Sequential Pneumonitis with Ground-glass Opacity during Durvalumab Therapy after Chemoradiation for Stage III Non-Small Cell Lung Cancer

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Abstract

Background: To investigate the clinical characteristics, radiographic pattern, and clinical course of radiation pneumonitis and programmed death ligand 1 inhibitor-related pneumonitis in patients with stage III non-small cell lung cancer (NSCLC) after definitive concurrent chemoradiotherapy (CCRT).

Methods: We retrospectively reviewed 22 patients who received definitive CCRT and consolidative Durvalumab for NSCLC between February 2018 and December 2019 at our hospital. Chest computed tomography scans were reviewed to assess the incidence, timing, relation to the field of radiotherapy, and radiographic patterns of pneumonitis.

Results: Among the 22 patients, six (27.3 %) developed grade 2 radiation pneumonitis. The median time from therapy initiation to pneumonitis was 1.5 months. Three patients had pneumonitis within the radiation treatment field, and the other three had pneumonitis spread outside the field. The radiographic pattern was organizing pneumonia with ground-grass opacity in five patients. All patients received corticosteroid therapy, and no patient experienced progression to grade 5 pneumonitis or recurrent pneumonitis after Durvalumab retreatment.

Conclusion: It is essential to understand the mechanism and radiographic pattern of immunotherapy-related pneumonitis and radiation pneumonitis to manage this potentially severe adverse event promptly.

Background

Concurrent chemoradiotherapy (CCRT) has been the standard treatment for patients with locally advanced non-small cell lung cancer (NSCLC) (1); however, the prognosis for these patients has remained poor since 2 decades, with an estimated 5-year overall survival (OS) rate of < 20% (range 15%-40%) (2). The treatment strategy for stage III NSCLC is complex and controversial because of the heterogeneity of these patients (3–5). After the PACIFIC trial, Durvalumab became the agent of choice for consolidation therapy in patients with stage III NSCLC, who did not show progress after chemoradiotherapy (6, 7). However, data on the incidence of radiation pneumonitis (RP) secondary to this regimen are limited. Pneumonitis is a major cause of dose-limiting toxicity occurring during thoracic radiation therapy and Durvalumab administration (6, 8). The pathogenesis of RP is thought to be partly immune-mediated and secondary to the release of inflammatory cytokines (9, 10). Data from prospective studies have demonstrated a higher incidence of pulmonary toxicity in patients who received thoracic radiation with concurrent or sequential programmed death 1/ programmed death ligand 1 (PD-1/PD-L1) therapies, suggesting a potential interaction between these therapies that may increase the risk of RP (11, 12).

The objective of this retrospective study was to assess the clinical characteristics, radiographic pattern, and clinical course of PD-L1 inhibitor-related pneumonitis in patients with stage III NSCLC after definitive CCRT.

Methods

Patients and Treatment

Patients who were treated with definitive chemoradiotherapy and consolidative Durvalumab for locally advanced NSCLC were eligible for this retrospective study. The diagnosis of NSCLC was confirmed through histological evaluation. All patients were staged using whole-body fluorodeoxyglucose-positron emission tomography and enhanced magnetic resonance imaging of the brain. The clinical stage at presentation was subsequently categorized according to the Tumor, Node, and Metastasis classification of malignant tumors (eighth edition). Medical records and clinical laboratory data were retrospectively collected and anonymized to exclude personal information. The study protocol was approved by the Institutional Review Board at our hospital (20–046).

The patients received CCRT and consolidative Durvalumab as the initial treatment. The prescribed radiation dose was 60 Gy delivered in 2.0 Gy daily fractions, five times a week. Patients were treated with involved field irradiation therapy with three-dimensional conformal radiotherapy, which delivers radiation to the initially involved nodal regions only. Patients were treated with at least two cycles of platinum-based chemotherapy concurrently with radiation therapy. Patients without disease progression received Durvalumab for up to 12 months of total consolidative therapy. Patients were followed up twice a month for the first year of Durvalumab therapy and every 3 months thereafter.

