Interstitial Lung Disease in Patients with Small Cell Lung Cancer

Abbreviated running title: Survival of SCLC patients with IP

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Abstract

Background: Interstitial lung disease (ILD) and lung cancer are two of the most common respiratory diseases. The aim of this study was to demonstrate the prognostic significance of the presence of ILD in patients with small cell lung cancer (SCLC).

Methods: All the patients with SCLC who were admitted to our hospitals over a 23-year period up to 2008 were retrospectively analyzed.

Results: During the study period, 332 SCLC patients were consecutively admitted to our hospitals. Among them, 15 (4.5%) were diagnosed as having both SCLC and ILD. In univariate and multivariate analysis, female sex, early stage, good performance status, and chemotherapy were favorable prognostic factors. The presence of ILD was confirmed as an unfavorable prognostic factor.

Conclusions: Existing ILD adversely affects the outcome of SCLC. When deciding whether to offer a standard therapy that may increase treatment-related mortality, the patient's medical condition, including ILD, should be taken into consideration.

Keywords: interstitial lung disease; survival; small cell lung cancer

Introduction

Lung cancer is still one of the most common fatal malignancies.[1] Despite the progress made in various therapeutic modalities, the overall outcome of patients with lung cancer, especially those with small cell lung cancer (SCLC), remains poor and has not decreased to a level with which we can be satisfied.[2,3] Cigarette smoking and occupational exposures are common contributors not only to SCLC but also to interstitial lung disease (ILD) such as idiopathic pulmonary fibrosis (IPF).[4,5] Collagen disease-associated pulmonary fibrosis (CDPF) and IPF are the most common ILDs. Irrespective of the etiology of ILD, the therapeutic approach to SCLC patients with ILD is very complex owing to high post-therapeutic pulmonary complications and mortality. However, the clinicopathological features of both limited and extensive SCLC patients with ILD have not been clarified, and the influence of the existence of ILD on survival in SCLC patients has not been well evaluated. In this study, therefore, we examined the prognostic significance of coexistent ILD in patients with SCLC.

Patients and Methods

All the patients with pathologically or cytologically proven SCLC who were admitted to Tsukuba University Hospital and Tsukuba Medical Center Hospital over a 23-year period up to

August 2008 were retrospectively analyzed. Patients were staged according to the staging system of the Veterans Administration Lung Cancer Study Group: limited stage (LD) or extensive stage (ED). Patients with LD-SCLC have involvement restricted to the ipsilateral hemithorax within a single radiation port. Extensive stage SCLC is defined as the presence of obvious metastatic disease. The records of these patients were studied to assess the indication of treatment and outcome. Pretreatment chest conventional or high-resolution computed tomography (HRCT) was evaluated in all cases to determine not only the extent of lung cancer but also the existence of ILD. Interstitial lung disease was diagnosed on the basis of medical history, physical examination, and abnormalities compatible with bilateral lung fibrosis detected on conventional CT or HRCT, such as peripheral reticular opacities.[6] As in previous studies,[6,7] this study included IPF and CDPF as ILD. We evaluated the number and seriousness of comorbid diseases using the Charlson index (CI) score.[8] This study was approved by the institutional ethics committee of each hospital.

We divided the SCLC patients into 2 groups: patients with ILD (ILD group) and those without ILD (non-ILD group). Statistical significance between the 2 groups was determined using the Mann-Whitney U test and chi-square test. The Kaplan–Meier method was used to assess survival curves and the log-rank test

to evaluate the statistical significance of differences between the 2 groups. The length of survival was defined as the interval in months from the date of the initial therapy or supportive care until the date of deaths or the date of last follow-up. The Cox proportional hazards model was used to study the effects of clinicopathological factors on survival.[9] All statistical analyses were performed using SPSS 10.1 for Windows (SPSS, Chicago, IL, USA) and a probability value less than 0.05 was considered to be significant.

