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Acute exacerbation predicting poor outcomes in idiopathic interstitial pneumonia and advanced lung cancer patients undergoing cytotoxic chemotherapy

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Effective treatment for advanced lung cancer and idiopathic interstitial pneumonia (IIP) remains an unmet medical need. The relationship between chemotherapy's effectiveness in advanced lung cancer and the risk of acute exacerbation of IIP is poorly investigated. There is limited evidence that patients who experience an acute exacerbation of IIPs during cytotoxic chemotherapy have poorer outcomes than those who do not. Among 1004 patients with advanced lung cancer and IIPs enrolled in our published multi-centre retrospective study from 110 Japanese institutions, 708 patients (male: female, 645:63; mean age, 70.4) received first-line chemotherapy. The occurrence of chemotherapy-triggered acute exacerbations of IIPs and overall survival (OS) were analysed. The OS between groups of patients with and without the occurrence of acute exacerbation was compared at four landmark time points (30, 60, 90, and 120 days), starting from the first-line chemotherapy, using the landmark method. The incidence of acute exacerbation in patients who received first-line chemotherapy with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) was more frequent in NSCLC patients than in SCLC (4.2% vs 12.6%; odds ratio [OR]: 3.316; 95% confidence interval [CI] 1.25–8.8). Median survival time was 9.9 months (95% CI 9.2–10.7). Patients who experienced acute exacerbation had significant worse survival outcomes than those who did not at various time points (30 days, hazard ratio [HR]: 5.191, 95% CI 2.889–9.328; 60 days, HR: 2.351, 95% CI 1.104–5.009; 90 days, HR:

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2.416, 95% CI 1.232–4.739; and 120 days, HR: 2.521, 95% CI 1.357–4.681). Acute exacerbation during first-line chemotherapy can predict poor survival.

Trial Registration number: UMIN000018227.

Abbreviations

CI	Confidence interval
DLco	Diffusing capacity of the lung for monoxide
ERS	European respiratory society
HR	Hazard ratio
HRCT	High resolution computed tomography
IIP	Idiopathic interstitial pneumonia
IPF	Idiopathic pulmonary fibrosis
JRS	Japanese respiratory society
KL-6	Krebs von den Lungen-6
MST	Median survival time
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall survival
PaO_2	Partial pressure of arterial oxygen
PS	Eastern cooperative oncology group performance status
SCLC	Small cell lung cancer
SMD	Standardized mean difference
SP-D	Surfactant protein-D
UIP	Usual interstitial pneumonia

Lung cancer is a major comorbidity of idiopathic interstitial pneumonia (IIP)[1–3]. The development of lung cancer negatively impacts prognosis compared to idiopathic pulmonary fibrosis (IPF) alone[2,4–6]. Male gender[3,4], smoking history[3,4], comorbidities with emphysema[3], impaired predicted forced vital capacity[3,4], and age at the IPF diagnosis[7] have been reported as significant risk factors for development of lung cancer in patients with IPF. The reported cumulative incidence of lung cancer development in patients with IPF is approximately 12.2–15.9% within five years and 23.3–31.1% within 10 years[3,4,7]. Lung cancer is sometimes difficult to identify on high-resolution computed tomography (HRCT) because of its atypical shape and unique tumour location adjacent to fibrotic lesions[8–10]. Not a small number of patients with lung cancer and IIPs receive a diagnosis at advanced stages. It has been observed that around 50% of patients who undergo surgical resection for lung cancer associated with IIP experience recurrence[11].

The guideline-based therapy in patients with stage IV or post-operative recurrent disease is systemic chemotherapy. However, patients in IIP in this setting may not always receive systemic chemotherapy[5], because the association of treatment efficacy of cytotoxic chemotherapy with advanced lung cancer and the risk of acute exacerbation of IIP remains inconclusive. Especially, acute exacerbation is a lethal complication typically occurring in patients with IPF provided approximately up to 50% mortality rate[12,13]. Acute exacerbation typically occurs in IPF patients. However, other fibrotic forms of IIPs also have the potential to cause acute exacerbation[14]. Most retrospective studies have included a small number of patients with some stage III locally advanced disease in addition to those of stage IV or post-operative recurrent disease[15,16]. In recent studies, various carboplatin-containing regimens have been investigated in a single-arm prospective manner[17–24]. It may be difficult to evaluate the risk of acute exacerbation because of the small number of patients in whom acute exacerbation was observed. There remains insufficient evidence regarding chemotherapy-related acute exacerbations, that is, triggered acute exacerbation[12]. A recent study from our group examining the use of chemotherapy in patients with advanced lung cancer and IIPs reported that administering chemotherapies to these patients improved survival outcomes and increased the risk of acute exacerbation compared to patients who received the best supportive care as an initial treatment[25].

We conducted subgroup analyses using a chemotherapy group from our previous large retrospective multi-centre study[25]. A landmark analysis was performed to address whether patients who experience an acute exacerbation of IIPs during first-line chemotherapy might influence survival compared to patients who did not experience an acute exacerbation. In addition, predictors of poor survival and risk of chemotherapy-triggered acute exacerbation during first-line chemotherapy in real-world settings were explored.

Materials and methods

Study participants

We included subjects who met the following criteria; individuals who received chemotherapy as their initial treatment in our previous study[25] and for whom data were available regarding the occurrence of acute exacerbation during first-line chemotherapy, the date of diagnosis with acute exacerbation, and the outcome. Considering these criteria, we aimed to ensure a focused and relevant sample for our research[25].

