Corticosteroid therapy against treatment-related pulmonary toxicities in patients with lung cancer

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Background: With the recent increased use of new anti-neoplastic agents, molecular-targeted drugs and radiation in patients with lung cancer, there has been an increase in the occurrence drug-induced or radiation-induced pulmonary toxicities. We conducted this study to evaluate the clinical characteristics of patients with lung cancer who presented with treatment-related pulmonary toxicities and to analyze the dosage pattern of corticosteroid therapy against them.

Methods: To collect the baseline data from the patients with lung cancer who developed treatment-related pulmonary toxicities, we initially selected those who were prescribed corticosteroids between January 1, 2008 and December 31, 2012. Depending on clinical and radiological diagnoses, we classified pulmonary toxicities into drug-induced interstitial lung disease (DILD), radiation pneumonitis, acute exacerbation of chronic obstructive pulmonary disease (AE COPD) and others.

Results: We divided total patients (n=398) into four groups, and these include 88 cases (22%) of DILD, 189 cases (47%) of radiation pneumonitis, 47 cases (12%) of AE COPD and 74 cases (19%) of others. The prescribed rate of pulse or high-dose steroid was measured as 73%, 20%, 40% and 38%, respectively (P<0.001). In DILD radiologic findings, the 2-month mortality was significantly higher in the patients with the diffuse alveolar damage (DAD) pattern (100%) as compared with those with the non-specific interstitial pneumonia (NSIP) or bronchiolitis obliterans with organizing pneumonia (BOOP) one (62% or 42%, respectively) (P=0.032).

Conclusions: This study showed that the natural course of DILD had more unfavorable outcome requiring higher dose steroid therapy as compared with those with radiation pneumonitis or AE COPD. According to a subgroup analysis of the patients with DILD, BOOP and NSIP radiographic patterns showed more favorable outcomes.

Keywords: Corticosteroids; drug-induced interstitial lung disease (DILD); lung cancer; pulmonary toxicity; radiation pneumonitis

Introduction

Lung cancer has been a leading cause of cancer-related death worldwide including South Korea (1). To date, chemotherapy, molecular-targeted therapy and radiation therapy (RT) have been known to be effective for the treatment of inoperable lung cancer. Still, however, much treatment-related pulmonary toxicity remains fatal (2,3). Currently, new anticancer agents and novel radiation techniques are becoming available for the treatment of lung cancer. This is also accompanied by increased risks of developing pulmonary toxicities in patients with lung cancer (4). It has been reported that the degree of the efficacy of epidermal growth factor receptor (EGFR)
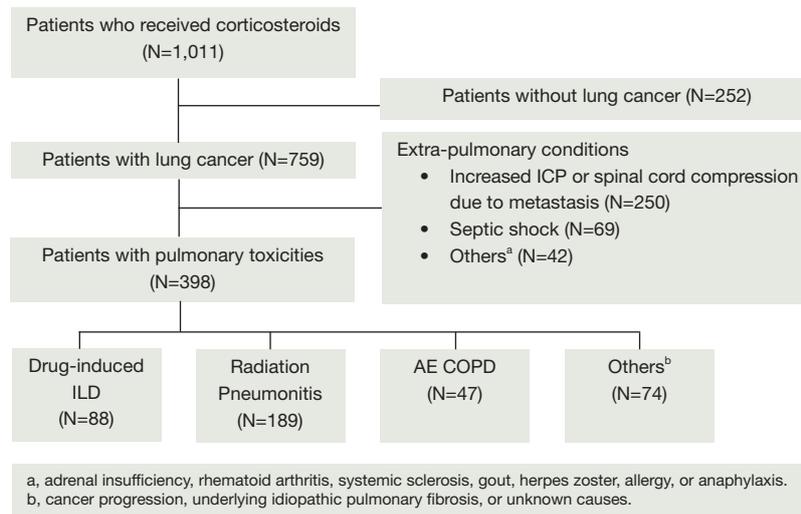
Figure 1 The selection and classification of the patients based on the CONSORT flow chart. Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ICP, intracranial pressure; ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease.

tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, is relatively higher compared with chemotherapy in patients with EGFR mutations (5,6). It remains problematic, however, EGFR-TKIs can cause interstitial lung disease (ILD); overall, the incidence of erlotinib-induced and gefinitib-induced ILD has been reported to reach 0.8% and 1%, respectively. Moreover, the incidence of gefitinib-induced ILD is estimated at 2% in Japan and 0.3% in the United States (7-13). Furthermore, the mortality of gefitinib-induced ILD exceeds 30% (14). The incidence of symptomatic RT-induced lung injury is estimated at 20% in patients with lung cancer who were treated with RT. In patients with severe RT-induced lung injury, the survival period is relatively shorter (2).

To date, there are no established treatment guidelines for patients with pulmonary toxicities due to anticancer therapies. In these patients, however, clinicians have attempted to discontinue the use of the causative agents and to administer systemic corticosteroids on empirical basis (3,4). It has also been reported that corticosteroid therapy is effective against the episodes of acute exacerbation of chronic obstructive pulmonary disease (AE COPD) and ILD; both entities may be concurrently present in patients with lung cancer (15-18). Nevertheless, there is a paucity of data regarding the optimal timing, dosage and duration of corticosteroid therapy in the treatment of patients with lung cancer (19).

Given the above background, we conducted this study to evaluate the clinical characteristics of patients with lung cancer who presented with treatment-related pulmonary

toxicities and to analyze the dosage pattern of corticosteroid therapy against them.

Materials and methods

Study population

To collect the baseline data from the patients with lung cancer who developed treatment-related pulmonary toxicities, we initially selected those who were prescribed corticosteroids at Lung and Esophageal Cancer Clinic of Chonnam National University Hwasun Hospital between January 1, 2008 and December 31, 2012.

We excluded the patients without lung cancer and patients who received corticosteroid therapy to control extra-pulmonary conditions like increased intracranial pressure or spinal cord compression, septic shock, adrenal insufficiency, rheumatoid arthritis or systemic sclerosis (*Figure 1*). The current study was approved by the Institutional Review Board (IRB) of Chonnam National University Hwasun Hospital (IRB approval number: 2013-118). Informed consent was waived due to the retrospective nature of the current study.

Classification of pulmonary toxicities

Two chest radiologists comprehensibly reviewed all X-ray and computed tomography (CT) scans, thus attempting to determine the imaging characteristics of pulmonary
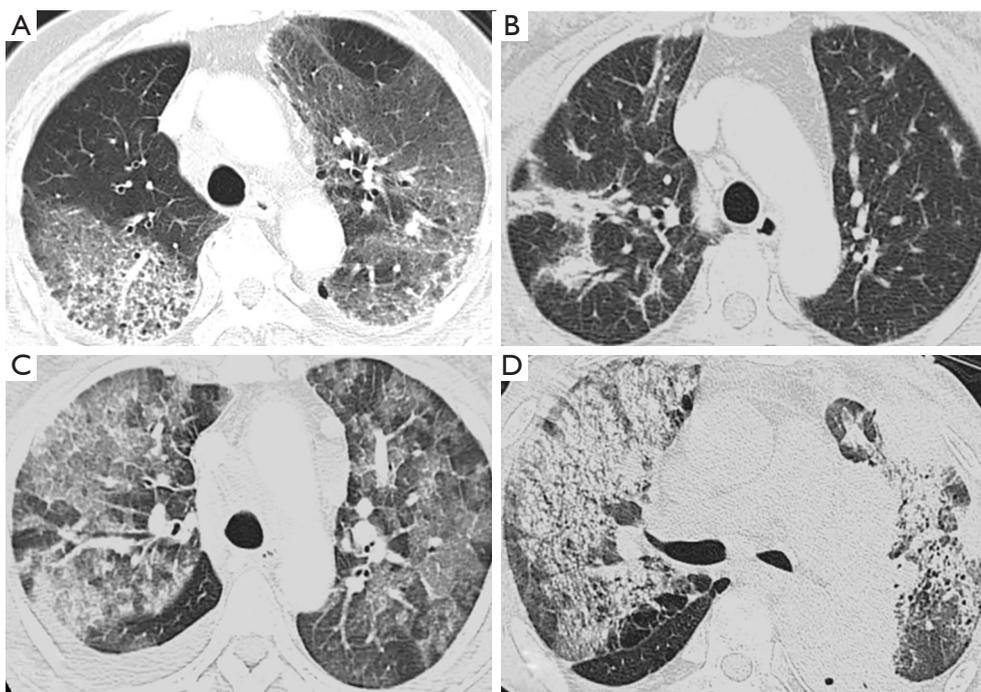
Figure 2 Computed tomography (CT) findings of drug-induced interstitial lung disease. (A) Nonspecific interstitial pneumonia pattern shows bilateral patchy areas of ground glass opacity, accompanied by some thickening of interlobular septa and minimal bronchiectasis; (B) bronchiolitis obliterans organizing pneumonia pattern shows multifocal peripheral areas of peribronchial consolidation and bronchial wall thickening; (C) diffuse alveolar damage (DAD) pattern shows diffuse thickening of interlobular septa, scattered areas of ground glass opacity and right pleural effusion; (D) mixed pattern (diffuse alveolar pattern and radiation pneumonitis) shows bilateral patchy areas of consolidation and perilesional ground glass opacities in both lungs, mixed with volume loss in the left upper lobe.

