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ILD-NSCLC-GAP index scoring and staging system for patients with non-small cell lung cancer and interstitial lung disease

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ABSTRACT

Background and objective: Patients with advanced non-small cell lung cancer (NSCLC) and interstitial lung disease (ILD) are commonly excluded from most clinical trials because of acute exacerbation (AE) of ILD triggered by chemotherapy. Data on the efficacy and feasibility of chemotherapy are limited in this patient population. Recently, the ILD-GAP index and staging system was reported as a clinical prognostic factor associated with mortality in patients with ILD. Therefore, we evaluated the incidence of ILD-AE during the surveillance term in this study and the prognosis in patients with NSCLC and ILD using a modified ILD-GAP (ILD-NSCLC-GAP) index scoring system.

Materials and methods: The medical records of patients with NSCLC and ILD who underwent a pulmonary function test before initiation of platinum-based chemotherapy as first-line treatment at the Shizuoka Cancer Center between September 2002 and December 2014 were reviewed retrospectively. Among these patients, we compared the incidence of ILD-AE, one-year survival rate, and overall survival (OS) between the ILD-NSCLC-GAP index scores and stages.

Results: Of the 78 patients included, 21 (27%; 95% confidence interval [CI], 18%–38%) had ILD-AE during the surveillance term in this study. The one-year survival and median OS rates were 49% and 11.3 months, respectively. The incidence of ILD-AE increased gradually and the one-year survival and median OS rates decreased gradually with increasing ILD-NSCLC-GAP index scores and stages.

Conclusion: The ILD-NSCLC-GAP index scoring and staging system may be a useful tool to calculate a prediction of the incidence of ILD-AE and its prognosis for patients with NSCLC and ILD.

1. Introduction

Interstitial lung disease (ILD) occurred at a frequency of 3% to 17% among patients with lung cancer undergoing surgery in Japan [1–4], and the concomitant existence of ILD contributed to their increased mortality [5,6]. Therefore, ILD is considered to be a prognostic factor in many patients with early stage lung cancer. However, patients with advanced non-small cell lung cancer (NSCLC) and ILD are commonly excluded from most clinical trials because of the acute exacerbation (AE) of ILD caused by chemotherapy. ILD-AE is the most common cause of death in patients with ILD in Japan, unlike in Western countries [7]. Therefore, data on the efficacy and feasibility of chemotherapy are limited in this patient population. Chemotherapy is often used for patients with advanced NSCLC and ILD in clinical settings, although evidence for improved prognosis with chemotherapy is unclear. Some studies showed that the incidence rate of ILD-AE ranged between 5% and 35% among patients with NSCLC and ILD receiving chemotherapy [8–15]. Based on an original GAP index and staging system [16], we recently reported that a modified GAP index score and stage can predict the risk of incidence of idiopathic pulmonary fibrosis (IPF)-AE and the prognosis in patients with NSCLC and IPF [17]. However, it cannot be used as a tool in patients with NSCLC and ILD except IPF because the

Abbreviations: ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; AE, acute exacerbation; IPF, idiopathic pulmonary fibrosis; %FVC, percent predicted forced vital capacity; %DLCO, percent predicted diffusion capacity of lung for carbon monoxide; TKI, tyrosine kinase inhibitor; OS, overall survival; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval

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original GAP index and staging system was intended only for patients with IPF.

Recently, the ILD-GAP index and staging system, which was based on the ILD subtype, sex, age, and two lung physiology tests (percent predicted forced vital capacity [%FVC] and percent predicted carbon monoxide diffusing capacity [%DLCO]), was reported as a clinical prognostic factor associated with mortality in patients with ILD (Appendix A in Supplementary material) [18]. Therefore, we evaluated the incidence of ILD-AE during the surveillance term in this study and the prognosis in patients with NSCLC and ILD using a modified ILD-GAP (ILD-NSCLC-GAP) index scoring system including the ILD subtype, sex, age, and%FVC, and excluding%DLCO as reported in our previous study [17].

2. Methods

The medical records of patients with NSCLC and ILD who underwent a pulmonary function test before initiation of platinum-based chemotherapy as first-line treatment at the Shizuoka Cancer Center between September 2002 and December 2014 were reviewed retrospectively. The tumor, nodes, and metastasis (TNM) stage was evaluated based on the 7th edition of the TNM classification of lung cancer [19]. Platinum-based chemotherapy was defined as doublet or triplet chemotherapy regimens that included cisplatin or carboplatin. Patients received the physicians' choice chemotherapy. However, contraindicated chemotherapeutic drugs in Japan for patients with ILD (i.e., amrubicin, irinotecan, gemcitabine) were excluded from the analysis. Also, Epidermal Growth Factor Receptor–tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase–TKIs avoided in Japanese clinical practice were excluded from the analysis.

