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Drug-induced interstitial lung disease after chemoimmunotherapy for extensive-stage small cell lung cancer

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ABSTRACT

Objectives: The combination of chemotherapy and immune checkpoint inhibitors (chemo-ICI) has become the new standard of treatment for extensive-stage small cell lung cancer (ES-SCLC). Recently, slight changes in interstitial shadows, defined as interstitial lung abnormalities (ILA), have been identified. In patients with ES-SCLC who received chemo-ICI, there are limited data on the incidence of drug-induced interstitial lung disease (D-ILD) in daily practice and the association between the development of D-ILD and ILA in the baseline computed tomography (CT).

Materials and methods: A multicenter, retrospective study was conducted to investigate the incidence of D-ILD, the risk factors for developing D-ILD, progression-free survival (PFS), and overall survival (OS) in patients with ES-SCLC who received chemo-ICI between August 2019 and November 2021.

Results: This study enrolled 70 patients (median age, 71 years; including 58 men) from nine institutions in Japan. There were 62 patients (89%) treated with carboplatin/etoposide/atezolizumab and 8 patients treated with carboplatin or cisplatin/etoposide/durvalumab. Twenty-nine patients (41.4%) were found to have ILA at baseline CT. Eleven patients (15.7%) developed D-ILD. The proportion of patients with ILA was significantly higher in the group who developed D-ILD than in the group who did not (9/11 (81.8%) vs. 20/59 (33.9%), respectively, P = 0.0057). In addition, the frequency of ground glass attenuation (GGA) and reticulation was higher in patients

Abbreviations: SCLC, small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; NSCLC, non-small cell lung cancer; ILA, Interstitial lung abnormalities; D-ILD, drug induced interstitial lung disease; ICI, immune checkpoint inhibitors; Chemo-ICI, chemotherapy and immune checkpoint inhibitors; CT, computed tomography; GGA, ground glass attenuation, immune-related Adverse Events (irAE); ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

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who developed D-ILD. There was no significant difference in PFS and OS between patients who developed D-ILD and those who did not (median PFS, 8.0 (95% confidence interval (CI), 5.5–9.5) months vs. 5.0 (95% CI, 4.5–5.6) months, respectively, P = 0.11 and median OS, not reached (NR) (95% CI, 8.7–NR) vs. 18.2 (95% CI, 13.2–NR) months, respectively, P = 0.20).
Conclusion: The incidence of D-ILD in patients with ES-SCLC who received chemo-ICI in clinical practice was higher than that in clinical trials. Patients with pre-existing ILA were more likely to develop D-ILD.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. The standard treatment for extensive-stage small cell lung cancer (ES-SCLC) has historically been platinum-based chemotherapy, but the IMpower 133 and CASPIAN trials demonstrated the efficacy and safety of the chemotherapy and immune checkpoint inhibitors (chemo-ICI), which have become the new standard of treatment [2,3]. Recently, it has been reported that slight changes in the interstitial shadows can be observed on computed tomography (CT). Interstitial lung abnormalities (ILA) are defined as interstitial shadows (ground glass attenuation (GGA), reticulation, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis) occupying more than 5% of the total lung field on chest CT [4]. The reported prevalence of ILA is 14% in patients with lung cancer. Furthermore, ILA are reported to be a poor prognostic factor for non-small cell lung cancer (NSCLC) [5]. Pre-existing ILA are risk factors for drug-induced interstitial lung disease (D-ILD) in patients treated with ICI monotherapy. D-ILD by ICI is considered as immune-related Adverse Events (irAE), and it has been reported that 43% of NSCLC patients with ILA who were treated with ICI monotherapy developed D-ILD [6]. In the IMpower133 and CASPIAN trials, the incidence of D-ILD in ES-SCLC patients was 4.0% [2] and 2.6% [3], respectively, but there is a lack of real clinical data. In addition, there are no reports investigating the relationship between the incidence of D-ILD and ILA in ES-SCLC patients administered chemo-ICI despite chemo-ICI being used in daily practice for ES-SCLC patients with ILA. Therefore, we aimed to reveal the incidence and risk factors for D-ILD in patients with ES-SCLC who received chemo-ICI in daily practice. We also investigated the association between the development of D-ILD and pre-existing ILA.

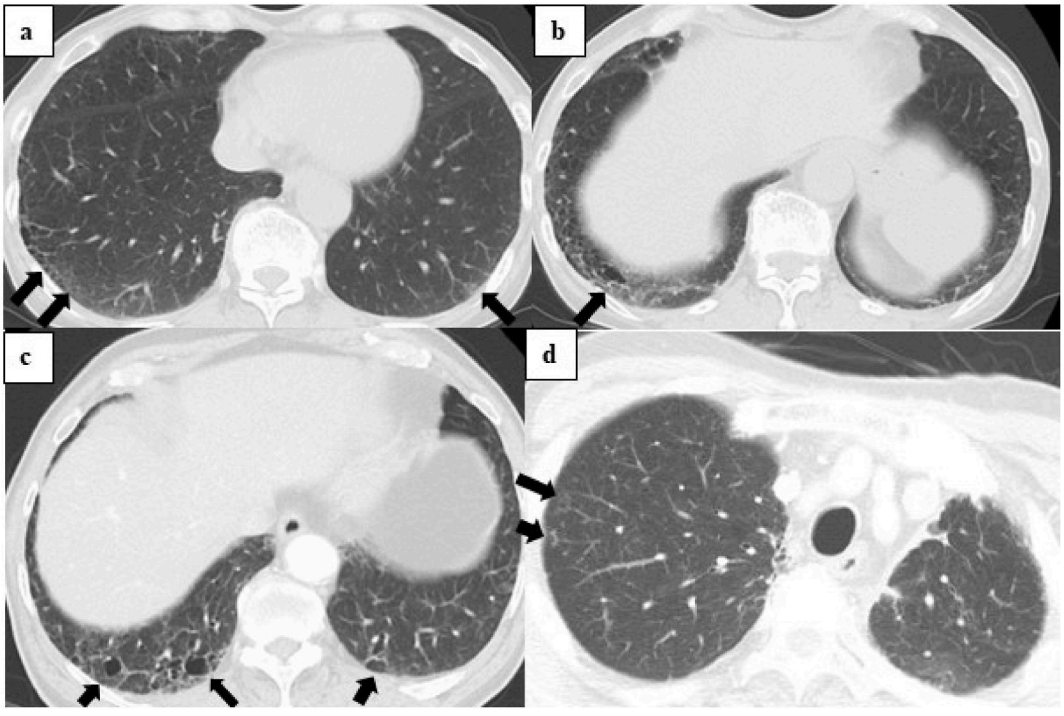

Fig. 1. Examples of interstitial lung abnormalities, with arrows indicating (a) ground glass attenuation, (b) reticulation, (c) nonemphysematous cysts, and (d) diffuse centrilobular nodularity.

2. Materials and Methods

2.1. Study design and patients

A multicenter, retrospective study was conducted to investigate the incidence of D-ILD and the risk factors for the development of D-ILD in patients with ES-SCLC who received chemo-ICI between August 2019 and November 2021. Patients aged ≥20 years who had received at least one course of chemo-ICI for ES-SCLC, relapsed after surgery, or treated with chemoradiotherapy were enrolled. The presence of ILA and emphysema before chemo-ICI administration was assessed using CT (5 mm slice thickness). The CT images were assessed independently by two respiratory physicians. The primary outcome was the incidence of D-ILD in all patients. The secondary outcomes were the association between D-ILD and background of the lung in the image, time to D-ILD onset, severity of D-ILD, overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). This study was approved by the ethics review board of each participating institute. We included an opt-out method on the hospital's website. Informed consent was not required for this study as it was the retrospective study (UMIN000044552).

2.2. Definition of ILA and ILA area

ILA were defined as GGA, reticulation, nonemphysematous cysts, diffuse centrilobular nodularity, honeycombing, or traction bronchiectasis [7,8] [Fig. 1 (a)-(d)]. The area of the ILA in the total lung field was measured every 5% by visual assessment.

2.3. Definition of D-ILD

D-ILD was defined as a new GGA or consolidation that occurred during treatment and was considered noninfectious or nonneoplastic. We classified the radiologic patterns of D-ILD on CT scans according to the American Thoracic Society/European Respiratory Society (ATS/ERS) international multidisciplinary classification of interstitial pneumonia [9]: 1) non-specific interstitial pneumonia pattern, 2) organizing pneumonia (OP) pattern, 3) hypersensitivity pneumonitis (HP) pattern, 4) diffuse alveolar damage pattern, or 5) simple pulmonary eosinophilia pattern. The D-ILD grade was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

2.4. Statistical analysis

Comparisons between the two groups were performed using univariate analysis (Mann-Whitney *U* test and Fisher's exact test). Kaplan-Meier analysis was used to estimate survival curves. We conducted all statistical analyses using EZR Ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [10].

3. Results

3.1. Overall characteristics

This study enrolled 70 patients from nine institutions. We summarized the clinical characteristics of the patients in Table 1.The median age of the patients was 71 years old, and most patients were male (82.9%) and current or ex-smokers (91.4%). There were 62 patients (88.6%) treated with carboplatin/etoposide/atezolizumab and 8 patients with carboplatin or cisplatin/etoposide/durvalumab. Twenty-nine patients (41.4%) were found to have ILA at baseline CT (Table 2). The number of patients with GGA, reticulation, or nonemphysematous cysts was 27 (38.6%), 34 (48.6%), or 10 (14.3%), respectively. None of the patients had traction bronchiectasis or honeycombing.

Table 1
Overall characteristics (n = 70).

	n (%)
Age, years: Median (range)	71 (42–84)
Sex: Male	58 (83)
ECOG PS: 0/1/2/3	23 (33)/37 (53)/8 (11)/2 (3)
Smoking history: Current, ex	64 (91)
Prior thoracic radiation therapy	4 (6)
CBDCA + VP-16 + Atezolizumab/ CDDP/CBDCA + VP-16 + Durvalmab	62 (89)/8 (11)
Induction therapy cycles: 1/2/3/≧4	7 (10)/4 (6)/7 (10)/52 (74)
Consolidation therapy cycles: 0/1/2/3/≧4	18 (26)/7 (10)/15 (21)/7 (10)/23 (34)
Best tumor response: CR/PR/SD/PD/NE	3 (4)/49 (70)/12 (17)/5 (7)/1 (1)

Abbreviations: PS, performance status; CBDCA, carboplatin; VP-16, etoposide; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluate.

Table 2
Overall CT characteristics (n = 70).

	n (%)
Interstitial lung abnormalities (ILA)	29 (41.4)
Type of ILA	
Ground glass attenuation	27 (38.6)
Reticulation	34 (48.6)
Diffuse centrilobular nodularity	1 (1.4)
Nonemphysematous cysts	10 (14.3)
Traction bronchiectasis	0
Honeycombing	0
ILA (0/5/10/15–30/30–50)	41 (58.6)/5 (7.1)/14 (20.0)/6 (8.6)/4 (5.7)
Emphysema	54 (77.1)

The proportion of the ILA area in each total lung field (0%, 5%, 10%, 15–30%, and 30–50%) was 41/70 (58.6%), 5/70 (7.1%), 14/70 (20.0%), 6/70 (8.6%), and 4/70 (5.7%), respectively.

3.2. D-ILD incidence and characteristic comparison in patients with or without D-ILD

Among the 70 patients, 11 (15.7%) developed D-ILD (Table 3). The median age of the patients was 72 years old. Most patients were men (81.8%), and all patients with D-ILD had a smoking history. Ten patients (90.9%) were treated with carboplatin/etoposide/atezolizumab therapy. The median number of induction and maintenance therapy cycles was the same in both groups (median induction cycles: 4.

(range, 2–4) vs. 4 (range, 1–5), median maintenance cycles: 2 (range: 0–5) vs. 2 (range: 0–32)). The main reasons for discontinuation of treatment were adverse events in patients with D-ILD (81.8%) and disease progression in patients without D-ILD (74.6%). There were no differences in age, sex, Eastern Cooperative Oncology Group
(ECOG) performance status, smoking history, history of chest radiation, chemo-ICI regimen, induction therapy cycles, consolidation therapy cycles, or best tumor response.

In the group with D-ILD, there were no irAE other than D-ILD, but in the group without D-ILD, there were 12 cases (5 cases of hypothyroidism (grade 1/grade 2: 2/3), 3 cases of colitis (grade 2/grade 3: 1/2), 2 cases of liver dysfunction (grade 2/grade 3: 1/1), adrenal insufficiency (grade 3), diabetic ketoacidosis (grade 3), pancreatitis (grade 2), erythema multiforme exudative (grade 2) and polymyalgia rheumatica (grade 2) each) (Table 4).

3.3. Patient CT characteristics with or without D-ILD

The proportion of patients with ILA was significantly higher in the group who developed D-ILD than in the group who did not (9/11 (81.8%) vs. 20/59 (33.9%), P = 0.0057) (Table 5). The proportion of patients with the ILA area (0, 5%, 10%, 15–30%, and 30–50%) in the total lung field was significantly higher in patients who developed D-ILD than in those who did not (2/11 (18.2%), 1/11 (9.1%), 1/11.

(9.1%), 5/11 (45.5%), and 2/11 (9.1%), respectively, vs. 39/59 (66.1%), 3/59 (5.1%), 4/59 (6.8%), 9/59 (15.3%), and 4/59 (6.8%), respectively, P = 0.014). In addition,

The incidence of D-ILD was higher in patients with GGA and reticulation than in those without them (8/11 (72.7%) vs. 19/59 (32.2%), P = 0.017 and 9/11 (81.8%) vs. 25/59 (42.4%), P = 0.022, respectively).

Patients with D-ILD had more frequent emphysema than those without, but the difference was not statistically significant (11/11

Table 3
Patient characteristics with or without D-ILD.

	With D-ILD (n = 11)	Without D-ILD (n = 59)	p-value
	n (%)	n (%)	
Age, years: Median (range)	72 (69–81)	71 (42–84)	0.332
Sex: Male	9 (81.8)	49 (83.1)	1
ECOG PS: 0/1/2/3	4(36.4)/5(45.5)/2(18.2)/0	19(32.2)/32(54.2)/6(10.2)/2 (3.4)	0.749
Smoking history: Current, ex	11 (100.0)	53 (89.8)	0.58
Prior thoracic radiation therapy	1 (9.1)	3 (5.1)	0.504
CBDCA + VP16+Atezolizumab/ CDDP/CBDCA + VP16+Durvalmab	10 (90.9)/1 (9.1)	52 (88.1)/7 (11.9)	1
Induction therapy cycles: Median (range)	4 (2–4)	4 (1–5)	0.934
Consolidation therapy cycles: Median (range)	2 (0–5)	4 (0–32)	0.466
Best tumor response: CR/PR/SD/PD/NE	1(9.1)/8(72.7)/2(18.2)/0/0	2(3.4)/41(69.5)/10(16.9)/5 (8.5)/1 (1.7)	0.677

Table 4
Incidence of immune-related Adverse Events (irAE) other than D-ILD.

	With D-ILD (n = 11)		Without D-ILD (n = 59)	
	n (%)		n (%)	
	Any Grade	Grade≧3	Any Grade	Grade≧3
Hypothyroidism	0	0	5 (8.5)	0
Colitis	0	0	3 (5.1)	2 (3.4)
Liver dysfunction	0	0	2 (3.4)	1 (1.7)
Adrenal insufficiency	0	0	1 (1.7)	1 (1.7)
Diabetic ketoacidosis	0	0	1 (1.7)	1 (1.7)
Pancreatitis	0	0	1 (1.7)	0 (1.7)
Erythema multiforme exudative	0	0	1 (1.7)	0 (1.7)
Polymyalgia rheumatica	0	0	1 (1.7)	0 (1.7)

Table 5
Patient CT characteristics with or without D-ILD.

	With D-ILD (n = 11)	Without D-ILD (n = 59)	p-value
	n (%)	n (%)	
Interstitial lung abnormalities (ILA)	9 (81.8)	20 (33.9)	0.006
Type of ILA			
Ground glass attenuation	8 (72.7)	19 (32.2)	0.017
Reticulation	9 (81,8)	25 (42.4)	0.022
Diffuse centrilobular nodularity	1 (9.1)	0	0.157
Nonemphysematous cysts	1 (9.1)	9 (15.3)	1
Traction bronchiectasis	0	0	
Honeycombing	0	0	
Emphysema	11 (100.0)	43 (72,9)	0.058
ILA (5–10%/15–30%/30–50)	2(18.2)/5(45.5)/2(18.2)	7(11.9)/9(15.3)/4(6.8)	0.874

(100.0%) vs. 43/59 (72.9%), P = 0.058).

3.4. D-ILD pattern, severity, and survival

The radiologic patterns of D-ILD were OP (9/11 patients (81.8%)) and HP (2/11 patients (18.2%)). Among the 11 patients with D-ILD, three (4.3%) patients experienced grade 1 pneumonitis, three (4.3%) experienced grade 2 pneumonitis, and five (7.1%) experienced grade 3 pneumonitis. The median time from the first dose of chemo-ICI to the onset of D-ILD was 3.7 months (range; 0.7–5.8 months). There was no significant difference in PFS and OS between patients who developed D-ILD and those who did not (median PFS; 8.0 (95% confidence interval (CI), 5.5–9.5) vs. 5.0 (95% CI, 4.5–5.6) months, respectively, P = 0.11, and median OS: not reached (NR) (95% CI, 8.7–NR) vs. 18.2 (95% CI, 13.2–NR) months, respectively, P = 0.20).The Kaplan-Meier survival curves for PFS and OS are shown in Fig. 2 (a, b).

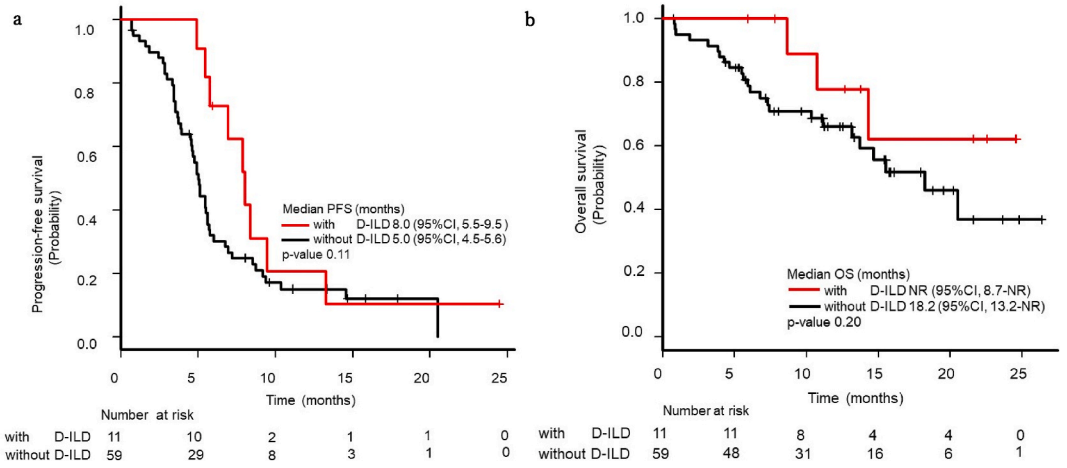

Fig. 2. Kaplan-Meier survival curves of progression-free survival (a) and overall survival (b).

4. Discussion

Our study showed that the incidence of D-ILD caused by chemo-ICI in ES-SCLC was 15.7%, and patients with pre-existing ILA were more likely to develop D-ILD. In a retrospective study of NSCLC in clinical practice, it was reported that the proportion of patients who received chemo-ICI and developed D-ILD ranged from 12.4% to 16.9% [6,11], and our study results were similar to those of these studies. We considered two explanations for the higher incidence of D-ILD in our study than in the clinical trials. The first explanation is the difference between the patient populations in real-world studies and those in clinical trials. In NSCLC, the incidence of D-ILD induced by chemo-ICI has been reported to range from 2.8% to 5.3% in clinical trials [12–14], but it is more frequent in clinical practice [6,11]. We thought this was because in clinical practice, there were more patients with ILA in the background lung compared to clinical trials, and patients with low PS were included. The second explanation is that Japanese people are more prone to develop D-ILD than Westerners [15–17]. Especially, it has been reported that Japanese patients may be more vulnerable to ICI-induced ILD than Caucasian patients [18]. In the phase III Checkmate 017 and Checkmate 057 trials, which were conducted globally for non-small cell lung cancer, D-ILD was reported in 4.6% [19] and 1.4% [20] of patients treated with nivolumab, respectively, while in Japanese patients with advanced or recurrent non-squamous non-small cell lung cancer in a multicenter phase II study of nivolumab, the rate was 7.9% [21].

This study included 70 patients diagnosed with ES-SCLC, of whom 29 (41.4%) had ILA. It has been reported that 38% of patients with limited-stage SCLC who received chemoradiotherapy had ILA [22], and the proportion of patients with ILA was similar to our study. In patients with SCLC, pre-existing ILA may be more frequent than in NSCLC patients. Many SCLC patients have a history of smoking, and smoking has been reported to be associated with ILA [8]. In this study, there was no significant difference between the presence or absence of ILA, smoking history, and the development of D-ILD, but all patients who developed D-ILD had a smoking history.

As mentioned before, patients with ILA were more likely to develop D-ILD. Comparing the extent of ILA with and without D-ILD showed no difference, but comparing by pattern of ILA, GGA and reticulation were found to be risk factors for D-ILD. There is no case with traction bronchiectasis or honeycombing as a result. Because fibrotic changes on baseline chest CT have been reported to be risk factors for anti- PD- 1induced ILD in retrospective study [23], it may suggest that clinicians in our study were aware that traction bronchiectasis and honeycombing are high risks for D-ILD and did not use ICI in such cases. Therefore, clinicians should be aware that GGA and reticulation are also risk factors for D-ILD. GGA and reticulation reflect alveolar septum thickening and lymphocyte infiltration into the interstitium of the lung. ICI have antitumor effects by promoting lymphocyte activity, which may explain why GGA and reticulation are risk factors for D-ILD [24]. Thus, if we administer chemo-ICI to patients with ILA, especially GGA and reticulation, then we should carefully monitor patients for symptoms, such as dyspnea and breathlessness, and perform imaging tests, such as X-rays or CT scans.

In our study, there was no difference in PFS and OS between patients with and without D-ILD. There was no difference between the number of treatment courses, although there were more discontinuations caused by adverse events in patients with D-ILD than in those without. The reason why there was no difference in PFS between D-ILD and non-D-ILD patients was thought to be that most of the patients with D-ILD had completed four courses of induction therapy. Additionally, the limited treatment regimens, their efficacy after first-line chemotherapy, and the poor prognosis of ES-SCLC may be related to the lack of significant differences in PFS and OS between the two groups.

Our study had several limitations. First, this was a retrospective study with a limited number of Japanese ES-SCLC patients; therefore, it is unclear whether our findings can be generalized to other populations. Second, ILA was assessed visually which may introduce bias due to the subjective nature of the evaluation method. Further studies are necessary to investigate the association between risk factors for D-ILD and the treatment of ES-SCLC.

5. Conclusion

In ES-SCLC, the incidence of D-ILD in patients who received chemo-ICI in clinical practice was higher than that in clinical trials, and patients with pre-existing ILA were more likely to develop D-ILD.

Credit authors statement

Kiyoko Fukuda: Investigation, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. Naoko Katsurada: Conceptualization, Investigation, Date curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. Yoshitaka Kawa: Investigation, Writing - review & editing. Miyako Satouchi: Investigation, Writing - review & editing. Kazumi Kaneshiro: Investigation, Writing - review & editing. Masataka Matsumoto: Investigation, Writing - review & editing. Rei Takamiya: Investigation, Writing - review & editing. Yukihisa Hatakeyama: Investigation, Writing - review & editing.

Ryota Dokuni: Investigation, Writing - review & editing. Kanoko Matsumura: Investigation, Writing - review & editing. Masahiro Katsurada: Investigation, Writing - review & editing. Kyosuke Nakata: Investigation, Writing - review & editing. Sho Yoshimura: Investigation, Writing - review & editing. Motoko Tachihara: Conceptualization, Investigation, Writing - review & editing, Project administration, Supervision.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Matters requiring disclosure of COI with regard to our presentation are lecture fee by Chugai Pharmaceutical Co Ltd and research expenses from company by AstraZeneca.

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