Characteristics and Prognostic Impact of Pneumonitis during Systemic Anti-Cancer Therapy in Patients with Advanced Non-Small-Cell Lung Cancer

Daichi Fujimoto[1]*, Ryoji Kato[1], Takeshi Morimoto[2,3], Ryoko Shimizu[1], Yuki Sato[1], Mariko Kogo[1], Jiro Ito[1], Shunsuke Teraoka[1], Kazuma Nagata[1], Atsushi Nakagawa[1], Kojiro Otsuka[1], Keisuke Tomii[1]

1 Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan, 2 Clinical Research Center, Kobe City Medical Center General Hospital, Kobe, Japan, 3 Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan

* daichianzen@yahoo.co.jp

Abstract

Background

Data on characteristics, outcomes, and prognosis of advanced non-small-cell lung cancer (NSCLC) patients who develop pneumonitis during systemic anti-cancer therapy (pneumonitis) are currently lacking.

Methods

We conducted a retrospective cohort study of 910 consecutive patients diagnosed with advanced NSCLC between January 2004 and January 2014. Of these, 140 patients were excluded because they did not receive systemic anti-cancer therapy at this hospital.

Results

A total of 770 patients were included in the study, of whom 44 (6%) were diagnosed with pneumonitis. The mortality rate of pneumonitis was 36%. The incidence of pneumonitis was independently associated with pre-existing ILD (adjusted odds ratio, 2.99, P = 0.008), and survivors were significantly associated with younger age (P = 0.003) and radiographic non-acute interstitial pneumonia pattern (P = 0.004). In all patients, pneumonitis was identified as an independent predictor of overall survival (OS) (adjusted hazard ratio 1.53, 95% CI, 1.09–2.09, P = 0.015). Performance status was poor in 82% of survivors of pneumonitis; in 62% of survivors, the PS worsened after the pneumonitis improved. Additionally, 54% of survivors received no further systemic anti-cancer therapy after pneumonitis. The median survival time of survivors after pneumonitis was 3.5 months (95% CI, 2.3–7.2 months).

Conclusions

Our study indicated that 6% of patients with advanced NSCLC developed pneumonitis during systemic anti-cancer therapy. The early mortality rate of pneumonitis is high, and the survival and PS after pneumonitis is extremely poor. Additionally, pneumonitis has an adverse impact on the survival of patients with advanced NSCLC. These data should be considered for the management of pneumonitis, and we recommend that future work focuses on pneumonitis particularly to improve the survival of patients with advanced NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1, 2]. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases, and the majority are at an advanced stage, that is, unresectable and metastatic upon their initial diagnosis. As systemic anti-cancer therapy is the main treatment option for these patients, some individuals develop interstitial lung disease (ILD) [1, 2]. Indeed, about 70% of severe pneumonitis cases are associated with systemic anti-cancer therapy, and the early mortality rate of these patients is high [3, 4]. Furthermore, pneumonitis during systemic anti-cancer therapy (pneumonitis) is the most frequent cause of systemic anti-cancer therapy-related mortality [5]. However, there are few data on pneumonitis, and most are in the form of case reports and review articles.

The clinical situation is quite different in patients with advanced NSCLC and pneumonitis, compared with those with pneumonitis without advanced cancer, because the prognosis of advanced NSCLC itself is generally poor [1]. Survival data and clinical characteristics of patients with pneumonitis and advanced NSCLC would be useful to assess the clinical importance of pneumonitis. Further knowledge of the mortality rate and the clinical course of pneumonitis can facilitate shared decision-making for the treatment of acute respiratory failure associated with pneumonitis in advanced NSCLC patients. Therefore, an understanding of pneumonitis in these subjects is important for improving the management not only of pneumonitis, but also advanced NSCLC. The aim of this study, therefore, is to understand the characteristics, outcomes, and survival of advanced NSCLC patients who developed pneumonitis.

Patients and Methods

Patients

We conducted a retrospective cohort study at Kobe City Medical Center General Hospital, a tertiary referral centre. We identified 910 consecutive patients diagnosed with advanced (stage IIIB or IV) NSCLC at this hospital between January 2004 and January 2014. Of these, 140 patients were excluded as they did not receive systemic anti-cancer therapy at this hospital (Fig 1). Patients who reported never having smoked were defined as never smokers, those who had smoked within 1 year of the diagnosis were categorized as current smokers and the rest were considered former smokers. The clinical stage of all patients was established according to the TNM classification, 7th edition [6]. Overall survival (OS) was measured as the period from the diagnosis of NSCLC until death from any cause or the end of the follow-up period. Worsening of performance status (PS) was defined as change from PS 0–1 to PS 2–4, or from PS 2 to a PS 3–4 after pneumonitis improvement. Pre-existing ILD was diagnosed based on clinical features and results of the pre-treatment high-resolution computed tomography (HRCT) of the
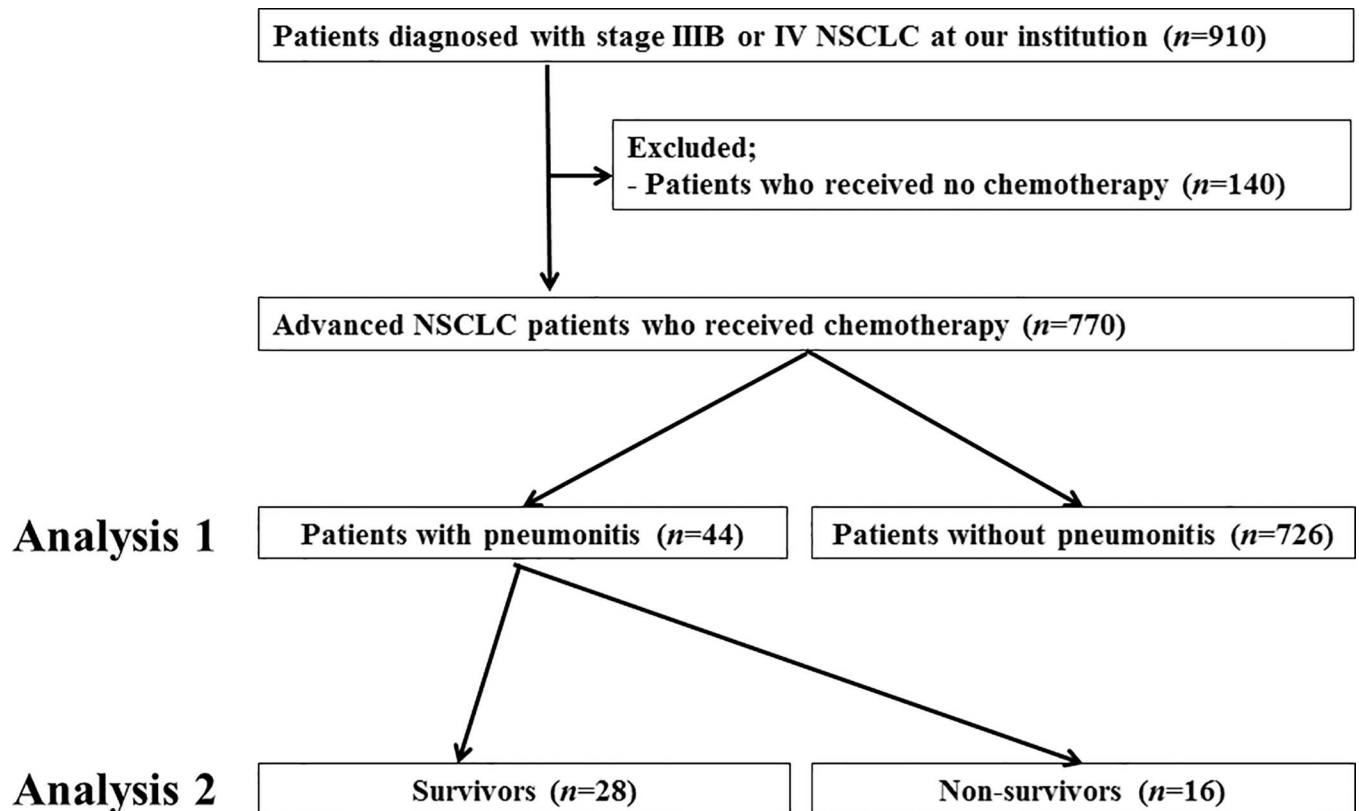
Fig 1. Patient selection and exclusion criteria. NSCLC: non-small cell lung cancer;

