Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Analysis of acute exacerbation of interstitial lung disease associated with chemotherapy in patients with lung cancer: A feasibility of S-1

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ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form
17 October 2016
Accepted 30 October 2016

Keywords:
Interstitial lung disease
Acute exacerbation
Chemotherapy
Lung cancer

ABSTRACT

Background: Interstitial lung disease (ILD) is commonly concomitant with lung cancer, and its acute exacerbation (AE) is the most serious complication in patients receiving treatment for lung cancer.

Methods: To investigate the incidence and characteristic features of AE of ILD, we conducted a retrospective study of 665 consecutive patients with lung cancer who were treated at our institute between 2008 and 2014.

Results: Among the 665 patients, 74 (11.1%) had preexisting ILD, and 64 of them received chemotherapy. Four of the 64 patients (6.3%) had experienced AE of ILD, and two (3.1%) died of respiratory failure during first-line chemotherapy. The use of a combination of carboplatin with tegafur-gimeracil-oteracil potassium (S-1) or paclitaxel as a first-line chemotherapy for non-small cell lung cancer led to a lower frequency of AE, at 8.3% (1/12) and 9.1% (1/11), respectively. The incidence of AE rose to 12.8% (5/39) during second-line treatment, and 14 (total: 15 times) of the 64 patients (21.9%) experienced AE from the time of diagnosis to the end of treatment. The incidence of AE was 17.7% (6/34), 15.8% (3/19), 5.0% (2/40), and 4.2% (1/24) in the paclitaxel-, vinorelbine-, etoposide-, and S-1-containing regimens, respectively. No difference in clinical features and laboratory data was detected between the AE and non-AE groups.

Conclusions: Although this was a small retrospective study, its findings showed that S-1 and etoposide may be relatively safe options for the treatment of patients with lung cancer and concomitant ILD.

http://dx.doi.org/10.1016/j.resinv.2016.10.008
2212-5345/

Please cite this article as: Kakiuchi S, et al. Analysis of acute exacerbation of interstitial lung disease associated with chemotherapy in patients with lung cancer: A feasibility of S-1. Respiratory Investigation (2016), http://dx.doi.org/10.1016/j.resinv.2016.10.008

1. Introduction

Lung cancer (LC) is the leading cause of cancer death worldwide, and its mortality rate has been increasing. Some clinical trials have demonstrated that the platinum doublet provides a survival benefit and symptom relief for patients with unresectable LC [1]. However, patients with severe complications, such as interstitial lung disease (ILD), have been excluded from most clinical trials; therefore, it remains uncertain whether chemotherapy can really provide a survival benefit to these patients.

ILD affects the parenchyma or alveolar region of the lung, and it is detected as an interstitial shadow on chest radiography or high-resolution computed tomography (HRCT). ILD is usually characterized by slowly progressive respiratory insufficiency. Nevertheless, some patients with ILD experience acute exacerbation (AE) generally characterized by suddenly progressive and severe respiratory failure not due to pulmonary infection, and new lung opacities that are considered pathological lesions of diffuse alveolar damage (DAD). This clinical condition is lethal in many cases and significantly affects the prognosis of patients with ILD because of the lack of an established treatment.

The possible association between ILD and LC was first noted in a series of cases described over 40 years ago [2]. Several subsequent studies have reported that the incidence of LC in patients with idiopathic pulmonary fibrosis (IPF), which is the most common subset of ILD, is higher than that in the general population, whose relative risk reportedly ranges between 7.0 and 14.0 [3–9]. Recent research has identified that IPF is associated with an increased risk of LC [4].

ILD is a common comorbidity in patients with LC, and it is an obstacle to the treatment of LC, because idiopathic or iatrogenic AE frequently occurs after various anticancer treatments, including surgery, irradiation, targeted therapy, and chemotherapy [10–15]. However, there is no consensus on whether non-curative treatments, such as chemotherapy for advanced LC with ILD, are worthwhile in view of the risk of AE. Therefore, we conducted a retrospective study on the treatment of patients with LC and concomitant ILD to identify more effective and safer therapies.

2. Patients and methods

2.1. Patients and study design

From April 2008 through March 2014, 665 consecutive patients (all Japanese) underwent chemotherapy for primary LC at our institute. We retrospectively analyzed their clinical features, treatment modalities, chemotherapy regimens, and outcomes, and evaluated the various pretreatment clinical features as potential risk factors for AE of ILD.

All patients were histologically or cytologically diagnosed as having LC. The histological types of LC were defined according to the WHO classification [16], and the staging of LC was based on the new international TNM criteria for cancer staging. The performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients with LC were considered eligible for chemotherapy if their estimated life expectancy was 3 months or longer; they had ECOG PS 0–2 for non-small cell lung cancer (NSCLC) or 0–3 for small cell lung cancer (SCLC); and if they had adequate bone marrow, hepatic, and renal functions. The key exclusion criteria for chemotherapy were the presence of active infection, severe heart disease, uncontrolled diabetes mellitus, ileus, and bleeding tendency. Written informed consent was obtained from all enrolled patients after disclosing any risk and benefit of chemotherapy.

In this study, we included patients with LC who not only had comorbidities like idiopathic interstitial pneumonias (IIPs) but also connective tissue disease-interstitial lung disease (CTD-ILD). Therefore, we used the diagnostic term "ILD," which includes both IIPs and CTD-ILD. A diagnosis of ILD was determined in accordance with the American Thoracic Society/European Respiratory Society criteria [8,9]. In the absence of histological evidence, the diagnosis of ILD patterns was based on evidence from chest HRCT reviewed by three pulmonologists (SK, MH, and YN) and clinical features. Patients with usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), lymphoid interstitial pneumonia (LIP), or pleuroparenchymal fibroelastosis (PPFE) patterns on histological analysis or HRCT were also classified into an ILD group. The patients were initially categorized as those with

Abbreviations: LC, lung cancer; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; AE, acute exacerbation; DAD, diffuse alveolar damage; IPF, idiopathic pulmonary fibrosis; PS, performance status; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; IIP, idiopathic interstitial pneumonia; CTD-ILD, connective tissue disease-interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-interstitial lung disease; LIP, lymphoid interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; HR, hazard ratio; 95% CI, 95% confidence interval; CBDCA, carboplatin; S-1, tegafur-gimeracil-oteracil potassium; VP-16, etoposide; PTX, paclitaxel; PFS, progression-free survival; PEM, pemetrexed; VNR, vinorelbine; DTX, docetaxel; nab-PTX, nanoparticle albumin-bound-paclitaxel

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Please cite this article as: Kakiuchi S, et al. Analysis of acute exacerbation of interstitial lung disease associated with chemotherapy in patients with lung cancer: A feasibility of S-1. Respiratory Investigation (2016), http://dx.doi.org/10.1016/j.resinv.2016.10.008