Radiation Pneumonitis Characterization

Chest computed tomography (CT) scans obtained at the time of the pneumonitis diagnosis were reviewed. To be diagnosed with RP, patients met the following criteria of clinical and imaging findings: (1) pulmonary symptoms, including dyspnea and/or cough, (2) CT-based imaging changes involving the radiated field, and (3) symptoms occurring within 12 months after the completion of radiation therapy. Patient characteristics including age, staging criteria of the Union for International Cancer Control (eighth edition), smoking history, and history of pulmonary disease were also retrospectively reviewed. Statistical analyses were performed using IBM SPSS® Statistics version 27. The patients were categorized into two groups (< 70 and ≥ 70 years) according to age. The cutoff values of V5Gy, V20Gy, and the mean values for developing RP were determined according to the receiver operating characteristic curve analysis and Youden index. These factors were evaluated using Fisher's exact test. Statistical significance was set at $p < 0.05$. Patients with clinical and imaging characteristics consistent with RP were assessed to determine the incidence, timing, relation to the field of radiotherapy, and radiographic patterns of pneumonitis. Toxicity grading was based on the Common Terminology Criteria for Adverse Events (ver. 5.0) scoring system. Follow-up chest imaging studies after the onset of pneumonitis were also reviewed to assess the resolution of the findings.

Results

We retrospectively identified 22 consecutive patients with locally advanced NSCLC, all of whom underwent definitive chemoradiotherapy and at least one dose of consolidative Durvalumab between February 2018 and December 2019 at our hospital. Patient characteristics are shown in Table 1.

Table 1
Patients` characteristics

Age (years)	**45–82**	**(median 69)**
Gender	15	(68.2 %)
Male	7	(31.8 %)
Female		
Histology	11	(50.0 %)
Adenocarcinoma	8	(36.4 %)
Squamous cell carcinoma	3	(13.6 %)
Other		
Stage (8th ed.)	10	(45.5 %)
IIIA	11	(50.0 %)
IIIB	1	(4.5 %)
IIIC		
Total dose of radiotherapy (Gy)	60	Median 60
Chemotherapy regimen	21	(95.4 %)
CBDCA/nabPTX	1	(4.5 %)
Other		
Abbreviations: CBDCA = carboplatin, nabPTX = nab-paclitaxel		

Six patients from this cohort (27.3 %) developed grade 2 RP. The median time from therapy initiation to pneumonitis was 1.5 months. Three patients had pneumonitis within the radiation treatment field, and the other three had pneumonitis spread outside the field. The radiographic pattern was organizing pneumonia with ground-glass opacity in five patients (Fig. 1). All patients received corticosteroid therapy, and no patient experienced recurrent pneumonitis after Durvalumab retreatment. In the subgroup analysis, there was no significant factor in RP incidence, other than age and Dose-Volume Histogram (DVH) parameters. (Table 2). The clinical details of the RP of the six patients are summarized in Table 3.

Table 2
Subgroup analysis

	Cut-off value	N (%)	Incidence of RP (%)	P value
Age	< 70	11 (50%)	45.5%	0.074
Gender	≧ 70	11 (50 %)	9.1%	0.651
Smoking	Male = 1	7 (31.8%)	28.6%	0.267
State	Female = 0	15 (68.2 %)	26.7%	0.375
Stage	Conc/Ex	15 (68.2 %)	20.0%	0.417
Histology	Never	7 (31.8 %)	42.9%	0.443
V5Gy	Right	11 (55 %)	27.3%	0.015
V20Gy	Left	9(45%)	11.1%	0.012
Mean	IIIA	10(45.5%)	20.0%	0.002
	IIIB/IIIC	12 (54.5 %)	33.3%	
	Adenocarcinoma	11(50%)	36.4%	
	Squamous cell ca.	8(36.4%)	12.5%	
	Other	3(13.6%)	33.3%	
	< 42.2 %	10(45.5%)	0.0%	
	≥ 42.2 %	12(54.5%)	50.0%	
	< 26.2 %	11(50.0%)	0.0%	
	≥ 26.2 %	11(50.0%)	54.5%	
	< 17.6 %	18(81.8%)	11.1%	
	≥ 17.6 %	4(18.2%)	100.0%	

