ORIGINAL RESEARCH

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Clinical and Radiological Features and Treatment of Pulmonary Toxicity Associated with Using Immune Checkpoint Inhibitors in Cancer Treatment: A Single-Center Experience

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ABSTRACT Objective: Immune checkpoint inhibitor-related pneumonitis (ICI-P), as a rare, immune-related adverse event, is difficult to diagnose and treat for clinicians because of its life-threatening adverse events and nonspecific clinical and laboratory findings. **Material and Methods:** Patients with newly developed pulmonary infiltrates receiving ICI for cancer treatment were included in this study, and their images were re-evaluated by a radiologist. **Results:** In this study, 32 (88.9%) male and four (11.3%) female patients with a median age of 62 years (range: 20-70 years) were enrolled, of whom 26 patients (72.3%) were diagnosed with non-small cell lung cancer. The most frequent ICI-P-related symptom was cough (63.9%). The median time to the occurrence of ICI-P was 3.5 months (range: 0.3-20 months), and the median number of cycles was four (range: 1-25). Ten patients needed hospitalization, 13 patients were found with permanent termination of ICI therapy, and ICI-P recurred in six patients (16.7%). Other immunosuppressive treatments, such as using mycophenolate mofetil and infliximab, were required in three steroid-refractory patients. No patient died due to uncontrolled ICI-P. **Conclusion:** In our study, consolidation was the most common radiological finding of ICI-P, which may involve the contralateral side as well as the tumor margin, possibly mimicking lymphangitic spread. Although ICI-P diagnosis is based on the exclusion of other differential diagnoses, it can mimic many other clinical conditions. Empirical use of steroids should not be avoided if there is clinical suspicion because of the risk of mortality.

Keywords: Immunotherapy; pneumonia; adverse effects

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies and include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1), which are becoming increasingly important in cancer treatment.[1] ICIs exert their anti-tumoral activity by increasing the activity of the immune system, especially T cells.[2] The United States Food and Drug Administration has approved many ICIs; for example, ipilimumab, an anti-CTLA-4 antibody, was the first agent approved in 2011 for melanoma patients.[3] PD-1 is targeted by pembrolizumab, nivolumab, and cemiplimab, while atezolizumab, durvalumab, and avelumab target PD-L1. They have been introduced for the treatment of many solid and liquid cancers, such as malignant melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and cancers with impaired DNA damage repair (MSI-high).[4] More than 233,000 patients receive these agents annually as first- or next-line therapy.[5]

ICIs are associated with several adverse events different from those of other conventional systemic therapies, such as cytotoxic chemotherapy, including decreased T-cell tolerance and uncontrolled activation of immunity, with unknown pathophysiology.[6] Although these adverse events can affect many organs and mostly the skin, they may affect the thyroid, adrenal, and pituitary glands, gastrointestinal tract, lung, kidney,

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and also the musculoskeletal, nervous, cardiovascular, hematological, and ocular systems.[7] ICI-related pneumonitis (ICI-P) is a highly fatal immune-related adverse event (irAE), which accounts for almost 30% of anti-PD-L1 adverse events-related deaths.[8]

ICI-P is defined as the development of dyspnea and/or other respiratory symptoms with new infiltrates on chest imaging and the exclusion of other possible causes.[9] ICI-P usually develops within the first months of ICI therapy.[10] Dyspnea and dry cough are common symptoms of ICI-P. Although fever, chest pain, shortness of breath, fatigue, or respiratory failure are other symptoms, it has no specific symptoms, and more than 30% of the patients are asymptomatic.[11] ICI-P has no specific histologic findings. It is mostly manifested by increased nodular opacification of different sizes and ground-glass infiltrates, which involve the lower lobes of the lung. ICI-P may present with different radiological patterns, such as cryptogenic organizing pneumonia (COP) pattern, nonspecific interstitial pneumonia (NSIP) pattern, acute interstitial pneumonia/acute respiratory distress syndrome pattern, hypersensitivity pneumonitis (HP) pattern, and unclassified pattern. However, they are not specific to ICI-P.[12]

Steroids are the first-line treatment for ICI-P; however, the optimal dosing strategy and duration of steroid therapy are still undefined.[7] The recurrence of irAEs is preventable using steroid therapy considering an appropriate duration and a careful reduction in dose. In very severe or steroid-resistant irAEs, additional immunosuppressive agents, such as infliximab, mycophenolate mofetil, intravenous (IV) immunoglobulin, and cyclophosphamide are often required within the first 48-72 h.[13,14] This retrospective study was done to share our experience regarding the clinical and radiological features, steroid therapy, and responses to treatment in patients with ICI-P with different tumor types at the initiation of ICI therapy.