toxicities. Depending on radiological diagnosis, we classified treatment-related pulmonary toxicities into drug-induced ILD (DILD), radiation pneumonitis, AE COPD and others. In addition, drugs were referred to as those that are used for both conventional chemotherapy and molecular-targeted therapy. In our series, we made a diagnosis of DILD after ruling out other possible diagnoses, such as infection, cancer progression, and acute exacerbation of underlying idiopathic pulmonary fibrosis or unknown conditions. We performed laboratory tests such as C-reactive protein, procalcitonin, serologic tests, sputum and blood cultures to rule out the patients with infection.

Demographics and clinical variables

Baseline demographics and clinical data include age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, cancer stage and pulmonary function test before corticosteroid treatment. Histology was classified as small cell lung cancer (SCLC)

and non-small cell lung cancer (NSCLC). NSCLC was divided into three categories: squamous cell cancer (SQC), adenocarcinoma (ADC) and others. Cancer stage was presented as non-metastatic or metastatic.

Corticosteroid treatment

We also collected the data about corticosteroid regimen. Corticosteroid treatments include three regimens: pulse, high-dose and low-dose therapy. Pulse was ≥500 mg/day methylprednisolone for 3 days followed by high-dose steroid, high-dose was ≥0.5 mg/kg/day prednisolone and low-dose was <0.5 mg/kg/day prednisolone.

Imaging characteristics of DILD

Chest CT findings of DILD were classified into non-specific interstitial pneumonia (NSIP) pattern, bronchiolitis obliterans organizing pneumonia (BOOP) pattern, diffuse alveolar damage (DAD) pattern and mixed pattern (*Figure 2*).

We examined the number of the involved pulmonary lobes in a total of five lobes.

Outcome measures

The prescribed dosage pattern of corticosteroid was served as the primary outcome measure in the current study, for which we evaluated the patient response to the corticosteroid therapy based on two categories: 'recovered' and 'fatal'. Thus, we defined 'fatal' cases as in-hospital death or death outside hospital and 'recovered' ones as better outcomes at discharge or tapered/discontinued use of corticosteroids in an outpatient setting.

We also performed a subgroup analysis of the patients presenting with DILD, for which we measured the 1-month and 2-month mortality after initiating the corticosteroid therapy.

Statistical analysis

We performed univariate analysis with the χ^2 test to analyze categorical variables. We also performed one-way analysis of variance (ANOVA) to analyze continuous variables. We performed stratified multivariate logistic regression analysis with a backward stepwise procedure to identify the factors that are associated with the fatality of treatment-related pulmonary toxicities. All the tests were two-sided, and a P value of 0.05 was considered statistically significant. Statistical analysis was done using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

We enrolled a total of 398 patients (n=398) in the current study, whose median age was 67 years. Our clinical series of the patients include men (n=340, 85%), thus showing a male predilection. We divided our patients into four groups, depending on the classification of pulmonary toxicities, and these include 88 cases (22%) of DILD, 189 cases (47%) of radiation pneumonitis, 47 cases (12%) of AE COPD and 74 cases (19%) of other conditions (Table 1).

In the patients with DILD, age of ≤65 years, female sex, never smokers, ADC histology and metastatic stage were more prevalent. In the patients with acute exacerbation of COPD, the pulmonary function was poor. In the patients with DILD, possible causative agents include gefitinib (n=32), erlotinib (n=27), docetaxel (n=9), gemcitabine (n=5),

paclitaxel (n=3), etoposide (n=3), pemetrexed (n=2), afatinib (n=2), belotecan (n=2), vinorelbine (n=2), dacomitinib (n=1) and tegafur-uracil (n=1). In our series, there were 14 patients who underwent platinum combination therapy.

