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Original article

An analysis of the clinical features of lung cancer in patients with connective tissue diseases

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ABSTRACT

Background: Patients with connective tissue diseases (CTDs) are at increased risk for lung cancer (LC); interstitial lung disease (ILD) is a common form of organ dysfunction in cases of CTD. However, the influence of ILD on the treatment and prognosis in LC patients with CTD is unclear.

Methods: Between January 2010 and December 2014, 27 patients among all patients with CTD at our institution were diagnosed with primary LC. We retrospectively analyzed the clinical features, treatment modalities, and outcomes of these patients, and evaluated the potential prognostic factors. Forty-four LC patients without CTD were also analyzed as a control cohort.

Results: LC patients with CTD had a significantly higher incidence of ILD as a complication compared with those without CTD (52% and 14%, respectively). CTD-associated ILD (CTD-ILD) at diagnosis was associated with significantly worse survival in LC patients with CTD. Multivariate analysis demonstrated that the complication of CTD-ILD was an independent poor prognostic factor in LC patients with CTD. The incidence of acute exacerbation (AE) of CTD-ILD was 21% among LC patients with CTD, and all of these patients died despite intensive treatment including high-dose corticosteroids. The restrictions in curative therapy for LC due to the presence of ILD and AE of CTD-ILD were thought to be the major reasons for the poor outcome.

Abbreviations: CTD, connective tissue diseases; LC, lung cancer; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; SSc, systemic sclerosis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; AE, acute exacerbation; PS, performance status; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; CTD-ILD, connective tissue disease-associated interstitial lung disease; OS, overall survival; NSCLC, non-small cell lung cancer; NSCLC-NOS, non-small cell lung cancer-not otherwise specified; SCLC, small cell lung cancer; RA, rheumatoid arthritis; MCTD, mixed connective tissue disease; CI, confidence interval; IIP, idiopathic interstitial pneumonia; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; SEM, standard error of the mean; CBDCA, carboplatin; PTX, paclitaxel; S-1, tegafur-gimeracil-oteracil potassium; CDDP, cisplatin; VP-16, etoposide; VNR, vinorelbine; GEM, gemcitabine; PEM, pemetrexed; bev, bevacizumab

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Conclusions: LC patients with CTD had a high prevalence of ILD, and the presence of CTD-ILD was significantly associated with poor prognosis.

1. Introduction

Connective tissue diseases (CTDs) are characterized by dysregulation of the immune response, which leads to chronic systemic inflammation and destruction of multiple organ systems [1]. Dysregulation of the immune system and chronic inflammation are also important in cancer formation [2]. Indeed, patients with CTD are at increased risk for various malignancies including lung cancer (LC) [3–5]. In a historical cohort study of 33 autoimmune diseases, discoid/systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM) and systemic sclerosis (SSc) were associated with a high incidence of LC [3]. Because all of these CTDs are well known to present with lung manifestations including interstitial lung disease (ILD), autoimmune disorders in the lung have been thought to contribute to the initiation of LC [3].

ILD is a common form of organ dysfunction of CTD, and a high prevalence of ILD is seen in LC patients with CTD [6]. Among ILDs, idiopathic pulmonary fibrosis (IPF) is one of the most common comorbidities of LC, and the presence of ILD is an obstacle to the treatment of LC because idiopathic or iatrogenic acute exacerbations (AEs) of ILD frequently occur following various anticancer treatments, including surgery, irradiation, targeted therapy, and chemotherapy [7–10]. Although a large proportion of LC patients with CTD have concomitant ILD and the lung involvement is thought to be a limiting factor for cancer treatment, as is also true for IPF, few studies have examined the clinical features of LC in patients with CTD. Furthermore, the influence of ILD on the treatment and prognosis in these patients is unclear. Therefore, we conducted a retrospective analysis of the clinical features of LC in patients with CTD.

2. Patients and methods

2.1. Study population and design

Between January 2010 and July 2015, 27 patients (all Japanese) were diagnosed with primary LC with CTD at Tokushima University Hospital. We retrospectively analyzed the clinical features of these patients, including age, sex, smoking history, performance status (PS), histology, clinical stage, prevalence of ILD, underlying CTD type, treatment modality, and outcome. As a control cohort, 44 consecutive patients diagnosed with primary LC without CTD between January and December of 2012 at the same institution were also evaluated.

In all patients, the diagnosis of LC was confirmed by cytological and/or histological examinations. Epidermal growth factor receptor (EGFR) mutation status was determined by polymerase chain reaction amplification of exons 18 through 21 of the EGFR gene [11]. Histological types of LC were defined according to the World Health Organization classification, and the clinical stage was determined on the basis of the international tumor, node, metastasis (TNM) criteria for cancer staging. PS was assessed according to the Eastern Cooperative Oncology Group (ECOG) classification. The cumulative cigarette exposure (pack-years) was calculated by multiplying the average number of packs of cigarettes smoked per day by the number of years for smoking. The diagnosis of CTD was made according to the classification or diagnostic criteria for each disease [12–18]. A diagnosis of ILD was determined comprehensively on the basis of clinical features, pulmonary function testing, and the characteristic clinical presentations of ILD on chest high-resolution computed tomography (HRCT). Cases in which there were possibilities of treatment-related complications such as drug-induced lung toxicity and opportunistic infection were excluded. A usual interstitial pneumonia (UIP) pattern was diagnosed according to chest HRCT findings consistent with UIP pattern [19]. AEs of CTD-associated ILD (CTD-ILD) were defined using the proposed definition and diagnostic criteria of IPF, with a slight modification for CTD [20,21]. The current study was conducted in accordance with the guidelines of the Declaration of Helsinki and the ethical guidelines for epidemiological research in Japan and approved by the Institutional Review Board of Tokushima University Hospital (approval date: 2015/10/26, approval number: 2423). Information regarding the current study was disclosed to patients instead of obtaining their written informed consent, and patients who declined to participate in the study were excluded.

2.2. Statistical analyses

All comparisons between populations were performed using the χ^2 test, Fisher's exact test, or Student's *t*-test, as appropriate. Overall survival (OS) was defined as the time from date of diagnosis of primary LC to date of death from any cause. Patients who were alive at the time of analyses were censored at the last known date of follow-up. OS was estimated using the Kaplan–Meier method, and the log-rank test was used to assess differences in the OS distributions between groups. Results are reported as the mean ± standard error of the mean (SEM). Multivariate analyses were performed with the Cox proportional hazards model to identify variables that were independently predictive of outcome. Factors with *p*-values less than 0.05 on univariate analyses and clinically important factors were entered as candidate variables. Resulting *p*-values of less than 0.05 were considered to be significant. Statistical analyses were performed using GraphPad PRISM (5.01; GraphPad Software, Inc., La Jolla, CA, USA)

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