MATERIAL AND METHODS

Based on a retrospective data analysis, this study evaluated newly developed pulmonary infiltrates in patients diagnosed with ICI-P who received ICI for cancer treatment in the Oncology Department of Trakya University Hospital between April 2015 and April 2022. The inclusion criteria were locally advanced cancer diagnosed by histopathological biopsy, using at least one cycle of ICIs either as monotherapy or in combination with other agents, the presence of newly developed pulmonary infiltrates following ICI therapy, and ICI-P diagnosed by the multidisciplinary team. The exclusion criteria included unawareness about using ICIs in double-blind clinical studies, radiation-induced pneumonitis, and patients with incomplete or missing data. This study was conducted in accordance with the principles of the 2013 version of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Faculty of Medicine on 31 May 2021, Trakya University (no: 2021/247). Due to the retrospective nature of the study, informed consent was waived.

The patient's files were reviewed retrospectively, and their information, including age, gender, smoking status, underlying pulmonary disease, tumor type and grade, previous treatments, the used ICIs, treatment line of ICIs, date of treatment onset, the best response to ICIs, date of ICI-P diagnosis, ICI-P stage, clinical symptoms of ICI-P, date of initiation of steroid therapy, duration of ICI therapy, additional immunosuppressive treatments, reinitiated ICIs after their discontinuation, and recurrent ICI-P was collected in detail. A radiologist expert in thorax and oncology re-evaluated the images. The initial scan was considered as a chest computed tomography (CT) scan performed three months before the initiation of ICI therapy, and its findings, including emphysema and pulmonary fibrosis, were recorded. Consolidation, ground-glass opacity, septal thickening, traction bronchiectasis, and ICI-P pattern were also recorded. To avoid missing unfavorable pulmonary events associated with ICI use, such as hyperprogression, we performed the first control imaging during the eighth week of the treatment, and the next images were captured at intervals of 12 weeks. Because radiation pneumonitis and ICI-P cannot be clearly distinguished by clinical, laboratory, and imaging studies, and both have steroid responses, patient management was done based on our clinical and radiological experience after chemoradiotherapy (CRT). These patients were evaluated and diagnosed in councils, including experienced physicians.

RESULTS

PATIENTS' CHARACTERISTICS

Of a total of 62 patients treated with an ICI, 68 cases were found with ICI-P. Excluding cases of infectious pneumonia, acute exacerbation of chronic obstructive pulmonary disease (COPD), lymphangitis carcinomatosis, cardiac pulmonary edema, and radiation-induced pneumonitis, evaluated by a multidisciplinary team, the analysis was done on 42 ICI-Ps in 36 patients (ICI-P recurred in six patients after reuse of ICIs). Sixty percent (42/68) of the pulmonary events developed after ICI therapy were associated with ICI-P. Table 1 presents the general characteristics of these 36 evaluated patients.

Twenty patients (55.6%) used ICIs as first-line treatment, four patients (11.1%) as second-line treatment, and only one patient as third-line treatment. Also, 11 patients (30.6%) used ICIs as maintenance therapy after CRT. Among ICIs, anti-PD-L1 and anti-PD-1 were mostly used as monotherapy by 21 and 15 patients, respectively. The dose of ICIs was adjusted based on the recommended dosing frequency.