Abbreviations: RP = radiation pneumonitis, Ca = cancer, Conc/Ex = concurrent/ ex-smoker

Table 3
Characterization of radiation pneumonitis in six patients with pneumonitis

Patients and treatment characteristics	Clinical presentation	Imaging findings	Pneumonitis treatment course
45-y-old non-smoker with stage IIIA adenocarcinoma of RUL, who completed 60 Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 2 weeks post-RT Mean lung dose: 17.6 % Lung volume ≥ 20 Gy: 31.0%	Dry cough and low-grade fever 7.6 weeks after final RT	Multiple patchy ground-glass opacities within the RT field RML and RLL OP pattern	Prednisone 40 mg daily started with subsequent tapering. Durvalumab administration continued during prednisone therapy. Symptoms improved within 1 week of steroid initiation.
56-y-old current smoker with stage IIIB adenocarcinoma of mediastinum, who completed 60Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 3 weeks post-RT Mean lung dose: 12.8 % Lung volume ≥ 20 Gy: 26.2%	Progressive dry cough SpO_2: 93% 38.1 weeks after final RT	Consolidation with patchy ground-glass opacities inside and outside of RT field Rt all lobes OP pattern	Prednisone 20 mg daily started with subsequent tapering. Durvalumab administration continued during prednisone therapy. Symptoms improved within 1 week of steroid initiation.
63-y-old current smoker with stage IIIB adenocarcinoma of LLL, who completed 60 Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 0.5 weeks post-RT Mean lung dose: 15.0 % Lung volume ≥ 20 Gy: 29.0%	Progressive dry cough SpO_2: 94% 11 weeks after final RT	Consolidation with patchy ground-glass opacities and pleural effusion inside and outside of RT field All lobes OP pattern	Prednisone 50 mg daily started with subsequent tapering. Durvalumab was discontinued because of the progressive disease. Symptoms improved within 2 weeks of steroid initiation.

Abbreviations: OP organizing pneumonitis, NSCLC = non-small cell lung cancer, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe

Patients and treatment characteristics	Clinical presentation	Imaging findings	Pneumonitis treatment course
69-y-old Ex-smoker with stage IIIA Squamous cell carcinoma of RUL, who completed 60 Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 2 weeks post-RT Mean lung dose: 18.4 % Lung volume ≥ 20 Gy: 34.9%	Progressive dyspnea and dry cough with low-grade fever SpO_2: 94% 6.4 weeks after final RT	Consolidation with patchy ground-glass opacities within RT field Rt all lobes OP pattern	Initially hospitalized to receive methylprednisolone 500 mg q12h and discharged on prednisone 40 mg daily with planned dose tapering. Durvalumab was skipped once and restarted during prednisone administration. Symptoms improved within 1 week of steroid initiation.
81-y-old non-smoker with stage IIIB NSCLC of mediastinum, who completed 60 Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 0.5 weeks post-RT Mean lung dose: 17.7 % Lung volume ≥ 20 Gy: 33.1%	Dry cough and dyspnea SpO_2: 94 % 4.6 weeks after final RT	Consolidation with patchy ground-glass opacities inside and outside of RT field All lobes OP pattern	Prednisone 20 mg daily started with subsequent tapering. Durvalumab was skipped once and restarted during prednisone treatment. Symptoms improved within 1 week of steroid initiation.
53-y-old non-smoker with stage IIIB adenocarcinoma of RUL, who completed 60 Gy RT concurrent with cisplatin/nab-paclitaxel followed by initiation of Durvalumab 1-week post-RT Mean lung dose: 18.2 % Lung volume ≥ 20 Gy: 33.7%	Progressive dry cough and dyspnea SpO_2: 98 % 7.9weeks after RT end	Consolidation with patchy ground-glass opacities within RT field Rt all lobes OP pattern	Prednisone 20 mg daily started with subsequent tapering. Durvalumab continued during prednisone treatment. Symptoms improved within 1 week of steroid initiation.
Abbreviations: OP organizing pneumonitis, NSCLC = non-small cell lung cancer, RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe			

Discussion

We present the largest detailed characterization to date of the onset and clinical course of RP among patients treated with CCRT and consolidative Durvalumab. Among these patients, symptomatic RP occurred in 27 %, and an organizing pneumonia (OP) pattern was the most common radiographic pattern of pneumonitis. The majority of RP patients responded to high-dose oral glucocorticoid therapy, and most continued Durvalumab with no recurrence of the dyspneic symptoms.

