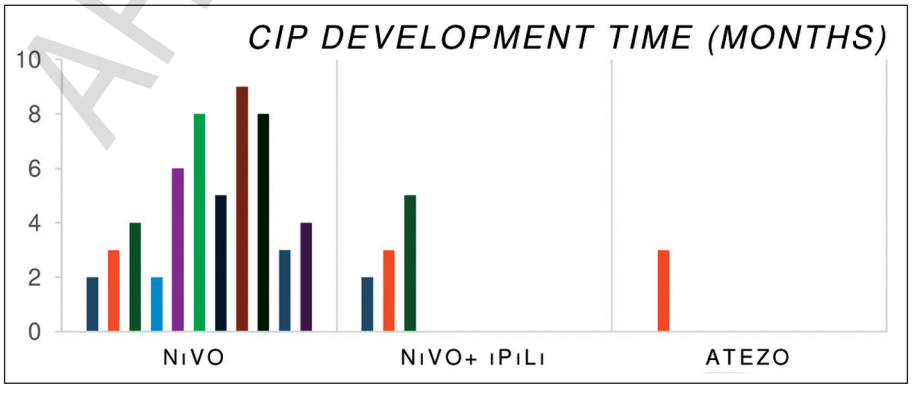

FIGURE 1: Time to development of pneumonitis in patients after ICI use
Nivo: Nivolumab, Ipili: İpilimumab, Atezo: Atezoluzumab

TABLE 3: Evaluation of risk factors affecting the development of ICIs-related pneumonitis (CIP) by multivariate logistic regression analysis

		Univariance analysis			Multivariate analysis		
Risk categories		**OR**	**p value**	**95% CI**	**OR**	**p value**	**95% CI**
Gender	Man Woman	0.667	0.513	(0.198-2.24)			
Age (years)	≥65 <65	0.917	0.882	(0.29-2.88)			
BMI	<21	1.060	0.268	(0.94-1.9)		O.087	
	21-25	0.129	0.109	(0.10-1.58)		0.29	
	25-30	0.808	0.809	(0.14-4.55)		0.81	
	≥30	1.184	0.856	(0.19-7.3)		0.100	
Malignancy	NSCLC		0.857				
	Melanoma	0.73	0.656	(0.18-2.9)			
	RCC	0.59	0.527	(0.11-2.98)			
	Other	0.47	0.420	(0.07-2.9)			
Smoking Habit	**5.12**	**0.037**	**(1.1-23.9)**	**8.01**	**0.055**	(0.95-67.4)	
Previous lung disease	**6.73**	**0.005**	**(1.78-25.4)**	**7.18**	**0.032**	**(1.18-43.7)**	
Previous RT history	**5.15**	**0.005**	**(1.66-15.9)**	**6.94**	**0.020**	**(1.35-35.5)**	
Eosinophil level	>0.125x10e3/uL	2.00	0.234	(0.63-6.26)			
Type of ICI	Nivolumab		0.201				
	Atezolizumab	1.18	0.882	(0.13-10.7)	0.22	0.364	
	Nivolumab&Ipilizumab	**10.6**	**0.015**	**(1.59-70.9)**	**46.2**	**0.010**	**(2.4-856.7)**
	Pembrolizumab		0.99			0.99	
	Ipilizumab		0.98			0.99	

ICIs: Immune checkpoint inhibitors; CIP: Checkpoint inhibitor pneumonitis; OR: Odds Ratio; CI: Confidence interval; BMI: Body mass index; NSCLC: Non-small-cell lung cancer; RCC: Renal cell cancer; RT: Radiotherapy

sion analysis [smoker and never-smoker; odds ratio (OR)=5.12; 95% confidence interval (CI)=(1.1-23.9); p=0.037].

Uchida et al. obtained significant results with univariate regression analysis of smoking as a risk factor for CIP in extrapulmonary malignancies (OR=3.49; 95% CI=1.06-15.77; p=0.038).[16]

In the same study, a significant relationship was found with the amount of cigarettes smoked in multivariate regression analysis, but in our study, risk analysis of the number of cigarettes could not be performed due to insufficient data. This is one of the limitations of our study. It has been reported that the incidence of CIP may increase as a result of pulmonary damage that may occur as a result of thoracic radiotherapy.[17,18] Therefore, one of the potential risks for the development of CIP that we included in our study was the presence of previous radiotherapy applied to the thoracic region. A significant relationship was found in multivariate regression analysis (OR=6.94; 95% CI=1.35-35.5; p=0.020).