RADIOLOGICAL FEATURES AND PATTERN OF ICI-P

Table 2 provides information regarding the features of the main pulmonary infiltrates detected on the initial chest CT scan of patients without steroid therapy for ICI-P. The predominant radiological finding was consolidation (n=18, 50%). On a chest CT scan, pulmonary infiltration had an asymmetric distribution in 55.6% of patients (20/36), and the remaining patients showed a symmetrical distribution. Pulmonary infiltration was predominantly peripheral in 58.3% of the cases, while both lobes were affected in 16 patients (44.4%), and three lobes and more were affected in 15 patients (41.7%). According to idiopathic interstitial pneumonia classification, the ICI-P pattern was COP in 12 patients (33.3%), diffuse alveolar damage (DAD) in 10 patients (27.8%), HP in 4 patients (11.1%), NSIP in 2 patients (5.6%), and nonspecific in 8 (22.2%) patients. Table 3 presents the radiological pattern and grade (G) of ICI-P by the PD-1/PD-L1 agent used.

TABLE 1: Patient characteristics.

	Median, n (%)
Age, years	62 (20-70)
Gender	
Male	32 (88.9)
Female	4 (11.3)
Smoking status	
Never smoked	3 (8.3)
Quit	17 (47.2)
Active smoker	16 (44.4)
Lung cancer	
Small cell lung cancer	3 (8.3)
Non-small cell lung cancer	
-Adenocarcinoma	11 (30.6)
-Squamous cell	15 (41.7)
Cancer type	
Head and neck cancer/Urinary cancer	2 (5.6)
Malignant melanoma/Osteosarcoma/Stomach cancer	1 (2.8)
Cancer stage	
III	11 (30.6)
IV	25 (69.4)
ECOG-PS	
0	27 (75.0)
1	9 (25.0)
History of pulmonary disease	
No	27 (75.0)
Chronic obstructive pulmonary disease	7 (19.4)
Pulmonary fibrosis or emphysema	2 (5.6)
History of lung operation	2 (5.6)
History of lung radiotherapy	21 (58.3)
Initial line of ICI	
1	20 (55.6)
2	4 (11.1)
≥3	1 (2.8)
Post-chemoradiotherapy	11 (30.6)
Treatment type	
Monotherapy	25 (69.4)
Combined therapy	
-Tyrosine kinase inhibitor	2 (5.6)
-Chemotherapy	9 (25.0)
ICI agent	
Anti-PD-1 inhibitor	15 (41.7)
Anti-PD-L1 inhibitor	21 (58.3)
Best response to treatment	
CR	2 (5.6)
PR	21 (58.3)
SD	10 (27.8)
PD	3 (8.3)

ECOG-PS: Eastern Cooperative Oncology Group Performance Score; ICI: Immune checkpoint inhibitor; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death-ligant 1; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

TABLE 2: Radiological features of ICI-P.

	n (%)
ICI-P site	
Tumor periphery	16 (44.4)
Contralateral side	20 (55.6)
Involved lobe	
Left	9 (25)
Right	11 (30.6)
Bilateral	16 (44.4)
Topography	
Peripheral	21 (58.3)
Central	7 (19.4)
Diffuse	8 (22.2)
Number of involved lobes	
1	8 (22.2)
2	13 (36.1)
3 and above	15 (41.7)
Infiltrative component	
Ground-glass opacity	10 (27.8)
Consolidation	18 (50.0)
Septal thickening	6 (16.7)
Traction bronchiectasis	2 (5.6)

ICI-P: Immune checkpoint inhibitor-related pneumonitis.

TABLE 3: ICI-P patterns and grades.

	Anti-PD1, n	Anti-PD-L1, n
Dominant pattern		
COP	5	7
DAD	2	8
NSIP	1	1
HP	3	1
Non-specific	4	4
ICI-P grade		
1	5	7
2	7	7
3	2	7
4	1	-

ICI-P: Immune checkpoint inhibitor-related pneumonitis; COP: Cryptogenic organizing pneumonia; DAD: Diffuse alveolar damage; NSIP: Nonspecific interstitial pneumonia; HP: Hypersensitivity pneumonia.

