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Low forced vital capacity predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer

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ABSTRACT

Objectives: Although acute exacerbation of pre-existing interstitial lung disease (AE-ILD) associated with cytotoxic chemotherapy has been recognized as a severe complication in lung cancer treatment, its risk factors have not been fully studied.
Materials and methods: Among lung cancer patients receiving cytotoxic chemotherapy, patients with pre-existing ILD were identified based on the pretreatment high-resolution computed tomography (HRCT) findings. Chemotherapy-associated AE-ILD was defined as deterioration or development of dyspnea and HRCT findings of new bilateral ground-glass attenuations with/without non-segmental consolidation superimposed on pre-existing interstitial shadows, without evidence of pulmonary infection, congestion, or pulmonary embolism, within four weeks after the last administration of chemotherapy. Baseline characteristics were reviewed and the risk factors for chemotherapy-associated AE-ILD were evaluated by logistic regression analyses.
Results: Among 85 patients identified as having pre-existing ILD, chemotherapy-associated AE-ILD occurred in 26 patients (30.6%); 8 patients died and 11 patients had a severely deteriorated general condition despite intensive treatment. Compared with those without AE-ILD, patients with AE-ILD had significantly lower forced vital capacity (FVC) (median: 91.1% versus 76.6%, $P = 0.01$). Univariate and multivariate logistic regression analyses identified baseline lower FVC and non-small cell lung cancer (NSCLC) as the risk factors for this severe event (odds ratio of FVC: 0.97, 95% confidence interval: 0.94–0.99; odds ratio of NSCLC: 4.65, 95% confidence interval: 1.10–19.76).
Conclusion: Chemotherapy-associated AE-ILD was a frequent and lethal complication in lung cancer treatment for patients with pre-existing ILD. Spirometric assessment of pulmonary function may be useful to predict the event.

1. Introduction

Patients with interstitial lung disease (ILD), particularly idiopathic pulmonary fibrosis (IPF) and the emphysema-combined case, frequently develop lung cancer [1–3]. Because cancer therapy including surgery, radiotherapy, and chemotherapy can cause a life-threatening complication, acute exacerbation of pre-existing ILD (AE-ILD), the treatment of lung cancer in patients with ILD is often challenging. Treatment options for inoperable cases are extremely limited because thoracic radiotherapy and most molecular-target drugs, such as epidermal growth factor receptor tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors, are generally contraindicated in patients with ILD [4,5]. Cytotoxic chemotherapy may be the only option for treatment in such patients, but the incidence of chemotherapy-associated AE-ILD is as high as 13.3–22.0% [3,6,7]. Therefore, clinicians have to carefully determine whether the benefits of the chemotherapy

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exceed the risk of chemotherapy-associated AE-ILD [2,4]. Identification of risk factors would be useful for designing treatment strategies.

In patients with IPF, the relationship between poor pulmonary function and "idiopathic" acute exacerbation has been reported. Song et al. demonstrated in their large cohort study that baseline lower forced vital capacity (FVC) was a risk factor for acute exacerbation of IPF [8]. On the other hand, there were two Japanese studies that attempted to identify the risk factors for chemotherapy-associated AE-ILD in patients with lung cancer and pre-existing ILD [6,7]. Kenmotsu et al. identified younger age (<70 years) and the usual interstitial pneumonia (UIP) pattern on computed tomography (CT) as risk factors [6]. Minegishi et al. suggested that higher pretreatment levels of serum C-reactive protein (≥2.5 mg/dL) could be a risk factor [7]. In those studies, however, spirometric data was completely or mostly unavailable. Therefore, the relationship between pulmonary function and risk of chemotherapy-associated AE-ILD is unclear.

In this retrospective study, we aimed to identify the risk factors for cytotoxic chemotherapy-associated AE-ILD in patients with inoperable lung cancer and pre-existing ILD by reviewing pretreatment baseline characteristics, including spirometric data.

2. Patients and methods

This study was approved by the review board of each participating institution (Hamamatsu University School of Medicine, approved number: 14–318; Kanagawa Cardiovascular and Respiratory Center, approved number: 27–21). Given the retrospective nature of the study, patient written informed consents were not required.