RP is one of the most common side effects in clinical oncology, limiting the dose of radiation that can be administered for the treatment of thoracic tumors. Symptomatic RP is characterized by dyspnea, cough, and occasional low-grade fever, typically occurring several weeks to months after radiation exposure. Changes in radiographs have been classically noticed predominantly in the radiation field but are not limited to the field (13–15). The incidence of symptomatic RP in lung cancer patients who received thoracic radiation therapy is estimated to be 10–40% (16), although the incidence of fatal pneumonitis in NSCLC patients treated with CCRT is estimated to be less than 2% (8). Any grade of pneumonitis with anti-PD-1/PDL1-directed therapies has been reported in 4% of patients of NSCLC, and higher grades of pneumonitis are estimated to occur in less than 2% of patients (17, 18). The onset of symptoms of pneumonitis in patients treated with anti-PD-1/PD-L1 therapies varies from days to 1 year or more after the start of treatment, with a median time to onset of 2.8 months, as described in this previous study. Prior studies have also found a variety of radiological features, with no specific pathognomonical features due to anti-PD-1/PD-L1 pneumonitis (18). A radiographic OP pattern was the most commonly observed pattern across all tumors and treatment regimens of Immuno-checkpoint inhibitors (ICIs). These radiographic patterns of pneumonitis were associated with clinical severity and toxicity grades of pneumonitis. An acute interstitial pneumonia/acute respiratory distress syndrome pattern was associated with the highest severity grades, followed by the cryptogenic OP pattern, while a nonspecific interstitial pneumonia pattern was related to a lower severity grade, thus highlighting the importance of classifying the radiographic patterns for proper patient management, follow-up, and monitoring. Nishino et al. (19) also noted ground-glass opacities (GGOs) in all patients with ICI-related pneumonitis. Although clinical data from prospective trials are limited, thoracic radiation therapy may potentially increase pulmonary toxicity due to concurrent or sequential anti-PD-1/PD-L1 therapies in patients with NSCLC (11, 12). These data suggest the existence of interaction mechanisms between thoracic radiotherapy and anti-PD-L1 therapies that may affect the development of pneumonitis. The PACIFIC trial, which led to the approval of Durvalumab after CCRT in stage III NSCLC patients, found that the risk of developing any grade and type of pneumonitis was higher in patients treated with Durvalumab vs. placebo (33.9% vs. 24.8%) (6). Additionally, any grade RP was more prevalent in patients treated with consolidative Durvalumab vs. placebo (20% vs. 15.8%), and grade 3 or 4 RP was more common in patients treated with Durvalumab compared to those treated with placebo (1.5% vs. 0.4%) (7). Pneumonitis was the most frequent adverse event leading to discontinuation of the trial regimen (4.8 % of patients in the Durvalumab group and 2.6 % of those in the placebo group). Our finding of 27% of patients treated with CCRT and Durvalumab who developed grade 2 or higher RP appeared to be consistent with the PACIFIC trial data. There was no significant difference in symptomatic RP in patients treated with consolidative Durvalumab compared to our reference cohort treated with CCRT alone (27% vs. 25%). The median time to RP onset was significantly shorter in patients treated with Durvalumab than in those treated with CCRT alone, which also suggests interactions between these therapies that modify the risk of developing RP. The clinical course of RP in patients treated with consolidative Durvalumab appears no worse than in patients treated with CCRT alone, as most patients were successfully treated with a course of oral glucocorticoids (20).