Cui et al. also published a case-control study, showing that previous thoracic RT was a major risk factor for pneumonitis (OR=3.34).[19] Similarly, Feliciano Barrón et al. found in their retrospective study of 101 patients with NSCLC that the incidence of pneumonitis associated with ICI was significantly higher in patients with a history of radiotherapy compared to patients who had not received radiotherapy before [OR=6.11; 95% CI=2.13-17.52; (p<0.001)].[20]

In contrast to these results in the literature, there are studies such as the study conducted by Saito et al. in 2021 with 29 patients, which reported that there was no significant relationship between the presence of a history of radiotherapy and CIP (p=0.331).[21] We believe that these studies should be supported by studies conducted with larger patient groups.

Another potential risk factor for the development of CIP was the presence of previous lung disease. In many studies, the presence of previous lung diseases such as pulmonary emphysema, asthma, chronic obstructive pulmonary disease, pleural effusion, and pneumothorax have been reported as risk factors for the development of CIP.[22-24]

The mechanism between the development of CIP and preexisting lung disease is not fully known. Although ICI was not subgroup-specific in our study, a significant association was found between preexisting lung disease and the development of pneumonitis associated with ICI use in multivariate regression analysis. We evaluated it as a potential risk factor (OR=7.18, 95% CI=1.18-43.7; p=0.032). Therefore, clinicians should be careful in the use of ICI in patients with preexisting lung disease.

However, ICI combination therapies generally show better antitumor efficacy than monotherapies.[25] Although this situation makes the potential toxicities more acceptable, reported studies have shown that combined treatments increase the incidence of pneumonitis compared to monotherapies.

In a meta-analysis reported by Su et al., PD-1 inhibitor and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor combination therapies showed a significant increase in all-grade pneumonitis compared with nivolumab (PD-1 inhibitor) or ipilimumab (CTLA-4 inhibitor) monotherapy (OR=3.47; 95% CI=1.76-6.83; p<0.001; OR=3.48, 95% CI=1.10-11.02; p<0.001).[26] Similarly, in the CheckMate 012, CheckMate 227 and CheckMate 568 clinical trials, combination therapies with nivolumab and ipilimumab antibodies also resulted in a higher incidence of pneumonitis than nivolumab monotherapy.[25,27,28]

The mechanisms underlying the increased incidence of CIP compared to monotherapy after combination therapies remain unclear, but the increased morbidity is thought to be a synergistic effect rather than an additive effect. This comparison was also made in our study, and in the multivariate regression analysis, it was found that PD-1 inhibitor and CTLA-4 inhibitor (nivolumab and ipilimumab) combination therapy showed a significant increase in the risk of pneumonitis compared to PD-1 inhibitor (nivolumab) monotherapy (OR=46.2; 95% CI=2.4-856.7; p=0.01).

In our study, a standardized protocol for excluding infectious causes in the diagnosis of pneumonitis was not applied. Specifically, the lack of bronchoalveolar lavage in all cases may affect diagnostic certainty. This has been acknowledged as one of the limitations of our study. Additionally, being a single-center study limits the generalizability of the findings, and the small number of patients receiving combination therapy has led to a wider confidence interval.

According to the results of existing clinical studies; when choosing a combination therapy, many factors such as the patient's general condition, degree of disease progression, and previous treatment should be taken into consideration. It is understood that further multicenter studies are needed to evaluate the safety and risk factors of combination therapies.

CONCLUSION

In summary, this study highlights critical considerations in the use of ICIs, particularly concerning the development of immune-related pneumonitis. Certain patient characteristics, such as a history of lung disease, prior thoracic radiotherapy, and the use of combination ICI therapy, appear to be associated with increased risk.

Clinicians should carefully evaluate populations with these features, especially patients with previous lung disease, in terms of ICI suitability, and carefully evaluate newly developed respiratory symptoms in populations that have received ICI treatment and discuss them in a multidisciplinary board including chest disease specialists if necessary. In addition, additional studies are needed to better understand the clinical features and timing of pneumonitis, to clarify the mechanism(s) that immunotherapy causes these immune-mediated events, and to determine possible other risk factors.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Furkan Kangül;* ***Design:*** *Furkan Kangül, Hadice Selimoğlu Şen;* ***Control/Supervision:*** *Hadice Selimoğlu Şen, Zuhat Urakçı, İbrahim Akbudak;* ***Data Collection and/or Processing:*** *Furkan Kangül, Zuhat Urakçı, İbrahim Akbudak;* ***Analysis and/or Interpretation:*** *Furkan Kangül, Hadice Selimoğlu Şen, İbrahim Akbudak;* ***Literature Review:*** *Furkan Kangül, Zuhat Urakçı, Hadice Selimoğlu Şen;* ***Writing the Article:*** *Furkan Kangül, Hadice Selimoğlu Şen;* ***Critical Review:*** *Hadice Selimoğlu Şen, Zuhat Urakçı;* ***Materials:*** *Zuhat Urakçı.*

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