CLINICAL FEATURES OF ICI-P AND STEROID THERAPY

The median time to ICI-P development was 3.5 months (range: 0.3-20 months), and the median number of cycles was four (range: 1-25). G1 ICI-P was developed in 12 patients (33.3%), G2 ICI-P in 14 patients (38.9%), G3 ICI-P in 9 patients (24.9%), and G4 ICI-P in only 1 patient (2.7%). ICI-P (Grade 3-4) was developed as a serious adverse event in approximately one in three analyzed patients. The most frequent complaints of patients with ICI-P were cough (n=23, 63.9%), followed by fatigue (n=16, 44.4%) and shortness of breath (n=15, 41.7%). Subfebrile or febrile fever was reported by 22% of the patients, while approximately one in ten patients were found with less frequent symptoms, such as chest pain and joint pain. Twelve patients were asymptomatic. Other irAEs following ICI therapy were thyroiditis in six patients, dermatitis in five patients, and colitis in two patients. The median time from ICI-P diagnosis to the initiation of steroid therapy was three days (range: 0-13 days). Fourteen and ten patients received oral and IV steroid therapy, respectively, with a mean initial steroid dose of 50-80 mg. The median time from the treatment onset to the first dose modification was ten days (range: 2-33 days), and the median duration of steroid therapy was 43 days (range: 16-93 days). Following steroid therapy, most patients achieved clinical response within the first few days, and the symptoms had completely resolved within about three weeks. The diagnosis, treatment, and features of recurrent immune pneumonitis are presented in Table 4.

DIAGNOSIS, TREATMENT, AND RECURRENT IMMUNE PNEUMONITIS

In 12 asymptomatic patients with G1 ICI-P, ICI therapy was continued with closer follow-ups before steroid therapy was initiated. During the follow-up period, immune pneumonitis recurred nine months later in one patient as G1, and in another patient as G2, ten months later. In all other patients, ICI therapy was definitively terminated and steroid therapy was started. ICI therapy was permanently discontinued in 13 patients due to immune pneumonitis.

Ten patients were hospitalized and received oxygen support, and during their follow-up, two cases were treated non-invasively, while five cases were treated invasively. Infliximab was prescribed as an additional immunosuppressive therapy for one patient who received non-invasive treatment due to worsening of clinical findings despite a week of receiving IV steroid therapy. Two hospitalized patients

TABLE 4: Clinical information about ICI-P and steroid treatment and follow-up process.

	Median, n, %
Time from ICI initiation to ICI-P development, months	3.5 (0.3-20)
Mean number of ICI cycles until ICI-P development	4 (1-25)
ICI-P symptoms	
Asymptomatic	33.3%
Subfebrile or febrile fever	22.2%
Fatigue	44.4%
Cough	63.9%
Shortness of breath	41.7%
Chest pain	13.9%
Joint pain	11.1%
Time from suspicion of ICI-P to initiation of steroid therapy, days	3 (0-13)
Steroid therapy	
Yes	24
Oral	
0-5 mg	7
1 mg	7
Intravenous	
1 mg	7
2 mg	3
No	12
Steroid starting dose	
30-50 mg	8
50-80 mg	10
80-150 mg	6
Duration of use of the starting dose, days	10 (2-33)
Duration of full dose steroid use, days	43 (16-93)
Symptom duration, weeks	3 (1-13)
Response to steroid therapy	
Yes	18
No	6
Hospitalization	10
Supportive treatment	
Oxygen	10
Non-invasive treatment	2
Invasive treatment	5
Immune colitis	2
Immune thyroiditis	6
Immune dermatitis	5
Mycophenolate mofetil use	2
Infliximab use	1
Steroid resistance	5
Recurrent ICI-P	6
Time from first ICI-P recovery to ICI-P recurrence, months	8.5 (4.2-9.8)
Discontinuation of ICI due to pneumonia	13
Death from other causes despite controlled pneumonitis	4

ICI: Immune checkpoint inhibitor; ICI-P: Immune checkpoint inhibitor-related pneumonitis.

(one with G3 and the other with G4 ICI-P) were treated with mycophenolate mofetil as an additional immunosuppressive therapy, initiated on IV steroid therapy; these patients experienced worsening of clinical findings three weeks later. One of these patients was intubated. All three patients who received additional immunosuppressive therapy responded to the treatment.

Although ICI-P was controlled by steroid therapy, four patients died of secondary causes, such as infectious pneumonitis, pulmonary embolism, decompensated heart failure, and tumor progression, for which a clear differential diagnosis was not possible. One patient died with a diagnosis of ICI-P but was not included in the study due to the missing file and insufficient data. No patient died because of uncontrollable ICI-P.