Results

There were 332 patients with pathologically or cytologically proven SCLC. The characteristics of these patients are summarized in Table 1. There were 294 (88.6%) men and 38 women. Two hundred twenty-one (69.6%) patients were 65 years of age or older. There were 278 (83.7%) patients with good performance status (PS) (ECOG 0-1), and 159 (47.9%) patients with LD-SCLC. Among all the patients, 15 (4.5%) were diagnosed as having ILD. Table 2 shows the differences between the SCLC patients with ILD and those without ILD. In the 15 SCLC patients with ILD, 14 were men, and 13 had good PS (PS 0-1). Thirteen patients received chemotherapy, but no patient with ILD had chest irradiation. There was no significant difference in proportion with regard to age, sex, PS, clinical stage, and treatment between the ILD group and non-ILD group (Table 2). There was no treatment-related death due to acute exacerbation of pneumonia in patients without ILD, but 1 patient with ILD had treatment-related death after the completion of sequential chemoradiotherapy. In addition, there was a difference between the ILD group and non-ILD group in the number of courses of chemotherapy performed. Fewer courses of chemotherapy were conducted in patients with ILD (median: 1 course; range: 1 - 4 courses) than in those without ILD (median: 2 courses; range: 1 - 6 courses)(P = 0.004).

In the univariate analysis, female sex, LD-SCLC, good PS (PS 0-1), and chemotherapy were favorable prognostic factors (Table 3). Figure 1 shows the survival curves of the patients in the ILD group and non-ILD group. Presence of ILD was an unfavorable prognostic factor (Table 3). However, age 65 years or younger, the number of comorbid diseases (2 or more), and the Charlson index (2 or more) were not prognostic (P = 0.4187, P = 0.1476, P = 0.2025, respectively). According to a multivariate Cox proportional hazards model, female sex, LD-SCLC, good PS (PS 0-1), and chemotherapy were favorable prognostic factors. Presence of ILD was confirmed as an unfavorable prognostic factor in the multivariate analysis (Table 3).

Discussion

Interstitial lung disease, such as IPF and CDPF, remains a devastating and progressive pulmonary disease characterized by alveolar destruction, excess matrix production, and varying levels of inflammation leading to impaired gas exchange.[10] As patients with ILD have pulmonary functional impairment and poor cardiopulmonary reserve, many of them may not match the indications for standard therapies and may need palliative care. Moreover, ILD is associated with an increased risk of lung cancer, with a relative risk of 7.0 to 14.0 compared with the general population.[11,12] On the other hand, only a few studies have shown the incidence of ILD in SCLC patients.[13-15] Park et al showed that 12 (3.1%) out of 390 SCLC patients were diagnosed as having IPF.[13] Kushibe reported that 33 (3.1%) out of 1063 lung cancer patients had IPF.[16] In the present study, we showed that 15 (4.5%) out of 332 SCLC patients were diagnosed as having IPF. This result was almost the same incidence of ILD in SCLC patients as those in previous studies,[13,16] although the definition of ILD was different.

Because of the design of clinical trials in which eligibility criteria preclude involvement of patients with impairment of organ function, many published studies have not shown the outcome of treatment of SCLC patients with comorbid disease such as ILD. As a result, there is little published information

regarding the results of treatment and prognostic factors in unselected groups of SCLC patients including those with both SCLC and ILD. Therefore, we evaluated the results of treatment and prognostic factors in unselected SCLC patients who were admitted to our 2 hospitals. In the present series of patients, we confirmed that female sex, LD-SCLC, and good PS were favorable prognostic factors for SCLC, as has been reported in a previous study.[17] Additionally, we revealed that patients with ILD had worse overall survival than did those without, and existence of ILD was one of the unfavorable prognostic factors for survival in SCLC patients.

It is very important to report why ILD worsened the prognosis of SCLC in our patients. We observed treatment-related death due to acute exacerbation of pneumonitis in 1 patient with ILD. Moreover, fewer courses of chemotherapy were conducted in the ILD group in this study. Eight of 13 patients in the ILD group had deterioration of PS after the first course of chemotherapy, and they did not continue with additional courses. Therefore, we supposed that fewer courses of chemotherapy in the ILD group resulted in worse survival.