Study design

Following the amended Declaration of Helsinki, this retrospective multi-centre cohort study was conducted in 110 facilities. From each facility, we collected data from consecutive patients aged 20 years who were

pathologically diagnosed with stage IV lung cancer or demonstrated post-operative recurrent disease from January 2012 to December 2013 and underwent chemotherapy or BSC as initial treatment[25]. The institutions that contributed to this study included academic medical centres and citizen hospitals belonging to the Japanese Respiratory Society (JRS). The protocol was approved by the local ethics committee of Toranomon Hospital (approval number: #1067) (ID: UMIN000018227). The committee of Toranomon Hospital waived the written informed consent requirement due to the study's retrospective nature. Instead, a summary of the study protocol was posted on the hospital website in an opt-out format, allowing candidates the opportunity to express their desire not to participate in the study. The same protocol was applied and approved to the local committees of all collaborating facilities listed in acknowledgement section.

Methods

We retrospectively reviewed the patient's medical records, including their demographic characteristics, as in our previous study using the data of chemotherapy group[25]. Radiological diagnoses were made based on HRCT patterns according to the international consensus guidelines provided by the American Thoracic Society/European Respiratory Society/JRS/Latin American Thoracic Association in 2011[26]. A lung cancer diagnosis was defined as the date of clinically confirmed stage IV or postoperative recurrence, in addition to the pathologic diagnosis. The Eastern Cooperative Oncology Group performance status (PS) system indicates the patients' general status[27]. Clinical data were collected during lung cancer diagnosis or as close to the diagnosis as possible.

As in our previous report displayed[25], an acute exacerbation was defined based on the JRS guidelines[14]. The American Thoracic Society/European Respiratory Society[12] proposed a set of criteria to identify triggers for acute exacerbations. Our study defined overall survival (OS) as the duration from the start of first-line chemotherapy to the time of death, which differed from our previous report[25]. We evaluated the initial treatment overall response and disease control rates (ORRs and DCRs) using the Response Evaluation Criteria in Solid Tumours (RECIST). The primary focus of this study was to investigate the impact of acute exacerbations on OS and the risks of chemotherapy-triggered acute exacerbation during first-line chemotherapy.

Statistical analysis

We conducted a landmark analysis to compare OS between patients who developed acute exacerbation during the first-line chemotherapy period and those without exacerbation. This analysis was conducted at specific landmark time points at 30, 60, 90, and 120 days from the initiation of first-line chemotherapy. Landmark analysis is a valuable method for mitigating the potential bias known as 'the guarantee-time bias' when assessing OS between two groups of patients with and without acute exacerbation. To address this bias, patients who had died prior to each landmark time point were excluded from subsequent time point analyses. The remaining survivors at each successive landmark point were then used for the next survival analysis. The group of acute exacerbation (AE group) included survivors who experienced acute exacerbation until the date of each landmark point. Conversely, survivors who had not experienced acute exacerbation events up to each landmark date were included in the non-acute exacerbation group (non-AE group), even if some of them later experienced acute exacerbation events beyond each respective date. From each landmark time point, the survival of these two groups was compared using the Kaplan–Meier survival curve. Statistical differences in time-to-event outcomes were assessed using either the log-rank test or a Cox regression model.

For identifying individual risk factors associated with acute exacerbation and patient survival during first-line chemotherapy, univariate logistic and Cox regression models were employed, respectively. To address missing data within the entire cohort, a comprehensive dataset was constructed. Univariate analyses were performed on this complete dataset, which included cases with no missing clinical data, using logistic regression and Cox regression models. Additionally, multivariate logistic and Cox regression models were used to estimate the joint effects of risk factors on acute exacerbation and patient survival during first-line chemotherapy. In the multivariate analyses, only variables that were statistically significant in the univariate analysis were included.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). Two-tailed p-values were reported. A p-value of < 0.05 was considered statistically significant.

Results

The dataset comprised 708 cases (Fig. 1). Table 1 presents the patient characteristics. Table 2 lists the first-line chemotherapy regimens utilised in the study. Acute exacerbation during first-line chemotherapy was observed in 71 patients. Of 22 patients (31.0%) were died with median survival time with 2.14 [95% CI 1.05–2.73] months. Pulmonary function test results were relatively preserved with predicted forced vital capacity, but moderately impaired predicted diffusion capacity of the lung for carbon monoxide (%DLco). Nine patients were observed with %DLco less than 30%, and 59 patients were observed with %DLco of 30% or more but less than 50%.

The first-line chemotherapy regimens used

In NSCLC patients, there were several treatment options available, and the ORR and DCR were estimated at 29.3% and 58.7%, respectively. Among SCLC patients, the most commonly used regimen was carboplatin (CBDCA) + etoposide (VP16) in 160 patients, which had a relatively low incidence rate of acute exacerbation (3.1%). In contrast to NSCLC regimens, most SCLC patients received CBDCA or cisplatin (CDDP) + VP16 (160/34; 89.8%), with a relatively homogeneous selection of regimens. The ORR and DCR in SCLC were 51.4% and 65.7%, respectively. Overall, the incidence of acute exacerbations was lower in SCLC (4.2%) than in NSCLC (12.6%).

Few patients (N = 13) whose epithelial growth factor receptor mutation status was positive were observed. Three of 13 patients received gefitinib as first-line chemotherapy, resulting that acute exacerbation occurred

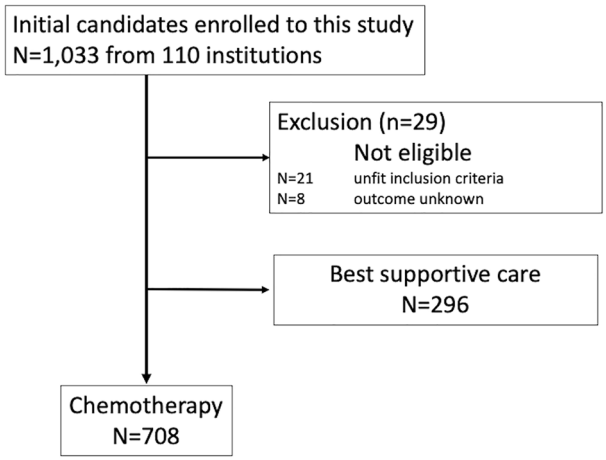

Figure 1. Flow chart for patients' selection of this study.

in 2 of three patients. Among other 10 patients, 8 received platinum doublet regimens (CBDCA + paclitaxel in three and CDDP + TS-1, CDDP + pemetrexed [PEM], CBDCA + PEM, CBDCA + PEM + Bevacizumab, CDDP + vinorelbine [VNR] in one each, respectively) and remaining two patients received DOC monotherapy. Acute exacerbation was occurred none of these 10 patients.

Occurrence of acute exacerbation predicts poor survival

Landmark analysis indicated that patients who experienced acute exacerbation divided by landmark points (30, 60, 90, and 120 days from the date of initiation of first-line chemotherapy) had poorer OS than those who did not experience acute exacerbation (30 days, $p < 0.0001$; 60 days, $p = 0.02$; 90 days, $p = 0.008$; 120 days, $p = 0.002$) (Fig. 2).

The OS for the entire cohort was 9.9 months (95% CI 9.2–10.7), while for patients with SCLC, it was 9.6 months (95% CI 8.6–11.4), and for those with NSCLC, it was 9.9 months (95% CI 9.0–10.9) (Fig. 3).

Predictors of the risks of chemotherapy-triggered acute exacerbation and poor survival

The univariate analyses conducted using data from the entire cohort (n = 708) revealed that advanced age (≥ 70) (OR: 1.844, 95% CI 1.082–3.142, $p = 0.0245$) and the use of regimens specifically designed for NSCLC histology (OR: 3.316, 95% CI 1.617–6.803, $p = 0.0011$) were identified as potential predictors of acute exacerbation during first-line chemotherapy. In the analysis of the complete dataset (n = 397), the results of the univariate analyses demonstrated that regimens specifically designed for NSCLC were found to be statistically significant (OR: 3.258, 95% CI 1.249–8.498, $p = 0.0158$). In the multivariate logistic regression analysis, adjusted for age and gender, it was found that regimens specifically designed for NSCLC were an independent risk factor for predicting the occurrence of chemotherapy-triggered acute exacerbation during first-line chemotherapy (OR: 3.316, 95% CI 1.25–8.8, $p = 0.016$); this may indicate that the choice of NSCLC regimens significantly influenced the risk of acute exacerbation during the first-line treatment. These findings are summarised in Table 3.

In the univariate analyses conducted on the entire cohort (n = 708), several factors were identified as potential predictors of poor survival. These included male sex (HR: 1.363, 95% CI 1.01–1.839, $p = 0.0427$), PS of 1 (HR: 1.546, 95% CI 1.273–1.876, $p < 0.0001$) and PS of ≥ 2 (HR: 3.331, 95% CI 2.548–4.355, $p < 0.0001$), higher serum levels of Krebs von den Lungen-6 (KL-6) (500≦KL-6 < 1000: HR: 1.305, 95% CI 1.04–1.638, $p = 0.0216$; 1000 ≦ KL-6 < 2000: HR: 1.441, 95% CI 1.105–1.879, $p = 0.007$), and the presence of desaturation on exertion (HR: 1.57, 95% CI 1.177–2.096, $p = 0.0022$). Using the complete dataset (n = 397), the results of the univariate analyses were almost the same as those of the entire cohort. The multivariate Cox regression analysis adjusted for age and sex demonstrated that poor PS of 1 (HR, 2.222; 95% CI 1.682–2.936; $p < 0.0001$) and ≥ 2 (HR: 4.006, 95% CI 2.627–6.108, $p < 0.0001$) was a significant predictor of death. These findings are summarised in Table 4.

Discussion

The current study demonstrated that patients who experienced acute exacerbations during first-line chemotherapy had significantly worse survival rates than those who did not. Poor PS was significantly associated with poor survival. Compared with SCLC, some NSCLC regimens may potentially lead to acute exacerbation of IIP in patients who received first-line chemotherapy.

No appropriate first-line chemotherapy has been established for IIP patients with advanced NSCLC or SCLC. Several prospective, small-sized, single-arm studies have assessed the validity and/or feasibility of CBDCA + weekly paclitaxel (PTX)[22,23], CBDA + S-1[18,19], and CBDCA + nab-PTX[20,21,24] in patients with NSCLC and interstitial lung disease (ILD). These studies reported the following findings: OS ranged from 9.7 to 19.8 months, ORR ranged from 33.3 to 69.7%, DCR ranged from 66.7 to 93.9%, and the occurrence rates of acute exacerbation ranged from 4.3 to 12.1%. Otsubo et al.[28] prospectively investigated the acute exacerbation

	Chemotherapy group
Participants (n)	708
Age (years)[#]	70.4 ± 6.9
Sex (male/female)	645/63
Smoking history (presence/absence/unknown)	684/20/4
Smoking index (pack-years)[#]	N = 677, 55.3 ± 30
Emphysema (presence/absence/unknown)	326/381/1
Performance status	
0/1/2/3/4	226/378/84/16/4
Interstitial pneumonia	
Clinical diagnosis of IIP (IPF/non-IPF/unknown)	406/294/8
HRCT pattern	
UIP pattern	275
Possible UIP pattern	243
Inconsistent with the UIP pattern	190
History of acute exacerbation (presence/absence/unknown)	11/689/8
Desaturation on exertion (presence/absence/unknown)	80/418/210
%FVC (%)[#]	n = 441, 88.6 ± 19.14
%DLco (%)[#]	n = 238, 64 ± 22.56
KL-6 (U/mL)[#]	n = 564, 922.8 ± 985.25
SP-D (ng/mL)[#]	n = 406, 135.6 ± 102.9
Treatment	
None	678
Prednisolone	15
Prednisolone + immunosuppressants	5
Pirfenidone	7
NAC	1
Pirfenidone + NAC	1
Pirfenidone + prednisolone	1
Lung cancer	
Histopathologic type	
Small cell carcinoma	216
Non-small cell carcinoma	492
Adenocarcinoma	258
Squamous cell carcinoma	173
LCNEC	17
LCC	9
Others	35
EGFR mutation status	
Negative	274
Positive	13
L858R/deletion 21	9/4
Not evaluated	421
ALK re-arrangement	
Negative	124
Positive	2
Not evaluated	582

Table 1. Patients' demographics. *ALK* anaplastic lymphoma kinase, *BSC* best supportive care, *EGFR* epidermal growth factor receptor, %DLco percentage of predicted diffusing capacity of the lung for monoxide, %*FVC* percentage of predicted forced vital capacity, *HRCT* high-resolution computed tomography, *IIP* idiopathic interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, *KL*-6 Krebs von den Lungen-6, *LCC* large cell carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *NAC* inhaled N-acetylcysteine, *PS* eastern cooperative oncology group performance status, *SP-D* surfactant protein-D, *UIP* usual interstitial pneumonia. [#]Mean ± standard deviation.

Regimen	n	ORR (%)	DCR (%)	AE (n)	AE incidence (%)
< NSCLC >					
Tri-weekly CBDCA + PTX	113	32.7	62.8	13	11.5
CBDCA + PEM	61	21.3	54.1	10	16.4
CBDCA + S-1	42	23.8	50.0	2	4.8
CBDCA + PTX + Bev	32	59.4	81.3	4	12.5
CDDP + PEM	26	38.5	57.7	3	11.5
DTX	26	11.5	34.6	9	34.6
CBDCA + nab-PTX	26	42.3	69.2	1	3.8
CBDCA + PEM + Bev	23	43.5	87.0	3	13.0
Weekly CBDCA + PTX	21	42.9	71.4	1	4.8
PEM	17	11.8	23.5	3	17.6
CDDP + DTX	15	60.0	80.0	2	13.3
S-1	13	0	38.5	2	15.4
VNR	12	8.3	33.3	3	25.0
CDDP + VNR	11	27.3	63.6	0	0
CBDCA + VP16	11	9.1	45.5	1	9.1
Others[#]	43	–	–	5	11.6
Total	492	29.3	58.7	62	12.6
< SCLC >					
CBDCA + VP16	160	51.2	64.4	5	3.1
CDDP + VP16	34	52.9	70.6	2	5.9
CDDP + CPT11	10	50.0	80.0	0	0
CBDCA + CPT11	6	66.7	66.7	1	16.7
Others[##]	6	–	–	1	16.7
Total	216	51.4	65.7	9	4.2

Table 2. Chemotherapy regimens. *AE* acute exacerbation, *AMR* amrubicin, *Bev* bevacizumab, *CBDCA* carboplatin, *CDDP* cisplatin, *CPT-11* irinotecan, *DTX* docetaxel, *NDP* nedaplatin, *nab-PTX* nanoparticle albumin-bound paclitaxel, *NGT* nogitecan, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *PEM* pemetrexed, *PTX* paclitaxel, *SCLC* small cell lung cancer, *VNR* vinorelbine; *VP*-16 etoposide. [#]'Others' includes regimens consisting of 10 cases or less, i.e. CDDP + S-1 (n = 9), CDDP + VP-16 (n = 4), CBDCA + DTX (n = 3), CBDCA + gemcitabine (GEM) (n = 3), CBDCA + VNR (n = 3), weekly CBDCA + PTX + Bev (n = 2), CBDCA + CPT-11 (n = 1), CBDCA + PTX + Bev (n = 1), CDDP + GEM (n = 2), CDDP + S-1 + Bev (n = 1), PTX (n = 5), Gefitinib (n = 3), GEM (n = 2), Nedaplatin (n = 1), Bev (n = 1), UFT (n = 1), and PEM + BEV (n = 1). [##]'Others' includes regimens consisting of five cases or less, i.e. AMR (n = 3), monthly CBDCA + PTX (n = 2), and VP-16 (n = 1).

rate by comparing patients with IPF and advanced lung cancer who received CBDCA + nab-PTX with and without nintedanib. No statistical difference was observed in the acute exacerbation rate between the groups (event free survival: 14.6 vs. 11.8 months). Furthermore, for patients with extensive SCLC and ILD, there is scarce evidence for suitable and established first-line chemotherapy. One prospective study has used CBDCA + VP-16 in lung cancer treatment. Reported outcomes include OS (8.7 months) and acute exacerbation occurrence rates (5.8%)[17]. Minegishi et al.[15] conducted a large retrospective multi-centre cohort study with 204 NSCLC and 74 SCLC patients. This study presented the OS of patients with NSCLC and SCLC at 14.3 and eight months after first-line chemotherapy, respectively. Patient demographics in these studies, including lung cancer stage (NSCLC: III/IV or SCLC: limited/extensive), pulmonary function status, ILD clinical diagnosis (IPF vs non-IPF), HRCT findings (UIP pattern or others), and the study period for acute exacerbation development (chemotherapy period only or inclusive of best supportive care period), exhibited considerable variability. Due to this diversity, these results remain inconclusive for even the occurrence rate of acute exacerbations in this population. The results of the present study correspond to real-world clinical settings during first-line chemotherapy. Notably, the stage of lung cancer was restricted to stage IV or postoperative recurrent disease in this study.

Landmark analysis has played a crucial role in addressing the clinical question regarding the prognostic implications of acute exacerbation during first-line chemotherapy compared with that noted in patients without such events. Consistently, our findings indicate that patients who experienced acute exacerbation during their first-line chemotherapy had poorer survival outcomes than those who did not, highlighting the significance of acute exacerbation as a prognostic factor in lung cancer treatment. Moreover, our previous study has shown that chemotherapy can predict the occurrence of acute exacerbation compared with that noted with the best supportive care[25]. Based on this prediction, patients who experience acute exacerbation during first-line chemotherapy might be reasonably advised to transition their treatment strategies to the best supportive care rather than further continuation of chemotherapy, whereas it may be difficult to design further studies to directly compare OS experiencing an acute exacerbation on chemotherapy versus best supportive care. In contrast, our

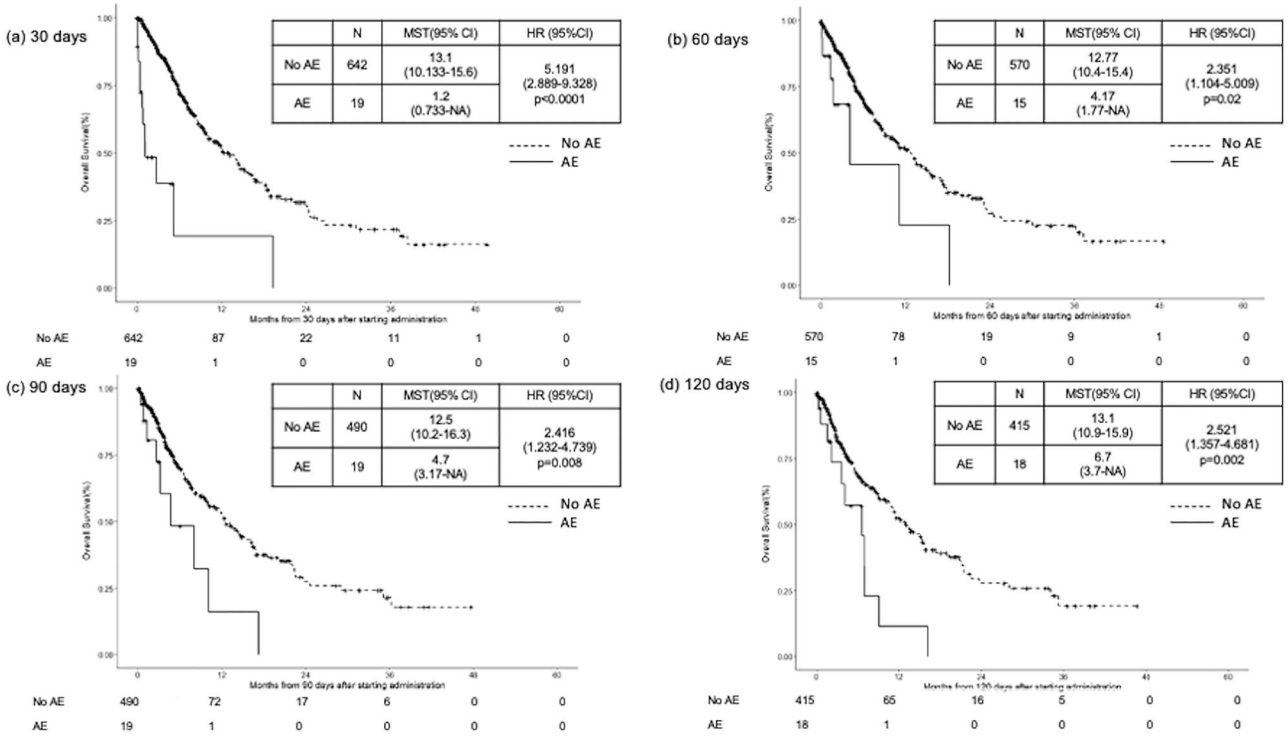

Figure 2. Landmark analysis. Kaplan–Meier survival curve for comparison of the group which experienced acute exacerbation (AE group) with one which did not experience acute exacerbation (no AE group) during the first-line chemotherapy with landmark points of (**a**) 30, (**b**) 60, (**c**) 90, and (**d**) 120 days, respectively, after the date of administration of the first-line regimen.

Group	MST (95% CI)	12 months (95% CI)	24 months (95% CI)	36 months (95% CI)	48 months (95% CI)
Total	9.9 (9.2 – 10.7)	0.42 (0.38 - 0.46)	0.15 (0.12 - 0.18)	0.08 (0.06 - 0.11)	0.05 (0.02 - 0.08)
SCLC	9.6 (8.6 – 11.4)	0.41 (0.34 - 0.48)	0.17 (0.11 - 0.23)	0.08 (0.04 - 0.14)	NA
NSCLC	9.9 (9.0 – 10.9)	0.42 (0.37 - 0.46)	0.14 (0.11 - 0.18)	0.08 (0.05 - 0.11)	0.05 (0.02 - 0.09)

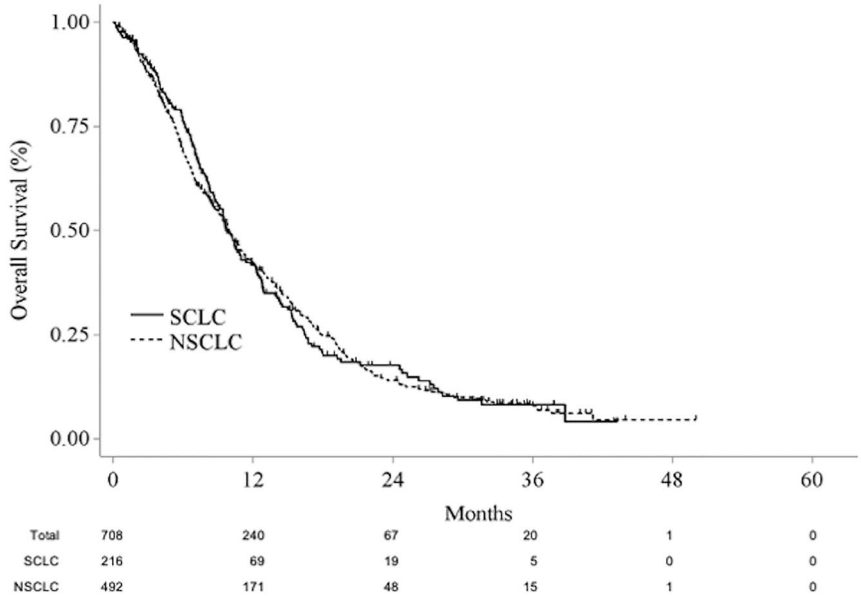

Figure 3. Kaplan–Meier survival curve for subgroups of NSCLC (n = 492) and SCLC (n = 216) with median survival time and 1, 2, 3 and 4 year-survival rates.

		Univariate (n = 708)				Univariate (N = 397)				Multivariate		
		N	OR	95% CI	P value	N	OR	95% CI	P value	OR	95% CI	P value
Sex	Female	63	Ref			39	Ref			Ref		
	Male	645	2.357	0.72–7.718	0.1576	358	2.458	0.572–10.572	0.2268	2.178	0.493–9.619	0.3042
Age	< 70	299	Ref			171	Ref			Ref		
	≧ 70	409	1.844	1.082–3.142	0.0245	226	1.531	0.793–2.955	0.2046	1.432	0.721–2.844	0.3051
PS	0	226	Ref			133	Ref			Ref		
	1	378	0.828	0.467–1.469	0.5197	212	1.05	0.496–2.226	0.898	0.945	0.435–2.053	0.8863
	≧ 2	104	1.941	0.991–3.8	0.0531	52	3.025	1.26–7.268	0.0133	2.603	0.992–6.83	0.052
Smoking index	< 50	345	Ref									
	≧ 50	352	1.01	0.614–1.66	0.9689							
Clinical diagnosis of IIPs	Not-IPF	294	Ref									
	IPF	406	0.817	0.499–1.337	0.4204							
HRCT pattern	Inconsistent with the UIP pattern	190	Ref									
	UIP pattern	243	0.975	0.524–1.814	0.9357							
	Possible UIP pattern	275	0.888	0.48–1.641	0.7037							
History of AE	Presence	11	Ref									
	Absence	689	–	–	0.9839							
Emphysema	Absence	381	Ref									
	Presence	326	0.788	0.479–1.297	0.3489							
KL-6	< 500	184	Ref			138	Ref			Ref		
	≧ 500, < 1000	221	1.373	0.697–2.701	0.3592	148	1.165	0.539–2.521	0.6974	1.04	0.466–2.322	0.9229
	≧ 1000, < 2000	124	1.55	0.729–3.299	0.255	87	1.539	0.668–3.547	0.3118	1.292	0.535–3.121	0.5686
	≧ 2000	35	1.878	0.635–5.552	0.2546	24	1.374	0.36–5.234	0.6419	1.258	0.317–4.985	0.7442
SP-D	< 110	203	Ref									
	≧ 110, < 150	71	1.794	0.78–4.125	0.1692							
	≧ 150, < 250	80	1.931	0.877–4.252	0.1024							
	≧ 250	52	2.29	0.956–5.485	0.063							
%FVC	≧ 80	296	Ref									
	≧ 50, < 80	137	1.014	0.53–1.943	0.9657							
	< 50	8	–	–	0.9859							
%DLco	≧ 80	55	Ref									
	< 80	183	1.656	0.604–4.541	0.327							
Desaturation on exertion	Absence	418	Ref			330	Ref			Ref		
	Presence	80	1.765	0.878–3.548	0.111	67	2.032	0.986–4.187	0.0547	1.416	0.622–3.224	0.4077
Treatment for IIPs	No	678	Ref									
	Yes	30	1.855	0.687–5.007	0.2229							
Histology of lung cancer	SCLC	216	Ref			109	Ref			Ref		
	NSCLC	492	3.316	1.617–6.803	0.0011	288	3.258	1.249–8.498	0.0158	3.316	1.25–8.8	0.016

Table 3. Univariate and multivariate analyses with a logistic regression model for the risk of acute exacerbation. *AE* acute exacerbation, *CI* confidence interval, *%Dlco* predicted diffusing capacity of the lung for monoxide, *%FVC* predicted forced vital capacity, *HRCT* high-resolution computed tomography, *Hx* histology, *IP* interstitial pneumonia, *KL-6* Krebs von den Lungen-6, *NS* not significant, *NSCLC* non-small cell lung cancer, *OR* odds ratio, *PaO2* partial arterial pressure of oxygen, *PS* performance status, *ref* reference, *SCLC* small cell lung cancer, *SP-D* surfactant protein-D, *UIP* usual interstitial pneumonia.

previous study demonstrated that first-line chemotherapy provided a survival benefit compared with that noted when choosing the best supportive care as the initial treatment[25]. Appropriate clinical follow-ups and evaluations are required during chemotherapy to confirm the occurrence of acute exacerbations. However, based on our current analyses, it remains unclear which patients have the potential to develop acute exacerbation.

Notably, NSCLC patients were identified as having a significantly higher risk of acute exacerbation during first-line chemotherapy than patients with SCLC, although this result should be interpreted with caution. Impaired lung function (lower predicted forced vital capacity)[29–31], histologic type of NSCLC[29], age < 70 years[32], poor PS (2, 3)[32], and UIP pattern on HRCT[32] have been reported as risk factors for chemotherapy-triggered acute exacerbations, as analysed by a logistic regression method. Whether the histopathological type itself could affect the occurrence of acute exacerbation remains to be elucidated. One possible interpretation may be that the relatively homogeneous usage of chemotherapy regimens with CBDCA/CDDP + VP16 in SCLC patients and other extremely varied regimens (N = 16) for NSCLC patients might affect the result. CBDCA/CDDP + VP16 was

		Univariate (n = 708)				Univariate (N = 397)				Multivariate		
		N	HR	95% CI	P value	N	HR	95% CI	P value	HR	95% CI	P value
Sex	Female	63	Ref			39	Ref			Ref		
	Male	645	1.363	1.01–1.839	0.0427	358	1.213	0.83–1.772	0.3189	1.322	0.898–1.945	0.1569
Age	< 70	299	Ref			171	Ref			Ref		
	≧ 70	409	1.057	0.892–1.254	0.5217	226	0.941	0.745–1.19	0.6131	0.937	0.739–1.189	0.5919
PS	0	226	Ref			133	Ref					
	1	378	1.546	1.273–1.876	< 0.0001	212	2.203	1.674–2.899	< 0.0001	2.222	1.682–2.936	< 0.0001
	≧ 2	104	3.331	2.548–4.355	< 0.0001	52	4.142	2.822–6.08	< 0.0001	4.006	2.627–6.108	< 0.0001
Smoking index	< 50	345	Ref									
	≧ 50	352	1.039	0.876–1.233	0.6581							
Clinical diagnosis of IIPs	Not-IPF	294	Ref									
	IPF	406	1.155	0.972–1.373	0.1022							
HRCT pattern	Inconsistent with the UIP pattern	190	Ref									
	UIP pattern	243	0.884	0.712–1.098	0.265							
	Possible UIP pattern	275	1.095	0.888–1.349	0.3973							
History of AE	Presence	11	Ref									
	Absence	689	1.45	0.775–2.714	0.2445							
Emphysema	Absence	381	Ref									
	Presence	326	1.109	0.936–1.315	0.2317							
KL-6	< 500	184	Ref			138	Ref			Ref		
	≧500, < 1000	221	1.305	1.04–1.638	0.0216	148	1.312	0.997–1.726	0.0522	1.161	0.871–1.547	0.308
	≧1000, < 2000	124	1.441	1.105–1.879	0.007	87	1.425	1.035–1.96	0.0298	1.323	0.952–1.841	0.0959
	≧2000	35	1.295	0.85–1.974	0.2292	24	1.367	0.804–2.323	0.2484	1.379	0.804–2.363	0.2428
SP-D	< 110	203	Ref									
	≧ 110, < 150	71	0.848	0.627–1.149	0.2882							
	≧ 150, < 250	80	1.128	0.835–1.524	0.433							
	≧ 250	52	0.862	0.604–1.231	0.4147							
%FVC	≧ 80	296	Ref									
	≧ 50, < 80	137	1.219	0.959–1.549	0.1053							
	< 50	8	1.64	0.674–3.99	0.2759							
%DLco	≧ 80	55	Ref									
	< 80	183	1.172	0.826–1.664	0.3726							
Desaturation on exertion	Absence	418	Ref			330	Ref			Ref		
	Presence	80	1.57	1.177–2.096	0.0022	67	1.663	1.209–2.288	0.0018	0.858	0.654–1.125	0.2681
Treatment for IIPs	No	678	Ref									
	Yes	30	1.11	0.724–1.702	0.6309							
Histology of lung cancer	SCLC	216	Ref			109	Ref			Ref		
	NSCLC	492	1.01	0.839–1.217	0.9134	288	0.962	0.738–1.254	0.7729	1.094	0.767–1.561	0.6191