doi:10.1371/journal.pone.0168465.g001

chest. All patients underwent HRCT as part of routine clinical practice, and the presence of ILD was evaluated by at least two pulmonologists who were unaware of the patients' clinical status. Pre-existing ILD was defined as ILD before the first-line therapy. We classified the radiographic HRCT images of ILD into usual interstitial pneumonia (UIP) and non-UIP patterns. The diagnosis of a UIP pattern was determined using CT features defined by the International Consensus Statement of the American Thoracic Society and European Respiratory Society [7]. The UIP and possible UIP patterns were all considered UIP patterns in this study. We isolated tumor DNA from various specimens and analysed epidermal growth factor receptor gene (*EGFR*) mutation status at exons 18–21 using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, as described previously [8]. The study was approved by the Ethics Committee of Kobe City Medical Center General Hospital.

Pneumonitis during systemic anti-cancer therapy (pneumonitis)

Pneumonitis was defined using the following criteria, which were based on the criteria proposed by the Idiopathic Pulmonary Fibrosis Clinical Research Network [9] and the definition used in a recent randomized control trial [10]: 1) unexplained worsening of dyspnea within the past 30 days; 2) high resolution computed tomography (HRCT) with new bilateral ground-glass opacity or consolidation; 3) no evidence of pulmonary infection by bronchoalveolar lavage (BAL), endotracheal aspiration or sputum culture, in combination with negative blood tests for other potentially infectious pathogens (e.g., *Pneumocystis jirovecii*, Cytomegalovirus); 4) no evidence of malignant cells in BAL fluid to exclude lymphangitic spread of the cancer, 5)

exclusion of left heart failure and other possible causes of acute respiratory failure [11]; 6) and less than a 4-week interval between the last administration of systemic anti-cancer therapy and the onset of a pulmonary shadow [12, 13]. Patients who developed acute ILD within 6 months after thoracic radiotherapy were not considered as having pneumonitis because the time for radiation pneumonitis onset is usually 6 months [14–16]. The pneumonitis cases were further divided into the following categories based on bronchoscopic test with bronchoalveolar lavage (BAL) [3, 4, 11, 17]: 1) possible pneumonitis, in which the diagnosis was based on physical examination, medical history, laboratory data, and HRCT scan images; 2) probable pneumonitis, in which the diagnosis was based on a bronchoscopic test with BAL in addition to the diagnostic examinations of possible pneumonitis mentioned above. Pneumonitis was categorised based on pneumonitis/pulmonary infiltrates by the National Cancer Institute Common Terminology Criteria version 4.0 as follows: Grade 2, symptomatic, medical intervention indicated, and limited instrumental activities of daily living; Grade 3, severe symptoms limiting self-care activities of daily living and oxygen indicated; Grade 4, life-threatening respiratory compromise and urgent intervention indicated; Grade 5, death. Patients with Grades 2–4 pneumonitis were defined as survivors. In each case, radiographic patterns of pneumonitis were classified according to previous reports, as 1) acute interstitial pneumonia (AIP) pattern, 2) non-specific interstitial pneumonia pattern, 3) organizing pneumonia pattern, 4) hypersensitivity pneumonitis (HP) pattern, and 5) unclassifiable pattern [18, 19].

Ethics statement

This study was conducted with the approval of the Kobe City Medical Center General Hospital Ethics Committee. Patient information was anonymized and de-identified prior to analysis. The need for written informed consent was waived for individual participants. We announced this study on the Internet, and patients had the option of refusing study participation.

Statistical analysis

Continuous variables were analysed using Student's t-tests. Dichotomous variables were analysed using χ^2 or Fisher's exact tests, as appropriate. The Kaplan–Meier method was used to estimate the survival outcomes, and groups were compared using the log-rank test. Univariate and multivariate logistic regression models were developed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate logistic regression model was constructed on variables selected by stronger relationships in univariate analyses (P<0.05) because of the small number of events. Cox proportional hazard models were used to estimate the hazard ratios (HRs) for factors associated with survival in both univariate and multivariate analyses. Multivariate analysis was performed on all important clinical factors (age, sex, smoking status, ECOG PS, *EGFR* status, stage, type of first-line therapy, pre-existing ILD, and pneumonitis). The results are expressed as HRs with 95% CI. A P value of <0.05 was considered to indicate statistical significance. We conducted the statistical analyses using JMP 11 software (SAS Institute, Cary, NC, USA).

