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Effectiveness of corticosteroids on immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia: A case series

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Abstract

There are few reports on the effectiveness of corticosteroids for immune checkpoint inhibitor-induced interstitial pneumonia in patients with a history of interstitial pneumonia. We report on 10 non-small cell lung cancer patients with a history of interstitial pneumonia who experienced immune checkpoint inhibitor-induced interstitial pneumonia. The immune checkpoint inhibitor-induced interstitial pneumonia lasted for a median duration of 41.5 days (range = 22–127 days). Eight of the ten patients responded to corticosteroid monotherapy; one patient responded to corticosteroids and the immunosuppressant, tacrolimus; and one patient did not improve after corticosteroid treatment. In non-small cell lung cancer patients with a history of interstitial pneumonia, immune checkpoint inhibitor-induced interstitial pneumonia was generally responds to corticosteroids.

Keywords

Interstitial pneumonia, immune checkpoint inhibitors, corticosteroids

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Introduction

Immune checkpoint inhibitors can cause immune-related adverse events, including interstitial pneumonia.[1] In phase III trials, the incidence of interstitial pneumonia in non-small cell lung cancer patients was 3.8% (n = 287) with nivolumab,[2] 5.8% (n = 154) with pembrolizumab,[3] and 2.3% (n = 609) with atezolizumab.[4] However, patients with a history of interstitial pneumonia were excluded from these clinical trials. Immune checkpoint inhibitors are rarely administered to lung cancer patients with a history of interstitial pneumonia. However, some patients with non-small cell lung cancer and a history of mild idiopathic interstitial pneumonia have been treated with nivolumab.[5,6] Nonetheless, there are few reports of the effectiveness of corticosteroids for immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia, particularly in patients who were treated with atezolizumab and pembrolizumab. Therefore, we report on the effectiveness of corticosteroid treatment in 10 non-small cell lung cancer patients with a history of interstitial pneumonia who subsequently re-experienced immune checkpoint inhibitor-induced interstitial pneumonia.

Case discussion

Patients

The study was conducted in the Showa University Northern Yokohama Hospital. The study period lasted from December 2015 to March 2020. Patients, who had non-small cell lung cancer with a history of interstitial pneumonia, were included in the study. Patients were treated with nivolumab, pembrolizumab, or atezolizumab. We surveyed 183 patients.

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Of the 183 patients surveyed, 10 patients with a history of interstitial pneumonia experienced immune checkpoint inhibitor-induced interstitial pneumonia. The patient characteristics are shown in Table 1. All 10 patients had a history of smoking. One patient received combination therapy, whereas nine patients were treated with single-agent corticosteroid regimens. Four patients had radiation pneumonitis, without radiation fibrosis; four patients had interstitial pneumonia secondary to immune checkpoint inhibitors; and two patients had idiopathic interstitial pneumonia. The condition of four patients (cases 2, 5, 6, and 7) with a history of immune checkpoint inhibitor-induced interstitial pneumonia had previously improved. However, when rechallenged with immune checkpoint inhibitors, these four patients suffered from immune checkpoint inhibitor-induced interstitial pneumonia again.

Effectiveness of corticosteroids on immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia

The corticosteroids used to manage immune checkpoint inhibitor-induced interstitial pneumonia are listed in Table 2. Immune checkpoint inhibitor-induced interstitial pneumonia occurred after a median of 3.0 doses (range = 1–6 doses). Immune checkpoint inhibitor-induced interstitial pneumonia lasted for a median duration of 41.5 days (range = 22–127 days).

The pneumonia in eight out of ten patients responded with corticosteroids alone. One patient responded to a combination of corticosteroids and the immunosuppressant tacrolimus. One patient did not improve after corticosteroid treatment and died, with persistent interstitial pneumonia as the probable cause of death.

Discussion

Ten non-small cell lung cancer patients experienced immune checkpoint inhibitor-induced interstitial pneumonia. Among them, eight responded well to corticosteroid monotherapy.

These cases indicate the effectiveness of corticosteroids against immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia. Interstitial pneumonia can have severe outcomes, including death. In this case series, interstitial pneumonia was the probable cause of death in one patient. On the basis of their risks and benefits, immune checkpoint inhibitors should be considered for non-small cell cancer patients with a history of interstitial pneumonia. Patients with non-small cell lung cancer with interstitial pneumonia or active radiation pneumonia have been excluded from phase III trials.[1–4] Therefore, it is necessary to consider the appropriateness of immune checkpoint inhibitors treatment among patients with a history of interstitial pneumonia.[7] Similarly in Japan, the Ministry of Health, Labor and Welfare, which controls the approval and proper use of medicines, has warned against the administration of immune checkpoint inhibitors to patients with, or with a history of, interstitial pneumonia.

Among 20 patients who developed interstitial lung disease due to anti-bodies against the programmed cell death-1 ligand, 18 patients had idiopathic organizing pneumonia and non-specific interstitial pneumonia.[8] There were only two cases of acute interstitial pneumonia and acute respiratory distress syndrome that were unresponsive to corticosteroids. In that study,[8] two patients with immune checkpoint inhibitor-induced interstitial pneumonia had melanoma and Hodgkin's lymphoma. Our case series differs from the previous study because it only includes patients with non-small cell lung cancer and interstitial pneumonia.

In a review of interstitial pneumonia caused by immune checkpoint inhibitors,[9] organizing pneumonia pattern (23%), hypersensitivity pneumonia pattern (16%), non-specific interstitial pneumonia (8%), respiratory bronchiolitis-associated interstitial pneumonia (6%), and an unidentifiable pattern (36%) were reported. There is no report of acute interstitial pneumonia that is refractory to corticosteroids. Similarly, in our case series, there were no patients with acute interstitial pneumonia. Corticosteroids may be able to control immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia.

There are a limited number of case reports on the use of corticosteroids to treat patients with immune checkpoint inhibitor-induced interstitial pneumonia and a history of interstitial pneumonia. This was a retrospective study and the histopathological classification of the interstitial pneumonia was not determined as this was a case series involving a limited number of cases in a single facility. Our case series contained patients with a history of immune checkpoint inhibitor-induced interstitial pneumonia, radiation pneumonitis, and idiopathic interstitial pneumonia. We did not determine the severity of interstitial pneumonia. Immune checkpoint inhibitors should be considered a cause of immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia. In the future, we would like to compare patients with and without exacerbation of interstitial pneumonia following the administration of immune checkpoint inhibitors among patients with a history of interstitial pneumonia.

Conclusion

In non-small cell lung cancer patients with a history of interstitial pneumonia, immune checkpoint inhibitor-induced interstitial pneumonia generally responded well to corticosteroids.

Table 1. Patient characteristics.

Case	Sex	Age (years)	Medical history	Smoking history	History of interstitial pneumonia	Stage[a]	History of surgery[b]	History of radiation therapy[c]
1	M	58	Adjustment disorder	Yes	Cause unknown; present from the time of lung cancer diagnosis	IV	No	No
2	M	74	Type 2 diabetes mellitus, hypertension, abdominal aortic aneurysm	Yes	Nivolumab-induced interstitial pneumonia[d]	IV	Yes	No
3	M	74	Osteoporosis	Yes	Cause unknown; present from the time of lung cancer diagnosis	IV	No	No
4	M	64	Hypothyroidism, hypertension	Yes	Radiation pneumonitis	IV	No	Yes
5	M	75	Type 2 diabetes mellitus, prostatic hyperplasia, dyslipidemia	Yes	Pembrolizumab-induced interstitial pneumonia[d]	IV	No	No
6	M	68	Type 2 diabetes mellitus	Yes	Nivolumab-induced interstitial pneumonia[d]	IV	Yes	No
7	M	69	Rectal cancer, hyperuricemia, hypertension	Yes	Pembrolizumab-induced interstitial pneumonia[d]	III	No	Yes
8	M	81	Bladder cancer	Yes	Radiation pneumonitis	III	No	Yes
9	M	50	Pulmonary emphysema, hypertension	Yes	Radiation pneumonitis	III	Yes	Yes
10	M	71	None	Yes	Radiation pneumonitis	IV	Yes	Yes