Outcome measures

As shown in Table 2, the patients with DILD were mainly treated with pulse (25%) or high-dose (48%) therapy. In addition, the patients with radiation pneumonitis were routinely treated with low-dose steroid therapy (80%). The prescribed rate of pulse or high-dose steroid was measured as 73% in DILD, 20% in radiation pneumonitis, 40% in AE COPD and 38% in others (P<0.001). We evaluated the response of corticosteroid therapy by measuring the rate of fatality and recovery in the patients who were treated with corticosteroids. This showed that the overall rate of fatality was 23% (92/398); the rate of fatality was 35% in the patients with DILD, 13% in those with radiation pneumonitis, 19% in those with AE COPD and 38% in those with other conditions (P<0.001). However, if we compared the number of patients who received pulse or high dose steroid treatment with the number of patients had fatal outcome among the four groups, actually the mortality rate of DILD (31/64, 48.4%) was lower than the radiation pneumonitis (24/38, 63.2%), and others (28/28, 100%) groups.

Odds ratio (OR) for the fatality

On stratified multivariate logistic regression analysis, only the steroid regimen was independently correlated with the fatality of treatment-related pulmonary toxicities (Table 3). In addition, such variables as the age, sex, smoking status, histology, cancer stage and ECOG PS had no significant correlation with the fatality of treatment-related pulmonary toxicities. Furthermore, the degree of the fatality of treatment-related pulmonary toxicities was significantly higher in the patients receiving higher-dose regimen (pulse and high-dose therapy) as compared with those doing low-dose one {DILD [OR 8.41, 95% confidence interval (CI), 1.81-39.04]}, radiation pneumonitis (OR 24.44, 95% CI, 7.77-76.90) and others (OR 21.00, 95% CI, 5.63-78.30). But this was not seen in the patients with acute exacerbation of COPD. In the patients with acute exacerbation of COPD, we could not estimate OR for the fatality of treatment-related pulmonary toxicities because of a smaller sample size.

Table 1 Baseline characteristics of patients

Characteristics	Drug-induced ILD (n=88)		Radiation pneumonitis (n=189)		AE COPD (n=47)		Others (n=74)		P[a]
	No.	%	No.	%	No.	%	No.	%	
Age, years[b]									0.009
<65	46	52	74	39	11	23	34	46	
≥65	42	48	115	61	36	77	40	54	
Sex[c]									0.009
Male	70	80	169	89	44	94	57	77	
Female	18	20	20	11	3	6	17	23	
Smoking status[d]									0.019
Never	23	26	25	13	5	11	17	23	
Ever	65	74	164	87	42	89	57	77	
Histology[e]									<0.001
SCLC	3	3	28	15	7	15	10	14	
NSCLC									
SQC	32	37	103	54	30	64	26	35	
ADC	44	50	43	23	9	19	30	40	
Others	9	10	15	8	1	2	8	11	
Cancer stage[f]									<0.001
Non-metastatic	20	23	169	89	33	70	29	39	
Metastatic	68	77	20	11	14	30	45	61	
ECOG PS[g]									<0.001
0-1	71	81	181	96	40	85	51	73	
2	16	18	7	3	6	13	19	26	
3	1	1	1	1	1	2	1	1	
PFT[h], mean ± SD									
FEV_1[i], L	2.0±0.6		1.9±0.6		1.3±0.5		2.0±0.6		<0.001
FEV_1[j], %	78±19		80±23		51±17		78±23		<0.001
FVC[k], %	79±17		87±18		76±18		80±23		0.001
DLco[l], %	83±30		87±23		76±27		86±27		0.035

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; SQC, squamous cell cancer; ADC, adenocarcinoma; ECOG PS, eastern cooperative oncology group performance status; PFT, pulmonary function test; FEV1, forced expiratory volume in a second; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide. [a]P value was calculated by χ^2 test except PFT. One-way ANOVA was performed for PFT; [b-g]comparison drug-induced ILD with radiation pneumonitis and AE COPD (P=0.04, P=0.026, P=0.008, P<0.001, P<0.001, P<0.001, and P=0.001, P=0.032, P=0.034, P<0.001, P<0.001, P=0.608, respectively); [h]PFT: n=352 for FEV1 and FVC; n=310 for DLco; [i-l]comparison AE COPD with drug-induced ILD and radiation pneumonitis (P=0.022, P=0.031, P=0.137, P=0.837, and P<0.001, P<0.001, P=0.002, P=0.002, respectively).

Table 2 The response of corticosteroid for the treatment-related pulmonary toxicities

	Drug-induced ILD (n=88)		Radiation pneumonitis (n=189)		AE COPD (n=47)		Others (n=74)		P[a]
	No.	%	No.	%	No.	%	No.	%	
Steroid regimen[b]									<0.001
Pulse	22	25	5	3	0	0	7	10	
High-dose	42	48	33	17	19	40	21	28	
Low-dose	24	27	151	80	28	60	46	62	
Corticosteroid response									<0.001
Fatal	31	35	24	13	9	19	28	38	
Recovered	57	65	165	87	38	81	46	62	

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease. [a]P value was calculated by χ^2 test; [b]Steroid regimen: Pulse, ≥500 mg/day methylprenisolone for 3 days, followed by high-dose steroid; high-dose, ≥0.5 mg/kg/day prednisolone; low-dose, <0.5 mg/kg/day prednisolone.

Table 3 Odds ratio for fatality of treatment-related pulmonary toxicities

	Steroid regimen (higher dose *vs.* low-dose)		
	OR	95% CI	P[a]
Drug-induced ILD	8.41	1.81-39.04	0.007
Radiation pneumonitis	24.44	7.77-76.90	<0.001
AE COPD	∞	0.00- ∞	0.998
Others	21.00	5.63-78.30	<0.001

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease; *vs.*, versus. [a]P value was calculated by stratified mutivariate logistic regression analysis.

Imaging characteristics and mortality of DILD

The mode and median of the number of involved lobes was 3 and 4, respectively. The 2-month mortality due to treatment-related pulmonary toxicities was higher in the patients where the number of involved lobes was 4-5 as compared with those where it was 1-3. But this was not statistically significant (P=0.090). In our series, the NSIP pattern was the most prevalent; it was seen at a frequency of 51% (45/88). In addition, there were 33 cases (38%) of the BOOP pattern and seven cases (8%) of the DAD one (*Table 4*). But there were only three cases of the mixed pattern; these include one case of the NSIP and BOOP pattern, one case of the BOOP and DAD one and one case of the DAD pattern and radiation pneumonitis. Furthermore, there was a significant correlation between the CT findings and the mortality due to treatment-related pulmonary toxicities. In other words, the 2-month mortality due to treatment-related pulmonary toxicities was significantly higher in the patients with the DAD or mixed pattern (100% or 67%, respectively) as compared with those with the NSIP or BOOP one (62% or

42%, respectively) (P=0.032).

On univariate analysis, the steroid regimen had a significant correlation with the mortality due to treatment-related pulmonary toxicities. In addition, the 2-month mortality due to treatment-related pulmonary toxicities was higher in the patients who received the pulse or high-dose therapy as compared with those who did the low-dose one (82% or 62% *vs.* 29%, P=0.001).

Discussion

With the recent increased use of new anti-neoplastic agents, molecular-targeted drugs and radiation in patients with lung cancer, there has been an increase in the occurrence drug- or radiation-induced pulmonary toxicities. In these patients, we empirically use corticosteroids for disease modulation and symptomatic improvement (4,20,21). Our study documented that the prescribed rate of higher-dose regimen (pulse or high-dose therapy) was higher in DILD (73%) than in radiation pneumonitis (20%) or AE COPD

Table 4 Clinical characteristics and mortality of patients with drug-induced interstitial lung disease

	All cases (n=88)		One month mortality[a] (n=32)		P[b]	Two months mortality[a] (n=51)		P[b]
	No.	%	No.	%		No.	%	
The number of involved pulmonary lobes					0.872			0.090
1-3	43	49	16	37		21	49	
4-5	45	51	16	36		30	67	
CT finding					0.132			0.032
NSIP pattern	45	51	15	33		28	62	
BOOP pattern	33	38	10	30		14	42	
DAD pattern	7	8	5	71		7	100	
Mixed pattern[c]	3	3	2	67		2	67	
Steroid regimen[d]					0.001			0.001
Pulse	22	25	13	59		18	82	
High-dose	42	48	17	41		26	62	
Low-dose	24	27	2	8		7	29	

Abbreviations: CT, computed tomography; NSIP, nonspecific interstitial pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; DAD, diffuse alveolar damage. [a]One month mortality and two months mortality are defined as numbers of death at the time of one month and two months since starting corticosteroid treatment; [b]P value was calculated by using χ^2 test; [c]Mixed pattern: one case of NSIP plus BOOP; one case of BOOP plus DAD; one case of DAD plus radiation pneumonitis; [d]Steroid regimen: Pulse, ≥500 mg/day methylprenisolone for 3 days, followed by high-dose steroid; high-dose, ≥0.5 mg/kg/day prednisolone; low-dose, <0.5 mg/kg/day prednisolone.