Results

Characteristics and survival of NSCLC patients (analysis 1)

In total, 770 patients with advanced NSCLC were included in the study. Of these, 44 (6%) were diagnosed with pneumonitis during systemic anti-cancer therapy (21 probable and 23 possible pneumonitis cases). There were 16, six, 17, and five patients with pneumonitis Grades 5, 4, 3, and 2, respectively. Patient characteristics and comparisons between pneumonitis and non-pneumonitis patients are summarised in Table 1. Most patients (77%) had a PS of 0 or 1. *EGFR*

Table 1. Characteristics of and comparison between patients with and without pneumonitis during systemic anti-cancer therapy

Patient characteristics	Total (%)	Pneumonitis (%)	Non-pneumonitis (%)	P-value
	(N = 770)	(N = 44)	(N = 726)	
Age (years), mean (SD)	67.8 (10.7)	69.7 (8.5)	67.7 (10.8)	0.217
Sex				
Male	506 (66)	35 (80)	471 (65)	0.047
Smoking status				
Never-smoker	240 (31)	7 (16)	233 (32)	0.024
Histology				
Adenocarcinoma	564 (73)	32 (73)	532 (73)	0.936*
Squamous	174 (23)	9 (20)	165 (23)	
NSCLC-NOS	30 (4)	1 (2)	29 (4)	
Other	2 (0)	2 (5)	0 (0)	
ECOG PS				
0 or 1	594 (77)	34 (77)	560 (77)	0.983
2–4	176 (23)	10 (23)	166 (23)	
Stage				
III B	154 (20)	11 (25)	143 (20)	0.393
IV	616 (80)	33 (75)	583 (80)	
EGFR status				
Mutated	174 (23)	4 (9)	170 (23)	0.027*
Wild-type	289 (38)	18 (41)	271 (37)	
Not investigated	307 (39)	22 (50)	285 (40)	
Pre-existing ILD	69 (9)	11 (25)	58 (8)	<0.001
UIP pattern	47	6	41	0.303
Non-UIP pattern	22	5	17	
Thoracic radiotherapy	94 (12)	4 (9)	90 (12)	0.641
First-line therapy				
Molecular-targeted therapy (TKIs)	140 (18)	6 (14)	134 (18)	
EGFR-TKIs	138	6	132	
Crizotinib	2	0	2	
Cytotoxic agents (combination **)	550 (72)	32 (72)	518 (71)	
Containing paclitaxel	168	7	161	
Containing vinorelbine	163	10	153	
Containing pemetrexed	73	2	71	
Containing gemcitabine	56	5	51	
Containing docetaxel	35	1	34	
Containing S1	28	3	25	
Containing etoposide	22	5	17	
Containing irinotecan	10	0	10	
Others	3	0	3	
Cytotoxic agents (monotherapy)	80 (10)	6 (14)	74 (11)	
Pemetrexed	24	2	22	
Paclitaxel	15	0	15	
S1	13	3	10	
Vinorelbine	9	0	9	
Gemcitabine	9	1	8	
Docetaxel	6	0	6	

(*Continued*)

Table 1. (*Continued*)

Patient characteristics	Total (%)	Pneumonitis (%)	Non-pneumonitis (%)	P-value
	(N = 770)	(N = 44)	(N = 726)	
Others	4	0	4	
Diagnosis of pneumonitis				
Probable		21 (48)		
Possible		23 (52)		
Pneumonitis grade				
Grade 5		16 (36)		
Grade 4		6 (14)		
Grade 3		17 (39)		
Grade 2		5 (11)		

SD, standard deviation; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; TKIs, tyrosine kinase inhibitors

*Patients with adenocarcinoma and non-adenocarcinoma, and patients with mutated and wild-type/not investigated EGFR were compared using χ2 tests.

** Eight patients received combination therapy other than platinum combination.

doi:10.1371/journal.pone.0168465.t001

mutations were investigated in 463 patients (60%) and were detected in 174 patients (38%). Sixty-nine patients (9%) had pre-existing ILD.

Comparison of the clinical profiles of pneumonitis and non-pneumonitis patients showed that pneumonitis patients included significantly higher proportions of current or former smokers (37/530 vs. 7/240, respectively, P = 0.024), patients with pre-existing ILD (11/69 vs. 33/701, respectively, P<0.001) and with wild-type or *EGFR* not assessed (40/596 vs. 4/174, respectively, P = 0.027). Fifteen patients developed pneumonitis during first-line therapy. Of these, patients with pneumonitis included significantly higher proportions of patients with pre-existing ILD (4/69 vs. 11/701, respectively, P = 0.038).

Multivariate logistic regression analysis showed that pre-existing ILD (OR, 2.99; 95% CI, 1.36–6.21; P = 0.008) was independently associated with pneumonitis. The results of this analysis are listed in Table 2.

The OS time from the diagnosis of advanced NSCLC is presented in Fig 2A and summarised in Table 3. At the time of analysis, the median OS was 18.4 (95% CI, 16.7–20.0) months. Shorter OS was significantly associated with older age, male sex, current or former smokers, poor PS, wild-type EGFR or not assessed, pre-existing ILD, and pneumonitis. A multivariate Cox model showed that independent predictors of OS were older age (HR 1.25, 95% CI, 1.04–1.50, P = 0.019), poor PS (HR 2.47, 95% CI, 2.03–2.98, P<0.001), wild-type or not investigated

Table 2. Factors associated with pneumonitis during systemic anti-cancer therapy (N = 770)

Variables	Multivariate analysis		
	OR	95% CI	P-value
Sex (female/male)	0.74	0.28–1.77	0.517
Smoking status (never-/current or former smoker)	0.70	0.24–1.91	0.508
EGFR mutations (yes/no)	0.49	0.14–1.32	0.167
Pre-existing ILD (yes/no)	2.99	1.36–6.21	0.008

OR, odds ratio; CI, confidence interval; EGFR, epidermal growth factor receptor gene; ILD, interstitial lung disease