We reviewed the medical records of 494 patients who received cytotoxic chemotherapy for inoperable lung cancer at each institution between January 2007 and June 2014. Baseline clinical factors within four weeks before administration of first-line chemotherapy were obtained. Two experienced pulmonologists (T.B. and M.K.) who had no knowledge of the patients' clinical information independently evaluated the high-resolution CT (HRCT) images of the chest performed within four weeks before first-line chemotherapy administration. The diagnostic criteria for ILD included the existence of chronic and bilateral reticulation or ground-glass attenuation on pretreatment HRCT. The images were assessed for findings such as UIP compatibility; presence of emphysema; and extent of normal lung area after exclusion of lesions caused by ILD, emphysema, and lung cancer. According to the recent guideline for IPF [1], UIP compatibility on HRCT was classified into three groups: the UIP pattern (subpleural and basal-predominant reticulation with honeycombing); the possible UIP pattern (without apparent honeycombing); and the other (named as inconsistent with UIP pattern in the IPF guideline). Disagreement in these HRCT findings between the reviewers was resolved by a consensus. On the basis of clinical, radiological, and if present, pathological findings, a final multidisciplinary diagnosis of ILD was retrospectively made. Patients with signs of pulmonary infection, congestion, carcinomatous lymphangitis, or post-radiation fibrotic changes were excluded. Chemotherapy-associated AE-ILD was diagnosed using the following criteria, which were modified from those for IPF [9] to practically adapt to the situation of cancer chemotherapy: (i) deterioration or development of dyspnea; (ii) HRCT findings indicating new bilateral ground-glass attenuations with/without non-segmental consolidation superimposed on pre-existing interstitial shadows; (iii) exclusion of pulmonary infection by negative respiratory culture; (iv) exclusion of apparent congestion and pulmonary embolism, based on the results of biochemical tests and echocardiography and subsequent clinical course; and (v) less than four weeks interval between the last administration of chemotherapeutic drug and onset of AE-ILD. The severity of AE-ILD (or pneumonitis) was graded using the Common Terminology Criteria for Adverse Events version 4.0.

Data were described as numbers (percentages) or median (range). For group comparison, Fisher's exact test and Mann–Whitney *U* test were used as appropriate. Inter-reviewer agreement with respect to the radiological evaluation was determined using kappa statistics (<0.4: poor; 0.4–0.6: moderate; 0.6–0.8: good; 0.8–1.0: excellent). Among baseline patient characteristics, the risk factors for chemotherapy-associated AE-ILD were identified using univariate and subsequent stepwise multivariate logistic regression models. Overall survival time was defined as the number of months from first-line chemotherapy administration until death or at censoring. Patients were censored if alive on June 30, 2015. The Kaplan–Meier survival method was used to estimate median survival. A survival comparison between groups was evaluated by log-rank test. All P values < 0.05 were considered to be significant. Statistical analyses were conducted using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics and prognosis in the study population

Among the 494 patients reviewed, 85 were identified to have pre-existing ILD. A diagnosis of IPF was made in 58 patients (68.2%), including 8 pathologically-proven cases. The remaining patients were diagnosed with idiopathic interstitial pneumonias (n = 19), ILD associated with collagen vascular diseases (n = 5), chronic hypersensitivity pneumonitis (n = 1), pneumoconiosis (n = 1), and IgG4-related lung disease (n = 1). The median age at the time of first-line chemotherapy administration was 71 years (range, 53–86 years). The majority were male with a heavy smoking history. Sixty-seven patients (78.8%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The most frequent histopathologic type was adenocarcinoma (n = 34, 40.0%), followed by squamous cell carcinoma (n = 20, 23.5%), small cell lung cancer (SCLC; n = 20, 23.5%), and other non-small cell lung cancer (NSCLC; n = 11, 13.0%). More than half of the patients were diagnosed with ILD at the time of lung cancer diagnosis, whereas the other patients developed lung cancer after a median of 5.8 years (range, 0.8–17.0 years) of ILD diagnosis. Median percent predicted FVC, forced expiratory volume in one second (FEV_1), and diffusing capacity of the lung for carbon monoxide (DLco) were 85.0% (range, 39.5–133.0%), 76.9% (range, 43.7–131.8%), and 63.4% (range, 34.4–108.2%; n = 35), respectively. Inter-reviewer agreement on the radiological assessment was good to excellent (UIP compatibility, $\kappa = 0.82$; presence of emphysema, $\kappa = 0.68$; extent of normal lung area, $\kappa = 0.75$). Emphysema and the UIP pattern were common findings on HRCT. The primary lesions of lung cancer were frequently located adjacent to or in the area of the fibrotic and/or emphysematous changes.

The overall median follow-up period was 14.7 months (range, 2.2–55.7 months). The Kaplan–Meier survival curve for overall survival is shown in Fig. 1. The median survival time was 9.7 month (95% confidence interval, 7.9–11.5 months). The unadjusted 1-year survival probability was calculated as 34.2%.

3.2. Chemotherapy-associated AE-ILD

A total of 142 cytotoxic chemotherapy regimens (first-line, n = 85; second-line, n = 42; third-line, n = 10; fourth-line, n = 5) were administered to the 85 patients and 27 events of chemotherapy-associated AE-ILD (first-line, n = 16; second-line, n = 9; third-line,