Unfamiliar drugs, by nature, can cause unexpected side effects. In the case of Durvalumab after CRT, radiological pattern and onset timing should be kept in mind for surveillance of potential side effects. As an image finding, GGO spread widely inside and outside the irradiation field. The appearance of GGOs on radiographs in patients undergoing chemotherapy is often fatal; however, if they appear in those undergoing immunotherapies, the patients have been reported to have a positive steroid response and good prognosis (21). The mechanism is not yet known, but in the case of Bronchoalveolar lavage (BAL) of chemotherapy-related pneumonitis, various cell growth such as lymphocyte dominant, eosinophil dominant, or neutrophil dominant is observed, whereas in ICI-related pneumonitis, the pathological condition is different from that presenting with a high percentage of lymphocytes. In addition, the time to onset of pneumonia is 3–6 months for RP, 3 months for ICI-related pneumonitis, and early compare from them, 1–2 months for Durvalumab after CRT. In the PACIFIC trial, the median time to onset of pneumonitis from the start of ICI therapy becomes shorter, at 55 days (range, 1–406 days) (22). The shorter time to onset in the PACIFIC trial may be due to the attribution of pneumonitis to both RT and ICI. Although potentially fatal, most cases of pneumonitis can be resolved successfully using an appropriate multidisciplinary management strategy. Patient education to report relevant symptoms early, prompt diagnosis, close monitoring, and early intervention are all essential to minimize the fatal risk of high-grade pneumonitis and to maximize the possibility of complete resolution not for discontinuation of Durvalumab in optimizing patient outcomes (17). In this study, Durvalumab was continued in most cases, with three consecutive and two single dose-skip cases.

The limitations of the present study include: first, the relatively small number of patients with CRT and Durvalumab-related pneumonitis treated in a single institution. Second, the retrospective design of the imaging review. Third, this study focused on the clinical and radiographic description of pneumonitis, and the assessment of risk factors and predictors of pneumonitis was not fully performed. This may be related to DVH parameters similar to CRT alone therapy, but more data is needed. Pneumonitis due to Durvalumab after CRT is considered to have a rather strong immunological aspect based on imaging findings and the time of onset. In an ICI study, it has been reported that the immune-related adverse effect (irAE) group is more effective for treatment. Further examination is needed to determine whether the pneumonitis group has a good prognosis after CRT therapy.

In thoracic radiotherapy, intensity modulated radiation therapy (IMRT) cases have increased, and this technique can reduce complications and escalate dose delivery. We demonstrated pneumonitis matching the dose line (for example, V50%) in our first case. In this study, the radiographic appearance for most pneumonitis cases was patchy and scattered, but in IMRT, pneumonitis demonstrated a more concentrated and complicated pattern along the complicated dose line. This theme will be discussed in the further study.

Conclusions

Understanding the mechanism and radiographic pattern of both immunotherapy-related and radiation pneumonitis is essential to identify and promptly manage this potentially serious adverse event.

Abbreviations

NSCLC
non-small cell lung cancer, CCRT = chemoradiotherapy, OS = overall survival, RP = radiation pneumonitis, PD-1 = programmed death 1, PD-L1 = programmed death ligand 1, CT = computed tomography, VxGy = volume receiving xGy, DVH = dose volume histogram, OP = organizing pneumonia, ICIs = imuno-checkpoint inhibitors, GGO = ground-glass opacities, BAL = Bronchoalveolar lavage, IMRT = intensity modulated radiation therapy.

Declarations

Ethics approval and consent to participate:

This study was approved by the local ethics committee of the National Hospital Organization Kyoto Medical Center of 20-046. Informed consent was obtained in the form of opt-put on the web-site.

Consent to publish

Informed consent for publication was also obtained in the form of opt-put on the web-site.

Availability of data and materials

The datasets analyzed during the current study are available from the all co-authors including the corresponding author on reasonable request.

Competing interest

We have no financial relationships to disclose.

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Authors' contributions

Study concept and design: MK and NA; data collection: MK, NK, and TS; analysis and drafting of the article: NS and MK; conducting the research: NA; radiographically assessment: SD, YH, and TM; supervision of the research: AN, YH, and TM. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship and were not listed. We further confirm that all authors have approved the order of authors listed in the manuscript.