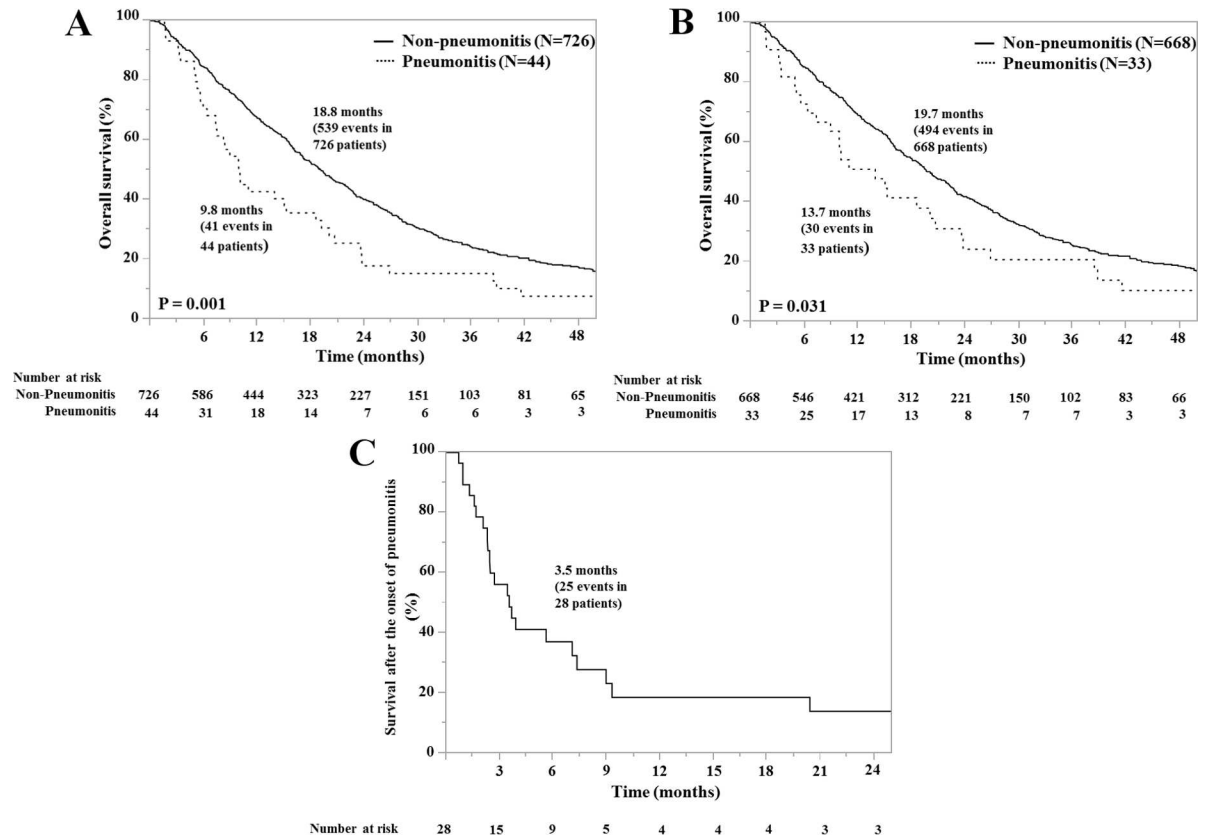doi:10.1371/journal.pone.0168465.t002

Fig 2. Kaplan–Meier overall survival curves after the diagnosis of NSCLC in all patients with or without pneumonitis during systemic anti-cancer therapy (pneumonitis) (Fig 2A) and those who did not have pre-existing ILD with or without pneumonitis (Fig 2B), and survival time after the onset of pneumonitis in survivors of pneumonitis (Fig 2C).

doi:10.1371/journal.pone.0168465.g002

EGFR (HR 2.08, 95% CI, 1.63–2.67, P<0.001), stage IV (HR 1.46, 95% CI, 1.18–1.82, P<0.001), pre-existing ILD (HR 1.90, 95% CI, 1.41–2.53, P<0.001), and pneumonitis (HR 1.53, 95% CI, 1.09–2.09, P = 0.015). We further investigated the prognostic impact of pneumonitis in NSCLC patients without pre-existing ILD (Fig 2B). Shorter OS was also significantly associated with pneumonitis in these patients.

Survival of the pneumonitis patients (analysis 2)

Among patients with advanced NSCLC and pneumonitis, the median time between the diagnosis of advanced NSCLC and onset of pneumonitis was 6.0 (95% CI, 4.3–8.8) months. Most pneumonitis cases (66%) occurred during the second, third, or subsequent lines of systemic anti-cancer therapy. Additionally, the median time between the start of the first cycle of therapy that triggered pneumonitis and the onset of pneumonitis was 1.3 (95% CI, 0.9–1.7) months. Thirty-two patients (73%) developed pneumonitis during one or two cycles of therapy.

Patient characteristics and comparisons between survivors (Grade 2–4 pneumonitis patients) and non-survivors (Grade 5 pneumonitis patients) are shown in Table 4. Survivors were significantly associated with younger age (P = 0.003) and radiographic non-AIP pattern (P = 0.004). Sixteen patients (36%) died from respiratory failure within 2 to 30 days (median, 10 days) of pneumonitis onset. All of the pneumonitis patients received steroid therapy. Seven of eight pneumonitis patients died while on mechanical ventilation.

Table 3. Analyses of overall survival time in all patients (N = 770)

Characteristics	No. of patients	Median survival	Univariate analysis		Multivariate analysis	
	(%)	(months)	HR (95% CI)	P-value	HR (95% CI)	P-value
Total						
Age				<0.001		0.019
≥75 years	219 (28)	15.1	1.46 (1.22–1.74)		1.25 (1.04–1.50)	
<75 years	551 (72)	20.0	referencereference		reference	
Sex				<0.001		0.076
Male	506 (66)	15.9	1.41 (1.19–1.68)		1.23 (0.98–1.55)	
Female	264 (34)	25.0	reference		reference	
Smoking status				0.007		0.692
Never-smoker	240 (31)	22.6	0.79 (0.66–0.94)		1.04 (0.83–1.33)	
Current or former smoker	530 (69)	15.9	reference		reference	
ECOG PS				<0.001		<0.001
ECOG 0,1	594 (77)	21.5	0.39 (0.32–0.47)		0.40 (0.33–0.49)	
ECOG 2–4	176 (23)	8.4	reference		reference	
EGFR mutations				<0.001		<0.001
Yes	174 (23)	28.7	0.54 (0.44–0.66)		0.48 (0.38–0.61)	
No or not investigated	596 (77)	15.4	reference		reference	
Stage				0.059		<0.001
IIIB	154 (20)	18.3	0.82 (0.66–1.01)		0.69 (0.55–0.85)	
IV	616 (80)	18.3	reference		reference	
Type of first-line therapy				0.518		0.106
TKIs	140 (18)	19.4	0.93 (0.74–1.15)		1.26 (0.95–1.64)	
Cytotoxic chemotherapy	630 (82)	18.3	reference		reference	
Pre-existing ILD				<0.001		<0.001
Yes	69 (9)	9.8	2.21 (1.65–2.90)		1.90 (1.41–2.52)	
No	701 (91)	19.3	reference		reference	
Pneumonitis during systemic anti-cancer therapy				0.003		0.015
Yes	44 (6)	9.8	1.68 (1.20–2.27)		1.53 (1.09–2.09)	
No	726 (94)	18.8	reference		reference	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; ILD, interstitial lung disease; HR, hazard ratio; CI, confidence interval; TKIs, tyrosine kinase inhibitors

doi:10.1371/journal.pone.0168465.t003

The PS was poor and worsened after improving pneumonitis in most survivors (82% and 62%, respectively), and over half of the survivors (54%) did not undergo systemic anti-cancer therapy after pneumonitis onset. The survival time of patients after pneumonitis onset is summarised in Fig 2C and Table 5. The median survival time was 3.5 (95% CI, 2.3–7.2) months. Findings from univariate analyses indicated that longer survival time was significantly associated with good PS after improving pneumonitis (P = 0.004).