The ILD-NSCLC-GAP index used in our study was derived from the original ILD-GAP index [18], with the exclusion of%DLCO reported in our previous study [17],because DLCO is not routinely performed in patients with advanced NSCLC and ILD in clinical settings. Briefly, the ILD-NSCLC-GAP index was used to obtain a total score ranging between 0 and 5: ILD subtype (IPF and unclassifiable ILD, 0; non-IPF, −2), sex (female, 0; male, 1), age (years; ≤60, 0; 61–65, 1; > 65, 2), and%FVC (> 75%, 0; 50%–75%, 1; < 50%, 2). Similarly to the original ILD-GAP index, patients were categorized into three groups based on the ILD-NSCLC-GAP index score: stages I (0–1), II (2–3), and III (4–5). In addition, we compared the incidence of ILD-AE, one-year survival rate, and overall survival (OS) among the three ILD-NSCLC-GAP index stages.

In our study, ILD was defined as chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring primarily in older adults or associated with connective tissue disease and occupation. On the other hand, infectious lung disease and drug-induced pneumonia were excluded from this study. ILD was divided into IPF, non-IPF, or unclassifiable ILD using chest computed tomography (CT). The diagnosis of an ILD pattern is based on the CT features as defined by the International Consensus Statement of the American Thoracic Surgery and the European Respiratory Society [20,21]. The Chest CT scans before the treatment were evaluated by one radiologist (M.E.) and three pulmonologists (H.K., T.N., and H.K.) without knowledge of the patient outcomes. The definition of ILD-AE included any acute respiratory event characterized by new bilateral ground glass-opacification/consolidation not completely explained by infectious disease and cardiac failure or fluid overload [22]. Infectious disease was excluded based on the following criteria: no purulent sputum, a negative result of the sputum or blood culture, within the reference values of serum β-D-Glucan and the cytomegalovirus antigenemia, and a lack of the predominance of segmental consolidations on CT findings. ILD-AE in our study was included based on grades 2–5 for pneumonitis using the National Cancer Institute Common Terminology Criteria version 4.0 [23]. Because radiotherapy was considered to be a risk factor for ILD-AE [24,25], patients who underwent chest radiotherapy as first-line treatment were excluded from this study.

Univariate and multivariate analyses of the incidence rate of ILD-AE, one-year survival rate, and OS were analyzed using the Cox proportional hazards approach. All categorical variables were analyzed using the Fisher's exact test. The incidence rate of ILD-AE in our study was evaluated using the cumulative hazard rate for each group. Also, the one-year survival rates were estimated from Kaplan–Meier survival probabilities. OS was defined as the time from the start of the platinum-based chemotherapy as first-line treatment to death. The event time was estimated using the Kaplan–Meier method. The log-rank test was used to compare the cumulative survival in each group. All P values were reported as two-sided, with values < 0.05 considered statistically significant. The end date for the survival analyses was defined as September 1, 2017. All statistical analyses were performed using the JMP® 11.2.0 software (SAS Institute, Cary, NC, USA). The study protocol was approved by the institutional review board of the Shizuoka Cancer Center (IRB No. 29-J112-29-1-3).

3. Results

3.1. Patient characteristics

During the study interval, 21 patients who did not undergo the pulmonary function test and 5 patients who underwent chest radiotherapy as first-line treatment were excluded from this study. A total of 78 patients diagnosed with NSCLC and ILD underwent pulmonary function test before first-line chemotherapy and were subsequently treated with platinum-based first-line chemotherapy. Their characteristics are shown in Table 1. The median patient age was 68 (range,

Table 1
Baseline characteristics of all patients in our study.

Characteristics	
No. patients	78
Age at time of first-line chemotherapy (years)	
Median	68
Range	53–81
≤60 years	8 (10.3%)
61–65 years	17 (21.8%)
> 65 years	53 (67.9%)
Sex (%)	
Male	71 (91.0%)
Female	7 (9.0%)
ECOG PS at time of first-line chemotherapy (%)	
0	19 (24.4%)
1	56 (71.8%)
2	3 (3.8%)
Smoking status (%)	
Current smoker or ever smoked	78 (100%)
Never smoked	0 (0%)
ILD subtype (%)	
IFP	58 (74.4%)
Non-IPF	19 (24.4%)
Unclassifiable ILD	1 (1.3%)
FVC, predicted	
Median	87.6%
Range	56.0%–137.8%
< 50%	0 (0%)
50%–75%	20 (25.6%)
> 75%	58 (74.4%)
Clinical stage at time of first-line chemotherapy (%)	
III	36 (46.2%)
IV	33 (42.3%)
Recurrent	9 (11.5%)
Pathological subtype (%)	
Squamous	42 (53.8%)
Nonsquamous	36 (46.2%)

ECOG PS, Eastern Cooperative Oncology Group performance score; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity.