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Clinical features, anti-cancer treatments and outcomes of lung cancer patients with combined pulmonary fibrosis and emphysema

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ABSTRACT

Background: Combined pulmonary fibrosis and emphysema (CPFE) patients may be at significantly increased risk of lung cancer compared with either isolated emphysema or pulmonary fibrosis patients. Acute exacerbation (AE) of interstitial lung disease caused by anticancer treatment is the most common lethal complication in Japanese lung cancer patients. Nevertheless, the clinical significance of CPFE compared with isolated idiopathic interstitial pneumonias (IIPs) in patients with lung cancer is not well understood.

Methods: A total of 1536 patients with lung cancer at Nippon Medical School Hospital between March 1998 and October 2011 were retrospectively reviewed. Patients with IIPs were categorized into two groups: (i) CPFE; IIP patients with definite emphysema and (ii) non-CPFE; isolated IIP patients without definite emphysema. The clinical features, anti-cancer treatments and outcomes of the CPFE group were compared with those of the non-CPFE group.

Results: CPFE and isolated IIPs were identified in 88 (5.7%) and 63 (4.1%) patients respectively, with lung cancer. AE associated with initial treatment occurred in 22 (25.0%) patients in the CPFE group and in 8 (12.7%) patients in the non-CPFE group, irrespective of treatment modality. Median overall survival (OS) of the CPFE group was 23.7 months and that of the non-CPFE group was 20.3 months ($P = 0.627$). Chemotherapy was performed in a total of 83 patients. AE associated with chemotherapy for advanced lung cancer occurred in 6 (13.6%) patients in the CPFE group and 5 (12.8%) patients in the non-CPFE group. Median OS of the CPFE group was 14.9 months and that of the non-CPFE group was 21.6 months ($P = 0.679$).

Conclusion: CPFE was not an independent risk factor for AE and was not an independent prognosis factor in lung cancer patients with IIPs. Therefore, great care must be exercised with CPFE as well as IIP patients when performing anticancer treatment for patients with lung cancer.

1. Introduction

Idiopathic interstitial pneumonias (IIPs) appear to be associated with lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is significantly higher than in the general population, and it has been recognized that IPF is an independent risk factor for lung cancer [1–5].

In lung cancer patients with interstitial lung disease (ILD) such as pulmonary fibrosis caused by any pathogenesis, iatrogenic acute exacerbation (AE) caused by various anticancer treatments, such as surgical resection, radiotherapy and chemotherapy, is the most common lethal complication and significantly affects the aprognosis. Therefore, treatment of lung cancer patients with ILD is a serious and difficult challenge in Japanese lung cancer patients. Nevertheless, it is not known what type of therapeutic strategy is optimal and what type of ILD carries a high risk of AE in such patients. To clarify this question, we have proposed chemotherapeutic strategies for advanced lung cancer patients with IIPs [6,7].

The syndrome of combined pulmonary fibrosis and emphysema (CPFE) has been proposed as an important phenotype of pulmonary fibrosis, defined by the coexistence of emphysema in the upper pulmonary area and parenchymal fibrosis in the lower area in the same patient [8]. Previous studies have shown that patients with CPFE

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display distinct clinical features and different outcomes compared to control patients without emphysema.

Interestingly, CPFE may indicate significantly increased risk of lung cancer compared with either chronic obstructive pulmonary disease or isolated pulmonary fibrosis alone [9–11]. Whether patients with CPFE have poorer survival than patients with pulmonary fibrosis alone is not well known; some reports have shown that CPFE is possibly associated with higher mortality compared with pulmonary fibrosis without emphysema [11,12]. Nonetheless, some inconsistencies have been seen in published studies, mainly regarding the prognosis of these patients [13–15]. However, most previous studies of CPFE have significant limitations; there has been no agreed definition of the CPFE syndrome, for example lack of definition of the extent of emphysema. Moreover, the presence of IPF is not necessary for the diagnosis of CPFE.

In lung cancer patients, especially those undergoing chemotherapy, the clinical significance of CPFE in prognosis and AE compared with isolated IIPs has not been investigated. We conducted this retrospective study to elucidate the impact of concomitant emphysema on AE due to lung cancer treatment and prognosis in lung cancer patients with IIPs.

2. Patients and methods

2.1. Patients and study design

A retrospective review was undertaken of the medical records of a consecutive series of patients with a definitive diagnosis of primary lung cancer, admitted to the Department of Pulmonary Medicine and Oncology, Nippon Medical School Hospital, between March 1998 and October 2011. We identified 188 patients with IIPs from 1536 lung cancer patients. Of these, 151 patients were reevaluated using chest Computed Tomography (CT) and categorized into CPFE and isolated IIPs (non-CPFE) groups.