Table 4. Univariate and multivariate analyses with the Cox regression hazard model for survival. *AE* acute exacerbation, *CI* confidence interval, *%Dlco* predicted diffusing capacity of the lung for monoxide, *%FVC* predicted forced vital capacity, *HRCT* high-resolution computed tomography, *Hx* histology, *IP* interstitial pneumonia, *KL-6* Krebs von den Lungen-6, *NS* not significant, *NSCLC* non-small cell lung cancer, *OR* odds ratio, *PaO2* partial arterial pressure of oxygen, *PS* performance status, *ref* reference, *SCLC* small cell lung cancer, *SP-D* surfactant protein-D, *UIP* usual interstitial pneumonia.

reported as the regimen that may have relatively low occurrence rate of acute exacerbation[15]. Conversely, some specific NSCLC regimens may indicate a high potential for acute exacerbation. The potential risk of a relatively high occurrence of acute exacerbation with specific regimens, including PEM or DOC monotherapy, has been discussed[33–35]. The current study could not determine which regimens were safer. In addition, in the previous study[25], chemotherapy predicted better survival than best supportive care in any subgroup analyses. Overall, the histological type of NSCLC itself does not negatively impact the initiation of chemotherapy in these patients. However, further studies are required to resolve this issue.

This study confirms that poor PS is a significant predictor of survival; this finding is consistent with previous studies based on SCLC and NSCLC[33,36,37]. PS is pivotal in treatment decision-making and evaluating patient outcomes. In addition, elevated serum lactate dehydrogenase levels[38] and C-reactive protein levels[37], along with a clinical diagnosis of IPF[33,38,39], have been identified as detrimental factors associated with poorer outcomes in SCLC or NSCLC. Importantly, these studies evaluated poor predictors of survival using a cohort that included

patients with and without pre-existing ILD[33,37–39]. This study identified poor PS as the sole independent predictor of poor outcomes. Interestingly, none of the other variables examined were found to be significant predictors. It is noteworthy that this study evaluated a large cohort of patients with stage IV or post-operated disease with ILD only, providing valuable insights into the predictive factors associated with adverse prognosis in this population. However, nothing can be concluded to date because no direct comparison of IIP and lung cancer with IIP alone was performed in the current study. Further studies are required to confirm this hypothesis.

This study had several limitations. First, this study was retrospective nature. Therefore, some defects in the clinical information regarding IIPs, lung cancer, and outcomes were included. Missing information made it difficult to achieve perfect results from the multivariate analyses. Second, due to the small numbers and various regimens used, assessing each regimen's comparative therapeutic benefits, including OS and PFS was challenging. In addition, it remains inconclusive whether adverse events other than acute exacerbation might influence the outcome because they were not collected due to per-protocol issues. Third, the participants in this study were recruited from January 2012 to December 2013 before an era in which immune checkpoint inhibitors were available. Because this study included the data regarding the patients who treat purely cytotoxic agents, this data would be valuable reference when further studies will be performed to investigate the additional efficacy and risk of combination regimens with cytotoxic agent plus immune checkpoint inhibitors in this population, thereafter one retrospective study was recently published in patients who treated with immune checkpoint inhibitor[40]. In addition, some prospectively assessed regimens (CBDCA + weekly paclitaxel (PTX)[22,23], CBDA + S-1[18,19], and CBDCA + nab-PTX[20,21,24] in patients with NSCLC) are possible candidates to date. However, at an enrolment, regimen selection was exploratory. The reason why various regimens were identified in NSCLC may be that the participants enrolment was before an era in which these prospective studies were actively published. Fourth, small number of patients (N = 14) who received antifibrotic therapy was identified in this study. This may also associate with the study period. Pirfenidone has been available since 2008 in Japan, however, nintedanib was not yet available. Pirfenidone was majorly prescribed in patients with IPF alone with severe disease due to medical insurance issues at that time. As J-SONIC study investigated the value to add-on nintedanib to cytotoxic agents[28], even recently, usage of antifibrotic agents in patients with interstitial pneumonia and advanced stage of lung cancer may be challenging[15]. Fifth, male predominance was shown in this study. Although it may be a common epidemiologic characteristic in previous studies[2,3], unequal gender distribution may be a bias for outcome analyses.

In conclusion, if acute exacerbation occurs during first-line chemotherapy, switching to the best supportive care instead of continuing chemotherapy may be a possible option. Despite the overall clinical benefit of chemotherapy in terms of OS, the decision should be made with caution whether second line chemotherapy should be subsequently performed. Further studies will be necessary to confirm safety of second line chemotherapy.

Notably, the lower acute exacerbation rate in patients with SCLC may support the safer use of CBDCA/CDDP + VP16. While the risk of exacerbation of IIP may be higher with certain regimens for NSCLC than with SCLC, these findings should not discourage the use of chemotherapy in patients with NSCLC and IIPs who have a good PS.

Data availability

All de-identified data that underlie the reported results of this study are available from a corresponding author on reasonable request.

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Author contributions

A.M. is responsible for the content of the manuscript, including the data and analysis. A.M., and H.M. conceived and designed the study. A.M. collected the data. H.M. performed statistic data analysis. A.M., H.M., Y.N., S.A., K.N., Y.M., T.O., S.H1., H.D., K.T., S.H2., and K.K analyzed the results and interpreted the comprehensive data. A.M. and H.M. drafted the initial manuscript. S.H2. and K.K., supervised overall study and analysis processes. All authors discussed the results and reviewed the manuscript.

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Additional information

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