Treatment with the same ICI was continued in ten and 13 patients with G2 and G3 ICI-P, respectively, after complete or almost complete recovery of immune pneumonitis with their consent, and ICI-P recurred in four patients. The median time from the initial diagnosis of ICI-P to the diagnosis of recurrent ICI-P was 8.5 months (range: 3.1-10.8 months). In two out of four patients, the initial ICI-P was G2, which recurred as G2. Of the other two patients, one experienced a higher grade, and another patient exhibited a lower grade ICI-P compared to the initial ICI-P. Patients respond well to steroid therapy for recurrent immune pneumonitis (one patient required hospitalization and non-invasive respiratory support) without the need for additional immunosuppressive therapy.

DISCUSSION

The exact prevalence of ICI-P-related immune pneumonitis remains to be fully characterized and has mainly been concluded based on clinical trial reports and real-world data. The incidence of nivolumab-related ICI-P was reported to be 4.6% and 1.4% in CheckMate 017 and CheckMate 057 studies, respectively, while the incidence rates of 5% and 5.8% were reported for pembrolizumab-related ICI-P in KEYNOTE-010 and KEYNOTE-024 studies, respectively.[15-18] The incidence of ICI-P is slightly lower during PD-L1 inhibitor monotherapy. The incidence of ICI-P was 3% and 1% in patients receiv-

ing atezolizumab in the POPLAR and OAC studies, respectively.[19,20] The incidence of G2 ICI-P reported in the PACIFIC trial evaluating durvalumab maintenance after CRT for NSCLC was 26.5%, whereas G3 ICI-P was reported in only two patients.[21] According to clinical studies on different tumor types, the overall incidence of ICI-P ranges from 3 to 5% for all grades, while it ranges from 0.8 to 1.0% for ≥G3 ICI-P.[22] According to the real-world data presented by Hindocha et al., the incidence rates of ≥G2 ICI-P and ≥G3 ICI-P were 5.4% and 1.49%, respectively, which were higher than the incidence rates reported in the literature.[23] In contrast to clinical studies, a real-world data study on NSCLC patients reported a higher incidence of ICI-P, with 19% for all grades and 11% for ≥G3 ICI-P.[24] The differences in results can be attributed, in part, to the increasing awareness of the medical community regarding ICI-P, which leads to more frequent clinical diagnoses of the disease.

Naidoo et al., for the first time, reported clinical, radiological, and pathological findings of immune pneumonitis in 915 patients based on Memorial Sloan Kettering Cancer Center and Melanoma Institute Australia data. They reported that in comparison with PD-L1 inhibitors (1.3%), PD-1 inhibitors were associated with a higher risk of ICI-P (3.6%), and the risk of ICI-P three times increased after combination therapy. The median time to the onset of immune pneumonitis was 2.8 months (range: 9 days-19.2 months), and the onset of pneumonitis in patients receiving combination therapy was earlier compared to those receiving monotherapy.[8] The median time to the onset of ICI-P was reported as 1.8 and 4.5 months by Wang et al. and Hindocha et al., respectively.[23,25] Delaunay et al. assessed 1,826 patients from several centers in Europe and reported that the onset of ICI-P was earlier in patients with NSCLC compared to melanoma patients (2.1 vs. 5.2 months).[26] In our study, the median time to the onset of ICI-P was 3.5 months (range: ten days to 20 months); 3.2 months in patients with NSCLC and 3.7 months in other cancer types. However, ICI-P can occur at any time, including after ICI therapy termination, and its incidence rate varies over time. Although anti-PD-1 or anti-PD-L1 therapy is sometimes provided for years, their long-term therapy increases the risk of developing ICI-P.[27]

Chennamadhavuni et al. assessed the risk factors in the development of ICI-P and found that the risk of developing ICI-P was higher in smoker patients younger than 60 years of age, with a high body mass index, sarcopenia, muscle wasting, diuretic use, and vitamin D deficiency. CTLA-4 and PD1/PD-L1 inhibitors for female and male patients were associated with a higher risk of ICI-P development, respectively.[28] In another study, the risk of developing ICI-P was three times higher in NSCLC patients with interstitial lung disease compared to the controls, and 2.3% higher in patients with COPD compared to the controls.[29] Moreover, in the Keynote-001 study, the incidence of ICI-P was 13% in patients who received radiotherapy (RT) before the administration of pembrolizumab and 1% in patients who did not receive RT.[30] Consistent with these studies on the risk factors for ICI-P, 91.7% of our patients had a history of smoking, 58.3% had a history of lung RT, and most patients were younger than 60 years.

Immune pneumonitis is difficult to diagnose as it has no specific clinical and radiological findings.[9] Most patients are asymptomatic (33.3% in our study), and the diagnosis can be made incidentally when chest CT is performed for another indication.[31] Our predominant radiological finding was consolidation (50%), while it was ground-glass opacity as reported by Delaunay et al.[26] The radiological pattern of ICI-P was determined based on the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines.[32] The most common pattern was COP (33.3%), followed by DAD (27.8%), HP (11.1%), and NSIP (5.6%), while the pattern in eight patients was nonspecific. According to the immunological agent used, PD-L1 inhibitors resulted in the DAD pattern in 80% of patients, while there was no difference between PD-1 and PD-L1 agents in terms of other patterns. None of these radiological changes are specific, and during the management, immune pneumonitis should be an exclusion diagnosis, and the diagnosis should be made with high clinical suspicion. Among the differential diagnoses, pulmonary embolism, tumor progression, lepidic or lymphan-

gitic spread, radiation-induced pneumonitis, secondary infections, pulmonary edema due to acute heart failure, and fulminant myocarditis should be considered and excluded.[33] Clinical deterioration due to empirical steroid therapy is preventable by an accurate differential diagnosis.

ICI-P should be considered first, especially in patients using ICI presenting newly developed dry cough, shortness of breath, and hypoxia or deterioration of respiratory symptoms. Fever, chest pain, rash, loss of appetite, fatigue, and joint pain may also occur, but there are no specific clinical symptoms.[11] In our study, 36 out of 62 patients with highly suspected ICI-P were diagnosed with immune pneumonitis, and almost all patients reported dry cough (63.9%), followed by fatigue (44.4%) and shortness of breath (41.7%). Nobashi et al. reported high fever (30%) as one of the main symptoms, which could last from a few days to weeks, and unlike our study, cough (15%) and fatigue (7%) symptoms were not frequent.[34] According to the National Comprehensive Cancer Network guideline, based on clinical symptoms and radiological findings, the severity of immune pneumonitis is divided into four grades as follows: G1: asymptomatic patient and the involvement of <25% of a lobe or lung parenchyma, G2: the presence of moderately severe symptoms, the need for oxygen support with effort, and the involvement of multiple lobes or 25-50% of the lung parenchyma, G3: limited daily activity and continuous oxygen requirement and the involvement of more than 50% of the lung parenchyma, and G4: life-threatening clinical picture requiring emergency hospitalization.[35] In our study, 24 patients were symptomatic, of whom 14 cases (38.9%) had G2, nine cases (25.0%) had G3, and only one patient had G4.

ICI-P is considered a self-limiting disease. ICI-P treatment should be started immediately without delay after the diagnosis is confirmed and when suspicion is high. Steroid therapy is the routine strategy for the management of ICI-P. To the best of our knowledge, no prospective clinical study has evaluated the optimal therapeutic modality.[24] According to the current consensus regarding ICI-P treatment, ICI should be terminated, and steroid therapy should be initiated after the diagnosis of ≥G2 ICI-P is confirmed. Clinical symptoms, radiological imaging, and pulmonary functions of patients with G1 ICI-P should be closely monitored at three-week intervals to delay ICI treatment for 1-2 weeks.[36] If clinical symptoms worsen, ICI treatment should be terminated, and steroid therapy should be started at a low dose of 0.5-1 mg/kg.[37] In our study, the diagnosis of G1 ICI-P was made in 12 asymptomatic patients, who were closely followed up without ICI treatment terminated; one patient developed recurrent ICI-P nine months later, and the rest ten months later. For patients with G2 ICI-P, empirical antibiotic therapy should be considered if an infection is suspected, and steroid therapy should be started at a dose of 1-2 mg/kg. After the symptoms regress to G1, the dose should be reduced gradually to 5-10 mg per week, and steroid therapy should be terminated within 4-6 weeks. If clinical improvement is not observed within two to seven days, the steroid dose should be increased and the immunosuppressive agent should be added to the treatment.[13] ICI therapy is often restarted in patients who achieve clinical response (≤G1 ICI-P or steroid requirement of ≤10 mg/day).[38] Clinical symptoms should be evaluated every three days, and radiological findings should be evaluated once a week for possible exacerbation and recurrent pneumonitis.[39]