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Figures

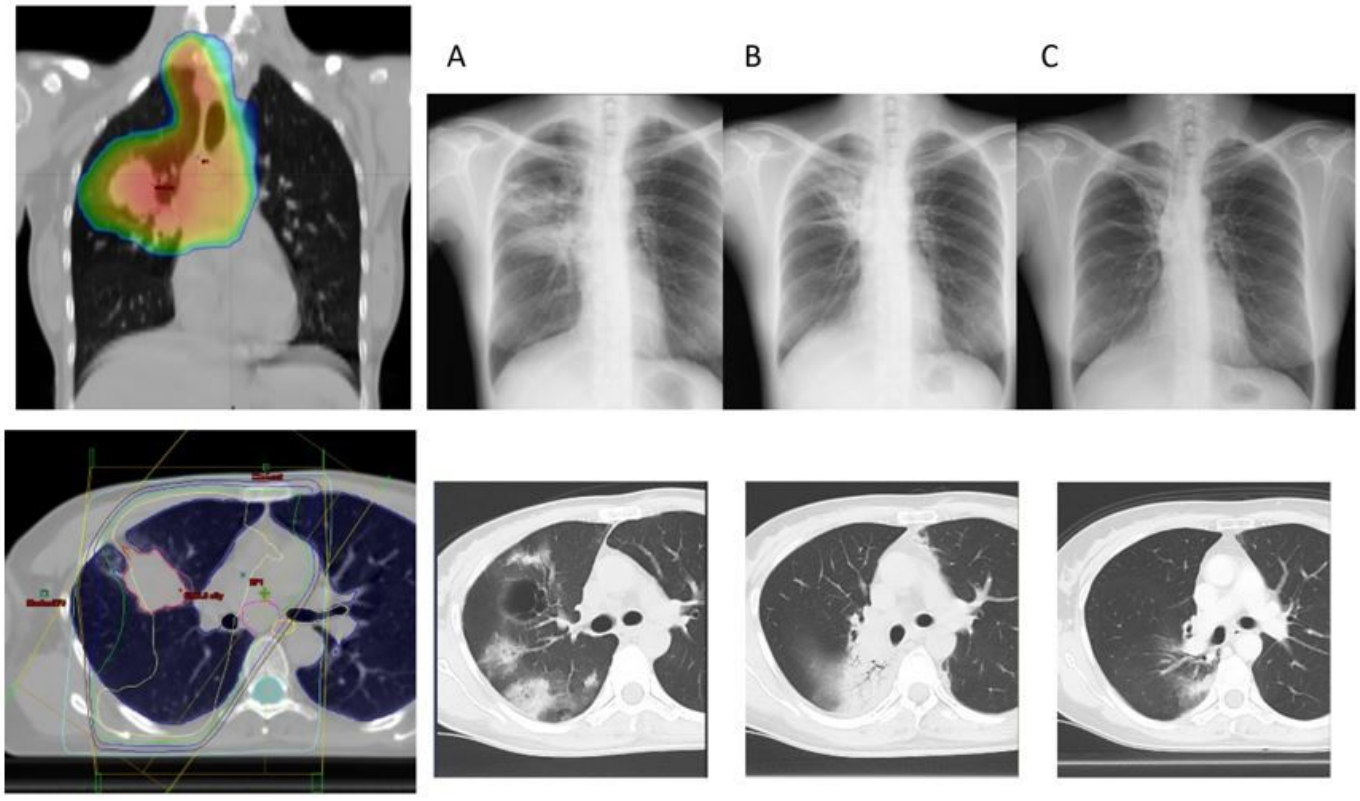

Figure 1

Pneumonitis with an organizing pneumonia (OP) pattern in a 45-year-old female with lung cancer; adenocarcinoma who received chemoradiotherapy and consolidative Durvalumab 2 months after the completion of radiation therapy. A evident ground-glass opacities and consolidations with multifocal distribution are indicative of an OP pattern of pneumonitis. The findings resolved after treatment with oral prednisone, only exhibiting shrinkage changes after 4 months (B). C shows clinical improvement on a follow-up computed tomography scan.