2.2. Evaluation of preexisting IIPs and definition of acute exacerbation

We classified preexisting IIPs into two types: an IPF pattern and non-IPF pattern. Diagnosis of IIPs was made in accordance with American Thoracic Society/European Respiratory Society criteria [5] in patients previously diagnosed with usual interstitial pneumonia (UIP) by either histological evaluation of open-lung biopsies or transbronchial lung biopsy specimens. In the absence of histological evidence, diagnosis of an IPF pattern was based on evidence from a high-resolution CT (HRCT) of the chest and other clinical features. Typical chest CT findings for the IPF pattern were basal predominant, subpleural reticular abnormality with traction bronchiectasis, honeycomb cysts, and no findings of atypical features such as peribronchovascular nodules, isolated cysts, or consolidation [16–18]. Non-IPF pattern was characterized by the presence of basal-predominant non-specific pulmonary fibrosis and/or ground glass opacities, and other infiltrative shadows inconsistent with IPF pattern. In addition, the presence of other typical clinical features, including bibasilar inspiratory crackles, abnormal findings of pulmonary function tests indicative of restrictive respiratory failure, and increased serum levels of markers of damaged pneumocytes (i.e., lactate dehydrogenase [LDH], C-reactive protein [CRP], KL-6, and surfactant protein D [SP-D]) were investigated.

Exclusion criteria were the presence of connective tissue disease and any other interstitial lung diseases (ILD), such as sarcoidosis, pulmonary histiocytosis, eosinophilic pneumonia, hypersensitivity pneumonitis and occupational lung diseases such as environmental exposure to asbestos. Moreover, we excluded patients in the acute and subacute phase of IIPs, such as cellular nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia and acute interstitial pneumonia.

Cases were defined as having AE of IIPs if they satisfied all the following criteria [19,20]: (1) exacerbation of dyspnea within 1 month; (2) newly developed diffuse pulmonary opacities on chest CT and/or chest X-ray; (3) decrease in arterial oxygen tension (PaO_2) of more than 10 mmHg under similar conditions; and (4) absence of heart failure or infectious lung diseases. Based on our previous report [21], AE occurring within 30 days after surgical resection and within 10 weeks after final treatment by chemotherapy and radiotherapy were considered to be related to chemotherapy.

Diagnosis of IIPs and AE were determined by at least two pulmonologists (Y.M., Y.S., A.A. and A.G.).

2.3. Evaluation of emphysema and pulmonary fibrosis

Low attenuation area (LAA) for pulmonary emphysema, fibrosis as reticular opacity or honeycombing, and ground glass attenuation (GGA) were semi-quantitatively evaluated independent of patient clinical information, using the emphysema and pulmonary fibrosis scoring methods proposed by Goddard et al. [22] and Kazerooni et al. [23], respectively.

The CPFE group was characterized by coexistence of significant emphysema (%LAA > 20% at the upper edge of the aortic arch) and diffuse parenchymal lung opacity with significant pulmonary fibrosis. The non-CPFE group was characterized by the presence of significant pulmonary fibrosis without significant emphysema (%LAA < 20%).

2.4. Statistical considerations

Examination values are reported as means ± standard deviation (SD). Comparisons between groups were performed using Student's unpaired *t*-test. All categorical variables were analyzed by chi-square test or Fisher's exact test as appropriate. Survival time was measured as the period from the initiation of first-line treatment and/or first-line chemotherapy until death by all causes. Overall survivals (OS) were analyzed using the Kaplan–Meier method and compared among groups by the log-rank test. To identify prognostic factors, a Cox proportional hazards model was used for univariate and multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) to assess the relative risk of AE were calculated by logistic regression analysis. Resulting *P* values, two tailed, of less than 0.05 were considered to indicate statistical significance. The threshold values for the examinations using the Cox proportional hazards model are the medians for each examination, or the upper or lower limit of each examination when the median value is within normal limits.

3. Results

3.1. Patient characteristics

One hundred and eighty eight (12.2%) of 1536 lung cancer patients were complicated with IIPs. Of these, 151 patients were available following pretreatment chest CT. CPFE was common in our cohort. Eighty eight (58.3%) of these 151 patients met the criteria for CPFE. The characteristics of lung cancer patients with and without CPFE are compared in Table 1. All patients were Japanese; patients with CPFE were commonly male (CPFE 92% vs. non-CPFE 73%; $P < 0.002$). There were no differences in average age at the start of initial anticancer treatment, the proportion of each smoking status or smoking index. With respect to the types of IIP, the

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