Some chemotherapeutic agents such as Adriamycin and CPT-11 are contraindicated for SCLC patients with ILD because of the development of respiratory failure due to worsening ILD.[18,19] Therefore, in many clinical trials, these SCLC patients were

excluded and there have been no apparent clinical data with regard to the treatment of SCLC patients with ILD. In addition, chest irradiation may accelerate pulmonary fibrosis inside as well as outside of the irradiation field, which causes deterioration of respiratory function and development of respiratory failure. Especially for LD-SCLC patients who have coexistent ILD, chemoradiotherapy is not indicated for the same reason that respiratory complication may ensue.[20,21] Post-therapeutic deterioration of pulmonary function necessitating mechanical ventilation and tracheostomy was also a cause of death and occurred more frequently in ILD patients than in non-ILD patients.[6,7,13] These contraindications narrow the choice of the treatment and may have some relationship with the poor prognosis of SCLC patients with ILD.

The limitations of this study are inherent in its retrospective design, making it therefore necessarily complicated by lead-time and length-time biases. In this study, pathological diagnosis in almost all of our patients was obtained using transbronchial biopsy specimens. Therefore, patients whose pulmonary functional impairment was too severe to permit carrying out diagnostic procedures might have been excluded, and only selected SCLC patients with ILD deemed able to tolerate these procedures were included. Another limitation is the lack of information about the assessment of respiratory function and

precise pathological diagnosis of ILD. Randomized, prospective studies comparing prognosis in SCLC patients with or without ILD are the only way to obtain an unconfounded estimate of the prognostic effect of ILD. However, we recognize that it has some clinical importance for the management of future patients of unselected groups. Our results apparently showed that the therapeutic approach is complicated when SCLC patients have ILD. Our results imply that existing ILD does adversely affect the outcome of SCLC. When deciding whether to offer an intensive therapy that may increase treatment-related mortality, the individual patient's medical condition, including coexistence of ILD, should be taken into consideration, although favorable results have been reported in a small number of patients with ILD.[6,7,13] Therefore, detailed history taking and physical examination are required to elucidate the presence of signs and/or symptoms of ILD.

In summary, chest CT scan is indicated not only to evaluate metastatic lesions from SCLC but also to detect ILD. Appropriate pre-evaluation for the indication of standard therapy or adequate palliative care is essential to provide prolonged quality survival, which is the primary goal of therapy for SCLC patients with ILD.

Conflict of interest

None of the authors have any conflict of interest which could inappropriately influence this work.

Role of the funding source

The authors received no funding for this study.

Acknowledgement

We are especially grateful to Ms. Flaminia Miyamasu for her review of the manuscript. We also thank Ms. Kikue Sato for her secretarial assistance.

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Figure legend

Figure 1. Survival curves of the 2 groups of SCLC patients with or without interstitial lung disease (ILD). The upper line is the survival curve of patients without ILD; the lower line is the curve of patients with ILD.

Table 1. Characteristics of patients with small cell lung cancer

No. of patients	332
Age (year)	median: 70 range: 27 - 86
Sex	
Male	294 (88.6%)
Female	38 (11.4%)
Performance status	
0-1	278 (83.7%)
2-4	54 (16.3%)
Interstitial pneumonia	
present	15 (4.5%)
absent	317 (95.5%)
Stage	
Limited	159 (47.9%)
Extensive	173 (52.1%)
Treatment	
Chemotherapy	276 (83.1%)
Others	56 (16.9%)

Table 2. Differences between SCLC patients with ILD and those without ILD.

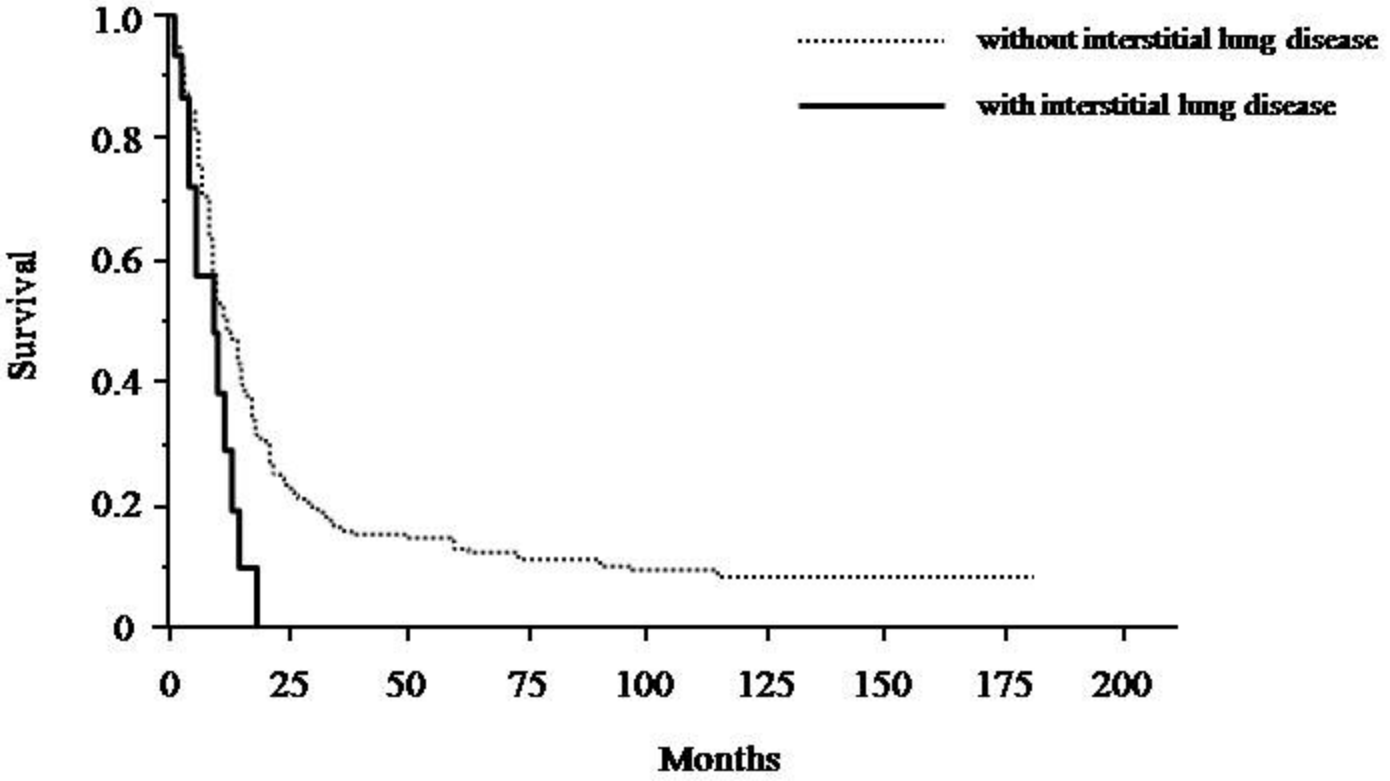
	Patients with ILD	Patients without ILD	*P*-value
Age			
median, range (years)	68, 58-80	70, 27-86	0.489
Sex			
Male	14	280	
Female	1	37	0.999
Performance status			
0-1	13	265	
2-4	2	52	0.999
Clinical stage			
Limited	7	152	
Extensive	8	165	0.999
Treatment			
Chemotherapy	13	263	
Surgery + chemotherapy	2	24	
Chest irradiation	0	25	0.079
Supportive care	0	5	

SCLC: small cell lung cancer; ILD: interstitial lung disease

Table 3. Univariate and multivariate analyses of prognostic factors in 332 patients with small cell lung cancer

Factors	Univariate analysis (log-rank test)	Multivariate analysis (Cox`s proportional hazards model)		
	P-value	hazard ratio	95%CI	*P*-value
Sex	0.040	0.65	0.44-0.97	0.033
Stage (limited, extensive)	0.001	0.52	0.39-0.67	0.001
Performance status (0-1, 2-4)	0.001	0.50	0.36-0.70	0.001
Interstitial lung disease	0.015	0.43	0.24-0.77	0.005
Treatment (chemotherapy, others)	0.005	1.45	0.96-2.19	0.077

95%CI: 95% confidence interval


1.0
0.8
0.6
0.4
0.2
0
Survival
0
25
50
75
100
125
150
175
200
Months
without interstitial lung disease
with interstitial lung disease