ICIs should be discontinued immediately and permanently in patients with G3-4 ICI-P. According to the consensus of current guidelines, the initial steroid dose is 2-4 mg/kg, and in case of respiratory symptom improvement, steroid doses should be gradually reduced and stopped after the sixth week.[13,35,40,41] However, no clinical study has indicated optimal steroid doses and duration of use; therefore, the duration of treatment has been mainly adjusted based on the response to steroid therapy. In our study, the mean time from the diagnosis of ICI-P to the steroid therapy onset was three days, and 83.3% of the patients responded to the initial steroid dose. The mean duration of initial steroid use was ten days, with a total duration of six weeks for G2 and ten weeks for G3. According to rheumatology practice, steroids have immunosuppressive effects and are associated with a higher risk of opportunistic infections.[42] Because opportunistic infections increase the risk of

mortality in patients with immune pneumonitis, a starting steroid dose of <1 mg/kg for G2 and 1-2 mg/kg for G3-4 and avoiding >30 mg/day has been recommended for more than 30 days.[25,43,44] However, the recurrence risk of ICI-P is higher in patients with G3-4 ICI-P at baseline and after using steroids for less than five weeks.[45] Tao et al. assessed 1102 patients with NSCLC and reported an ICI-P incidence of 7.26% and a recurrent ICI-P rate of 25.6%, with recurrent ICI-P being significantly higher in patients using >15 mg/kg of steroid for less than four weeks.[46] In our study, ICI-P recurred in six out of 36 patients (16.7%) after an average of 8.5 months.

Some patients are steroid-refractory or may become steroid resistant and need additional immunosuppressive therapy. Steroid refractory is defined as no clinical improvement and worsening of clinical course after the initiation of steroid therapy in patients with immune pneumonitis, while steroid resistance is the recurrence of immune pneumonitis with the gradual tapering of steroids that initially responds to steroid therapy.[47] In our study, additional mycophenolate mofetil was considered for one steroid-refractory patient, mycophenolate mofetil for one of the two steroid-refractory patients, and infliximab was prescribed for another patient. These three patients benefited from additional immunosuppressive therapy.

Because the number of all patients receiving ICI treatment was not fully screened, ICI-P incidence could not be determined, which is one of the limitations of this study. Because the differential diagnosis cannot be made accurately, some ICI-Ps were possibly associated with RT.

CONCLUSION

Although ICI-P diagnosis is based on the exclusion of other differential diagnoses, it can mimic many other clinical conditions. Empirical use of steroids should not be avoided if there is clinical suspicion because of the risk of mortality. It should be noted that some patients may be steroid refractory with the need for additional immunosuppressive treatments. ICI-P management requires the teamwork of experts, such as radiologists, pulmonologists, medical oncologists, radiation oncologists, and infectious diseases specialists.

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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: *İvo Gökmen, İrfan Çiçin;* ***Design:*** *İvo Gökmen;* ***Control/Supervision:*** *İrfan Çiçin, Ali Gökyer;* ***Data Collection and/or Processing:*** *İvo Gökmen, Fahri Akgül, Aykut Alkan, Erkan Özcan, Nazan Demir;* ***Analysis and/or Interpretation:*** *İrfan Çiçin, Ali Gökyer;* ***Literature Review:*** *İvo Gökmen;* ***Writing the Article:*** *İvo Gökmen;* ***Critical Review:*** *İvo Gökmen;* ***References and Fundings:*** *İvo Gökmen;* ***Materials:*** *İvo Gökmen.*

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