[a]At the time of initiating immune checkpoint inhibitors, doctor made a diagnosis based on the results of imaging and/or pathological examinations.
[b]Non-small cell lung cancer resected prior to administration of immune checkpoint inhibitors.
[c]Chest radiation therapy for non-small cell lung cancer.
[d]Immune checkpoint inhibitor-induced interstitial pneumonia improved initially and then reoccurred when patients were rechallenged with immune checkpoint inhibitors.

Table 2. Effectiveness of corticosteroids on immune checkpoint inhibitor-induced interstitial pneumonia among patients with a history of interstitial pneumonia.

Case	Immune checkpoint inhibitors	Anti-cancer drugs administered with immune checkpoint inhibitors	Therapeutic line	Pre-treatment with anti-cancer drugs	Radiological pattern of interstitial pneumonia	Number of immune checkpoint inhibitors used before onset of interstitial pneumonia	Time to immune checkpoint inhibitor-induced interstitial pneumonia (days)	CTCAE grade of pneumonitis	Initial corticosteroid therapy	Other treatment	Results of treatment
1	Pembrolizumab	Carboplatin and pemetrexed	1	None	Usual interstitial pneumonia	2	126	Grade 3	Methylprednisolone sodium succinate IV infusion 500 mg over 3 days	Oral tacrolimus 4 mg	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
2	Nivolumab	None	2	First: Cisplatin and pemetrexed	Organizing pneumonia pattern	3	28	Grade 3	Prednisolone sodium succinate IV infusion 20 mg	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
3	Atezolizumab	None	2	First: Cisplatin and pemetrexed	Organizing pneumonia pattern	5	127	Grade 2	Oral prednisolone 30 mg (0.5 mg/kg)	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
4	Nivolumab	None	3	First: S-1 and carboplatin Second: Pemetrexed and bevacizumab	Organizing pneumonia pattern	2	35	Grade 3	Methylprednisolone sodium succinate IV infusion 1000 mg over 3 days	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
5	Pembrolizumab	None	5	First: Afatinib Second: Gefitinib Third: S-1 and carboplatin Fourth: Afatinib	Organizing pneumonia pattern	1	22	Grade 3	Prednisolone sodium succinate IV infusion 50 mg (1 mg/kg)	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
6	Nivolumab	None	4	First: Cisplatin and vinorelbine Second: Carboplatin and etoposide Third: Nogitecan	Organizing pneumonia pattern	3	38	Grade 4[a]	Methylprednisolone sodium succinate IV infusion 1000 mg over 3 days	None	Prednisolone sodium succinate IV infusion 60 mg (1 mg/kg) Death due to disease progression
7	Pembrolizumab	None	1	None	Organizing pneumonia pattern	4	25	Grade 1	Oral prednisolone 20 mg	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
8	Nivolumab	None	2	First: Carboplatin, paclitaxel, and radiation	Nonspecific interstitial pneumonia	6	85	Grade 3	Prednisolone sodium succinate IV infusion 60 mg (1 mg/kg)	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
9	Nivolumab	None	5	First: Cisplatin, docetaxel, and radiation Second: Carboplatin, pemetrexed, and bevacizumab Third: Carboplatin and nab-paclitaxel Fourth: S-1	Organizing pneumonia pattern	1	55	Grade 2	Prednisolone sodium succinate IV infusion in 70 mg (1 mg/kg)	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia
10	Nivolumab	None	3	First: Carboplatin and nab-paclitaxel Second: Docetaxel and ramucirumab	Non-specific interstitial pneumonia	3	45	Grade 3	Prednisolone sodium succinate IV infusion 20 mg	None	Oral corticosteroid administration continued while IV prednisolone was tapered Remission of interstitial pneumonia

CTCAE: Common Terminology Criteria for Adverse Events; IV, intravenous.
[a]Respiratory failure present.

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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

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