Subgroup analysis of NSCLC patients with pre-existing ILD

We conducted a subgroup analysis of 69 patients with pre-existing ILD. Of these, 22 were diagnosed with non-UIP pattern, including two pathologically proven cases. Three had ILD associated with collagen vascular disease, and 3 with asbestosis. The OS was not significantly different between patients with UIP pattern and non-UIP patterns (median [95% CI] OS, 9.4 [6.9–14.0] months versus 11.1 (5.8–18.5) months, respectively; p = 0.672). Furthermore, the occurrence of pneumonitis was not significantly different between these two groups (6 out of

Table 4. Characteristics and outcomes of patients with pneumonitis during systemic anti-cancer therapy (N = 44)

Characteristics	Total (%)	Survivors	Non-survivors	P-value
	(N = 44)	(N = 28)	(N = 16)	
Age (years), mean (SD)	69.7 (8.5)	66.9 (7.4)	74.6 (8.3)	0.003
Sex				
Male	35 (80)	25 (89)	10 (62)	0.053
Smoking status				
Never-smoker	7 (16)	3 (11)	4 (25)	0.235
Pre-existing ILD	11 (25)	6 (21)	5 (31)	0.492
Stage				
IIIB	11 (25)	9 (32)	2 (13)	0.278
IV	33 (75)	19 (68)	14 (87)	
Number of chemotherapy line *				
1st	15 (34)	8 (29)	7 (44)	0.340
2nd	18 (41)	13 (46)	5 (31)	
3rd or beyond	11 (25)	7 (25)	4 (25)	
ECOG PS prior to pneumonitis **				
0 or 1	34 (77)	23 (82)	11 (69)	0.456
2–4	10 (23)	5 (18)	5 (31)	
ECOG PS after improving pneumonitis				
0 or 1		5 (18)		
2–4		23 (82)		
Patients characteristics after pneumonitis				
PS worsening		19 (68)		
Chemotherapy after pneumonitis		13 (46)		
Radiographic patterns of pneumonitis *				
AIP pattern	22 (50)	9 (32)	13 (81)	0.004
NSIP pattern	6 (14)	5 (18)	1 (6)	
OP pattern	2 (5)	1 (4)	1 (6)	
HP pattern	4 (9)	4 (14)	0 (0)	
Unclassifiable pattern	10 (22)	9 (32)	2 (13)	
Drug associated with pneumonitis *				
Molecular-targeted therapy (TKIs)	11 (25)	5 (18)	6 (38)	0.169
Gefitinib	8	3	5	
Erlotinib	2	1	1	
Crizotinib	1	1	0	
Cytotoxic agents ***	32 (73)	22 (78)	10 (62)	
Containing pemetrexed	4	3	1	
Containing docetaxel	6	6	0	
Containing paclitaxel	7	5	2	
Containing vinorelbine	6	4	1	
Containing gemcitabine	7	5	2	
Containing S1	4	0	4	
Containing etoposide	1	0	1	
Immune checkpoint inhibitors	1 (2)	1 (4)	0 (0)	

ILD, interstitial lung disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AIP, acute interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; HP, hypersensitivity pneumonitis; TKIs, tyrosine kinase inhibitors

* Patients who received 1st-line and 2nd-/3rd- or beyond chemotherapy, patients with AIP pattern and non-AIP pattern, and patients who received molecular-targeted therapy and cytotoxic/immunotherapy were compared using Fisher's exact test.

** Compared with PS at the diagnosis of lung cancer, two patients had improved PS and two patients had worse PS.

*** Two patients received gemcitabine plus vinorelbine, and one paclitaxel plus gemcitabine therapy.

doi:10.1371/journal.pone.0168465.t004

Table 5. Analyses of survival time after pneumonitis during systemic anti-cancer therapy (N = 28*)

Characteristics	No. of patients (%)	Overall survival time	P-value
	(N = 28)	(months)	
Age			0.8160.816
≥75 years	5 (18)	3.6	
<75 years	23 (82)	3.5	
Sex			0.7620.762
male	25 (11)	3.5	
female	3 (89)	7.2	
Smoking status			0.6860.686
never	3 (11)	3.4	
current or former-smoker	25 (89)	2.0	
ECOG PS prior to pneumonitis			0.5600.560
0 or 1	21 (75)	3.4	
2–4	7 (25)	3.8	
ECOG PS after improving pneumonitis			0.0040.004
0 or 1	5 (18)	28.5	
2–4	23 (82)	2.7	
Stage at the diagnosis of lung cancer			0.9500.950
IIIB	9 (32)	7.0	
IV	19 (68)	3.5	
Pneumonitis grade			0.3100.310
3 or 4	23 (23)	2.7	
2	5 (77)	8.8	
Pre-existing ILD			0.0750.075
yes	6 (21)	2.3	
no	22 (79)	3.6	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ILD, interstitial lung disease

* Only survivors from pneumonitis.

doi:10.1371/journal.pone.0168465.t005

47 versus 5 out of 22, respectively; p = 0.303). The tumor response of first-line therapy was not significantly different between patients with and without pre-existing ILD (22/69 vs 258/701, P = 0.413)

Discussion

To the best of our knowledge, this study is the first to report on the poor prognosis after the onset of pneumonitis and the adverse impact of pneumonitis on survival in patients with advanced NSCLC. We also identified some important characteristics of pneumonitis and confirmed the high mortality rate of pneumonitis patients in this Japanese cohort.

Our results indicated that 6% of patients with advanced NSCLC developed pneumonitis. This incidence rate is similar to that reported in a study of Japanese (7.2%) lung cancer patients, though that study included patients with small-cell lung cancer and early stage lung cancer [3]. Additionally, our study showed that 16% of advanced NSCLC patients with pre-existing ILD developed pneumonitis. Further, pre-existing ILD was found to be a risk factor of pneumonitis. Similarly, previous studies reported that approximately 20% of patients with pre-existing ILD developed pneumonitis, and that pre-existing ILD is the most significant risk factor [3, 20–24]. Based on these findings, pneumonitis seems to be a relatively common event in

patients with advanced NSCLC. It is therefore necessary to monitor NSCLC patients with pre-existing ILD very closely as they are at high risk of developing pneumonitis.

This study showed other important characteristics of pneumonitis. In this study, approximately 70% of pneumonitis cases occurred during the second or subsequent lines of systemic anti-cancer therapy. Additionally, patients tended to develop pneumonitis early on during the regimen that triggered pneumonitis. We observed that most patients (73%) developed pneumonitis during the first or second cycles of therapy, with an observed median time of 1.3 months between the start of the systemic anti-cancer therapy regimen that triggered pneumonitis and the onset of pneumonitis. From these findings, physicians had difficulty predicting the onset of pneumonitis according to the line of systemic anti-cancer therapy. However, increased physician awareness of pneumonitis risk factors, and particularly careful surveillance during the period immediately after the start of systemic anti-cancer therapy, are needed because of the increased risk during this time.

We clearly demonstrated that pneumonitis has an adverse impact on survival in patients with advanced NSCLC. Pneumonitis was an independent predictive factor for OS according to multivariate analysis. Additionally, pneumonitis was significantly associated with shorter OS in those patients without pre-existing ILD, which was found to be a risk factor of pneumonitis and a strong negative predictive factor of OS. These results suggest that the management of advanced NSCLC patients with pneumonitis, including prevention, detection, and treatment of pneumonitis, is an area where there is further scope for improvement. When we consider that pneumonitis is a prognostic factor and a common event in patients with advanced NSCLC, it is apparent that further studies focusing on pneumonitis would contribute to improving the prognosis of NSCLC patients as a whole.