(40%) group. As long as more intensive and higher dose steroid is administered for patients with severer conditions, patients treated with higher dose steroid would show the worse outcome. So our results may reflect the natural course of each disease. However, if we compared the mortality only in patients who received pulse or high dose steroid therapy, the mortality rates of DILD (48.4%) and AE COPD (47.4%) were lower than those of radiation pneumonitis (63.2%) and others (100%) groups. Further prospective studies are therefore warranted to conclude the prognosis and propose the treatment guidelines for the optimal regimen and schedule. Thus, efforts should be made to minimize risk and to maximize benefit of anti-cancer treatment in this series.

In a current clinical setting, drug-induced pulmonary toxicity poses diagnostic challenges for clinicians. It would therefore be mandatory to determine the time course of the disease and the timing of causative drug medication as well as to rule out other possible diagnoses, including infections in particular. In addition, it would also be mandatory to evaluate the degree of the treatment response to the discontinued causative drugs and corticosteroids (4,20). Furthermore, previous studies have shown that radiological findings are a key diagnostic clue (10,22-24). It has been reported that the

clinical and radiologic findings due to causative drugs are suggestive of the underlying histopathologic processes (23). Rossi *et al.* classified the radiologic manifestations as DAD, NSIP, BOOP, eosinophilic pneumonia, obliterative bronchiolitis, pulmonary hemorrhage, edema, hypertension, or veno-occlusive disease (23). And knowledge of the drugs most frequently involved, together with an understanding of the typical histopathologic and radiologic manifestations of toxicity are necessary for institution of appropriate treatment (23). In this study, we examined whether CT findings would be a prognostic factor in the patients with DILD. We analyzed chest radiographic images and this led to the clinical and radiologic diagnosis of NSIP, BOOP, DAD, and mixed pattern. Our results showed that the 2-month mortality due to treatment-related pulmonary toxicities was significantly higher in the patients with the DAD as compared with those with the BOOP or NSIP one on univariate analysis. This finding of DILD is not different from various ILD in which NSIP or BOOP have better response to steroid treatment and better outcome than DAD.

There are several limitations of the current study as shown below: (I) we conducted the current study under the retrospective design in the patients with moderate to severe

symptoms who were in need of in-hospital treatment and corticosteroid therapy. Our results cannot be applied to the patients with mild pulmonary toxicities who are not in need of corticosteroid therapy; (II) we classified the patients with pulmonary toxicities into four groups depending on the clinical and radiological diagnoses rather than biopsy and microbiological examinations. But we performed serologic tests and sputum and blood cultures to rule out the patients with infection; (III) we considered the fatality of treatment-related pulmonary toxicities to evaluate the efficacy of corticosteroids against them. But this may be insufficient for the assessment of the treatment response to corticosteroids, as previously shown in a report that a longitudinal data of carbon monoxide diffusing capacity would be a more objective indicator (25); (IV) we failed to identify the significant difference in the degree of treatment-related pulmonary toxicities between the causative drugs because we used many drugs in the treatment of our cases; (V) we failed to consider the accumulated toxicities from the previous several anti-cancer therapies. In other words, we failed to consider radiation recall pneumonitis that may occur during the follow-up chemotherapy after prior radiation therapy. Nevertheless, our study is of significance in that we have evaluated clinical characteristics of treatment-related pulmonary toxicities and the prescribed dosage pattern of corticosteroid therapy through a large-scaled clinical and radiological review of patients with moderate to severe respiratory symptoms.

Conclusions

In conclusion, our results showed that the natural course of DILD had more unfavorable outcome requiring higher dose steroid therapy as compared with those with radiation pneumonitis or AE COPD. And this study suggested that the patients with the BOOP and NSIP pattern on initial chest CT scans of DILD had more favorable outcomes.

Acknowledgements

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