As shown, the early mortality rate of pneumonitis was 36%. A previous study on 49 patients, who developed drug-induced acute lung injury (73% received chemotherapeutic/anti-inflammatory agents) at the intensive care unit (ICU), reported a higher ICU mortality rate (35%) than that of non-drug-induced acute lung injury [4]. Another small study reported that about 30% of patients with pneumonitis suffered an early death [3]. These findings are similar to our results and indicate the high mortality rate of pneumonitis. Additionally, though eight patients with severe pneumonitis (grade 4 or 5) required mechanical ventilation in this study, seven of them died. Consistently, extremely high mortality rates were reported in previous studies on lung cancer patients with acute respiratory failure requiring ICU admission and mechanical ventilation [25–28]. Therefore, we should present these severe mortality data to the patients and family members to help in the shared decision-making related to the management of acute respiratory failure, including the use of mechanical ventilation.

This study also showed that the survival time was extremely poor in survivors of pneumonitis. One possible explanation for this poor prognosis is the worsening of the PS after pneumonitis. Among survivors of pneumonitis, PS was poor and this worsened after improving pneumonitis (82% and 62%, respectively). Additionally, over half of the survivors (54%) did not receive systemic anti-cancer therapy after pneumonitis. Furthermore, subgroup analyses of survivors indicated that a good PS after improvement of pneumonitis, but not other clinical factors prior to the onset of pneumonitis, was the only significant predictive factor of longer OS. In general, PS is the most important factor for evaluating the prognosis and appropriateness of systemic anti-cancer therapy in patients with advanced NSCLC. The benefits of systemic anti-cancer therapy are speculative and the prognosis is poor in patients with poor PS [29–33]. For the management of patients with pneumonitis, we should consider the prognosis and potential worsening of the patient's condition after pneumonitis in order to make the most appropriate shared decisions [34, 35].

Pre-existing ILD was an independent predictive factor of OS in all patients, although the response rates to systemic anti-cancer therapy were not significantly different between patients with and without pre-existing ILD. These were similar to the results of previous reports [36–38]. In our study, we performed a subgroup analysis of 69 patients with pre-existing ILD. The occurrence of pneumonitis and OS were not significantly different between patients with UIP and non-UIP patterns. A previous study showed that according to CT findings, the UIP pattern was a risk factor of pneumonitis [12], while other studies did not find a significant association between these factors [39, 40]. Additionally, previous reports also indicated that the CT pattern was not associated with the survival [41, 42]. Larger studies are needed to investigate these associations in patients with pre-existing ILD.

This study had some limitations. First, we recognize the retrospective, single-center study design and the limited number of patients in the study group as important limitations. However, this is one of the largest studies of pneumonitis patients. Previous studies reported that Japanese may have an increased genetic susceptibility to ILD [21, 43]. Thus, the results of this study may be different in other ethnic groups. Second, the diagnosis of pneumonitis was based on physicians in charge without predetermined protocol because this study was conducted in a historical fashion. This limitation remains a challenge because attributing causality is an unavoidable problem in drug-related studies. From this aspect, in patients with pre-existing ILD, we could not separate cases of pneumonitis into acute exacerbation of pre-existing ILD and drug-related pneumonitis. The problem is the absence of gold-standard diagnostic tests and the definition of the time elapsed between the drug administration and the onset of pneumonitis. However, we carried out several tests, including bronchoscopic tests with BAL, to
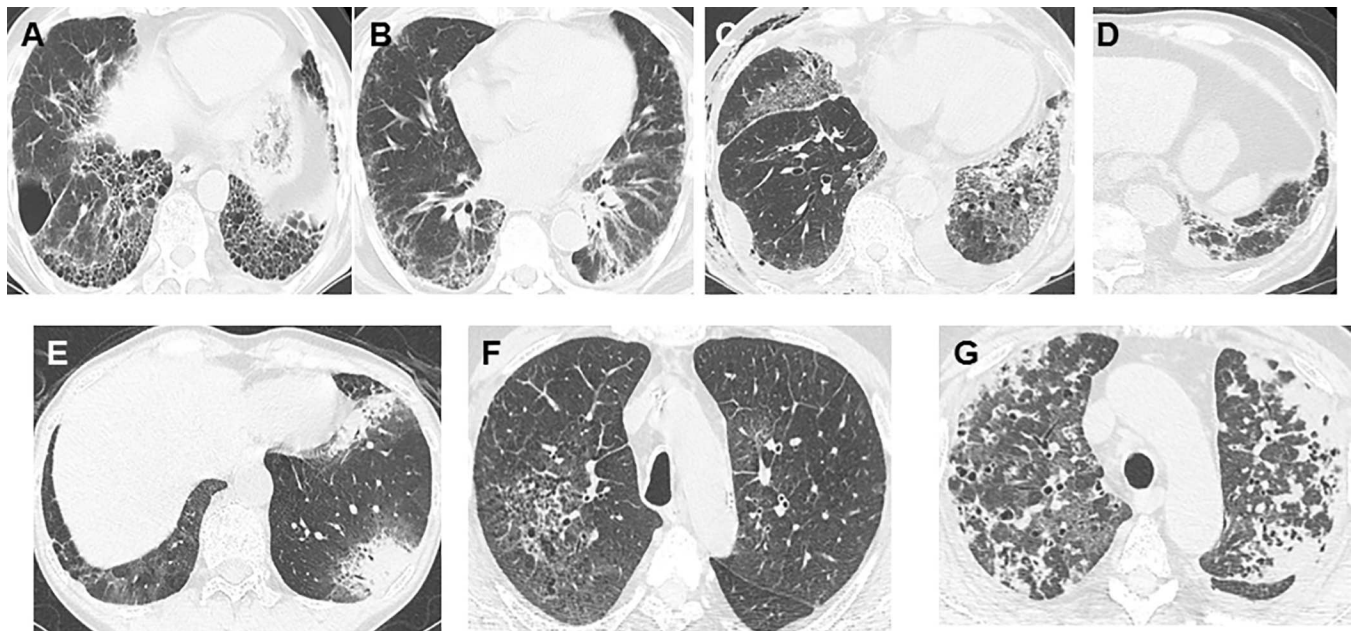

Fig 3. Pre-existing interstitial lung disease (ILD) showing subpleural distribution, honeycomb cysts, and bronchiectasis (usual interstitial pneumonia [UIP] pattern) (Fig 3A). Pre-existing ILD showing patchy ground-glass opacity with reticulation, traction bronchiectasis and bronchovascular bundle thickening (non-UIP pattern) (Fig 3B). Drug-related pneumonitis showing new diffuse ground-glass opacities, consolidation and traction bronchiectasis as well as pleural effusion, indicative of AIP pattern (Fig 3C). Drug-related pneumonitis showing new ground-glass opacities and bronchovascular bundle thickening, indicative of on-specific interstitial pneumonia (NSIP) pattern (Fig 3D). Drug-related pneumonitis showing new ground-glass opacities and consolidations with multifocal distribution, indicative of OP pattern (Fig 3E). Drug-related pneumonitis showing new diffuse faint ground glass opacities, indicative of HP pattern (Fig 3F). Drug-related pneumonitis showing diffuse new ground-glass opacities. Since the CT showed multiple consolidation (lung cancer) in both lungs, we could not classify the type of drug-related pneumonitis (unclassifiable pneumonitis) (Fig 3G).

doi:10.1371/journal.pone.0168465.g003

exclude other causes. Since pneumonitis is a diagnosis of exclusion, these tests are useful to exclude common causes of pulmonary infiltrates such as infection and lymphangitic spread of the cancer [11, 17]. In our study, we carried out the bronchoscopic tests with BAL in about half of our patients with pneumonitis (probable cases). In contrast, in previous studies, the diagnosis was based only on medical history, laboratory data, and CT scan images [3, 4, 12]. Therefore, we believe the diagnostic quality of pneumonitis was higher in this study. Third, the evaluation of the pattern of ILD was based only on HRCT findings in many patients (Fig 3). A recent paper demonstrated that the non-UIP pattern (inconsistent with UIP pattern) was miscategorised if the diagnosis is based solely on radiologic findings [44]. However, it was reported that in clinical practice, surgical lung biopsies were performed in only 8%–12% of patients [45]. Moreover, another recent report demonstrated that the radiologic evaluation was important to assess the survival and occurrence of pneumonitis [12]. Therefore, we evaluated these patterns in our study.

Conclusions

We found that 6% of patients with advanced NSCLC developed pneumonitis during systemic anti-cancer therapy. The early mortality rate of pneumonitis is high, and the survival and performance status after pneumonitis is poor. Additionally, pneumonitis has an adverse impact on the OS of patients with advanced NSCLC. We should consider these data for the management of pneumonitis in patients with advanced NSCLC, and conduct future studies focusing on pneumonitis to improve the survival of these patients.

Acknowledgments

Author Contributions

Conceptualization: DF RK TM.

Data curation: DF TM.

Formal analysis: DF TM.

Investigation: DF RK TM RS YS MK JI ST KN AN KO KT.

Methodology: DF RK TM RS YS MK JI ST KN AN KO KT.

Project administration: DF RK TM RS YS MK JI ST KN AN KO KT.

Resources: DF RK TM RS YS MK JI ST KN AN KO KT.

Supervision: DF.

Visualization: DF RK TM RS YS MK JI ST KN AN KO KT.

Writing – original draft: DF RK TM.

Writing – review & editing: DF RK TM RS YS MK JI ST KN AN KO KT.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014; 64 (1):9–29. Epub 2014/01/09.

2.   Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. CA: a cancer journal for clinicians. 2011; 61(2):91–112. Epub 2011/02/10.

3.   Sakurada T, Kakiuchi S, Tajima S, Horinouchi Y, Okada N, Nishisako H, et al. Characteristics of and risk factors for interstitial lung disease induced by chemotherapy for lung cancer. Ann Pharmacother. 2015; 49(4):398–404. Epub 2015/01/08. doi: 10.1177/1060028014566446 PMID: 25565405

4.   Dhokarh R, Li G, Schmickl CN, Kashyap R, Assudani J, Limper AH, et al. Drug-associated acute lung injury: a population-based cohort study. Chest. 2012; 142(4):845–50. Epub 2012/04/28. doi: 10.1378/chest.11-2103 PMID: 22539646

5.   Minami-Shimmyo Y, Ohe Y, Yamamoto S, Sumi M, Nokihara H, Horinouchi H, et al. Risk factors for treatment-related death associated with chemotherapy and thoracic radiotherapy for lung cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2012; 7(1):177–82. Epub 2011/12/03.

6.   Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2007; 2(8):706–14. Epub 2007/09/01.

7.   Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine. 2011; 183(6):788–824. Epub 2011/04/08. doi: 10.1164/rccm.2009-040GL PMID: 21471066

8.   Nagai Y, Miyazawa H, Huqun, Tanaka T, Udagawa K, Kato M, et al. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer research. 2005; 65 (16):7276–82. Epub 2005/08/18. doi: 10.1158/0008-5472.CAN-05-0331 PMID: 16105816

9.   Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr., et al. Acute exacerbations of idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine. 2007; 176 (7):636–43. Epub 2007/06/23. doi: 10.1164/rccm.200703-463PP PMID: 17585107

10. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med. 2015; 373(8):782.

11. Camus PH, Foucher P, Bonniaud PH, Ask K. Drug-induced infiltrative lung disease. Eur Respir J Suppl. 2001; 32:93s–100s. Epub 2002/01/31. PMID: 11816828

12. Kenmotsu H, Naito T, Kimura M, Ono A, Shukuya T, Nakamura Y, et al. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2011; 6(7):1242–6. Epub 2011/05/31.

13. Sakurada T, Kakiuchi S, Tajima S, Horinouchi Y, Okada N, Nishisako H, et al. Characteristics of and risk factors for interstitial lung disease induced by chemotherapy for lung cancer. The Annals of pharmacotherapy. 2015; 49(4):398–404. Epub 2015/01/08. doi: 10.1177/1060028014566446 PMID: 25565405

14. Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose—volume histogram parameters in lung cancer—a systematic review. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2004; 71(2):127–38. Epub 2004/04/28.

15. Niu X, Li H, Chen Z, Liu Y, Kan M, Zhou D, et al. A study of ethnic differences in TGFbeta1 gene polymorphisms and effects on the risk of radiation pneumonitis in non-small-cell lung cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2012; 7 (11):1668–75. Epub 2012/10/13.

16. Kim JY, Kim YS, Kim YK, Park HJ, Kim SJ, Kang JH, et al. The TGF-beta1 dynamics during radiation therapy and its correlation to symptomatic radiation pneumonitis in lung cancer patients. Radiat Oncol. 2009; 4:59. Epub 2009/12/01. doi: 10.1186/1748-717X-4-59 PMID: 19943923

17. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. Chest. 2008; 133(2):528–38. Epub 2008/02/07. doi: 10.1378/chest.07-0851 PMID: 18252919

18. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. Clinical cancer research: an official journal of the American Association for Cancer Research. 2016. Epub 2016/08/19.

19. Kubo K, Azuma A, Kanazawa M, Kameda H, Kusumoto M, Genma A, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respiratory investigation. 2013; 51(4):260–77. Epub 2013/11/19. doi: 10.1016/j.resinv.2013.09.001 PMID: 24238235

20. Togashi Y, Masago K, Handa T, Tanizawa K, Okuda C, Sakamori Y, et al. Prognostic significance of preexisting interstitial lung disease in Japanese patients with small-cell lung cancer. Clinical lung cancer. 2012; 13(4):304–11. Epub 2011/12/16. doi: 10.1016/j.cllc.2011.11.001 PMID: 22169479

21. Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. American journal of respiratory and critical care medicine. 2008; 177(12):1348–57. Epub 2008/03/14. doi: 10.1164/rccm.200710-1501OC PMID: 18337594

22. Usui K, Tanai C, Tanaka Y, Noda H, Ishihara T. The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology. 2011; 16(2):326–31. Epub 2010/12/01. doi: 10.1111/j.1440-1843.2010.01907.x PMID: 21114711

23. Tomassetti S, Gurioli C, Ryu JH, Decker PA, Ravaglia C, Tantalocco P, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest. 2015; 147(1):157–64. Epub 2014/08/29. doi: 10.1378/chest.14-0359 PMID: 25166895

24. Isobe K, Hata Y, Sakamoto S, Takai Y, Shibuya K, Homma S. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. Respirology. 2010; 15(1):88–92. Epub 2009/12/02. doi: 10.1111/j.1440-1843.2009.01666.x PMID: 19947998

25. Slatore CG, Cecere LM, Letourneau JL, O'Neil ME, Duckart JP, Wiener RS, et al. Intensive care unit outcomes among patients with lung cancer in the surveillance, epidemiology, and end results-medicare registry. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30(14):1686–91. Epub 2012/04/05.

26. Bonomi MR, Smith CB, Mhango G, Wisnivesky JP. Outcomes of elderly patients with stage IIIB-IV non-small cell lung cancer admitted to the intensive care unit. Lung Cancer. 2012; 77(3):600–4. Epub 2012/06/20. doi: 10.1016/j.lungcan.2012.05.103 PMID: 22709929

27. Soares M, Toffart AC, Timsit JF, Burghi G, Irrazabal C, Pattison N, et al. Intensive care in patients with lung cancer: a multinational study. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. 2014; 25(9):1829–35. Epub 2014/06/22.

28. Soares M, Darmon M, Salluh JI, Ferreira CG, Thiery G, Schlemmer B, et al. Prognosis of lung cancer patients with life-threatening complications. Chest. 2007; 131(3):840–6. Epub 2007/03/16. doi: 10.1378/chest.06-2244 PMID: 17356101

29. Fujimoto D, Shimizu R, Morimoto T, Kato R, Sato Y, Kogo M, et al. Analysis of advanced lung cancer patients diagnosed following emergency admission. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2015; 45(4):1098–107. Epub 2014/10/18.

30. Lilenbaum RC. Treatment of advanced non-small-cell lung cancer in special populations. Oncology (Williston Park). 2004; 18(10):1321–5; discussion 6, 9–33. Epub 2004/11/06.

31. Azzoli CG, Baker S Jr., Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009; 27(36):6251–66. Epub 2009/11/18.

32. Zukin M, Barrios CH, Pereira JR, Ribeiro Rde A, Beato CA, do Nascimento YN, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013; 31(23):2849–53. Epub 2013/06/19.

33. Morth C, Valachis A. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies. Lung Cancer. 2014; 84(3):209–14. Epub 2014/04/08. doi: 10.1016/j.lungcan.2014.03.015 PMID: 24702946

34. Kane HL, Halpern MT, Squiers LB, Treiman KA, McCormack LA. Implementing and evaluating shared decision making in oncology practice. CA: a cancer journal for clinicians. 2014; 64(6):377–88. Epub 2014/09/10.

35. Katz SJ, Hawley S. The value of sharing treatment decision making with patients: expecting too much? JAMA: the journal of the American Medical Association. 2013; 310(15):1559–60. Epub 2013/09/26. doi: 10.1001/jama.2013.278944 PMID: 24061082

36. Kinoshita T, Azuma K, Sasada T, Okamoto M, Hattori S, Imamura Y, et al. Chemotherapy for non-small cell lung cancer complicated by idiopathic interstitial pneumonia. Oncology letters. 2012; 4(3):477–82. Epub 2013/06/07. doi: 10.3892/ol.2012.753 PMID: 23741246

37. Nishino M, Cardarella S, Dahlberg SE, Araki T, Lydon C, Jackman DM, et al. Interstitial lung abnormalities in treatment-naive advanced non-small-cell lung cancer patients are associated with shorter survival. European journal of radiology. 2015; 84(5):998–1004. Epub 2015/03/03. doi: 10.1016/j.ejrad.2015.01.021 PMID: 25726730

38. Aubry MC, Myers JL, Douglas WW, Tazelaar HD, Washington Stephens TL, Hartman TE, et al. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. Mayo Clinic proceedings. 2002; 77 (8):763–70. Epub 2002/08/14. PMID: 12173712

39. Ozawa Y, Akahori D, Koda K, Abe T, Hasegawa H, Matsui T, et al. Distinctive impact of pre-existing interstitial lung disease on the risk of chemotherapy-related lung injury in patients with lung cancer. Cancer chemotherapy and pharmacology. 2016; 77(5):1031–8. Epub 2016/04/07. doi: 10.1007/s00280-016-3025-7 PMID: 27048413

40. Enomoto Y, Inui N, Kato T, Baba T, Karayama M, Nakamura Y, et al. Low forced vital capacity predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer. Lung Cancer. 2016; 96:63–7. Epub 2016/05/03. doi: 10.1016/j.lungcan.2016.03.017 PMID: 27133752

41. Minegishi Y, Kokuho N, Miura Y, Matsumoto M, Miyanaga A, Noro R, et al. Clinical features, anti-cancer treatments and outcomes of lung cancer patients with combined pulmonary fibrosis and emphysema. Lung Cancer. 2014; 85(2):258–63. Epub 2014/06/05. doi: 10.1016/j.lungcan.2014.05.016 PMID: 24894326

42. Kenmotsu H, Naito T, Mori K, Ko R, Ono A, Wakuda K, et al. Effect of platinum-based chemotherapy for non-small cell lung cancer patients with interstitial lung disease. Cancer chemotherapy and pharmacology. 2015; 75(3):521–6. Epub 2015/01/08. doi: 10.1007/s00280-014-2670-y PMID: 25563718

43. Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. Lung Cancer. 2015; 88(1):74–9. Epub 2015/02/24. doi: 10.1016/j.lungcan.2015.01.026 PMID: 25704957

44. Yagihashi K, Huckleberry J, Colby TV, Tazelaar HD, Zach J, Sundaram B, et al. Radiologic-pathologic discordance in biopsy-proven usual interstitial pneumonia. The European respiratory journal. 2016; 47 (4):1189–97. Epub 2016/02/27. doi: 10.1183/13993003.01680-2015 PMID: 26917616

45. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Introduction. Thorax. 1999; 54 Suppl 1:S1–14. Epub 2000/09/28.