Feasibility Study of Combined Chemotherapy for Advanced Lung Cancer with Idiopathic Interstitial Pneumonias and Proteomic Analysis to Detect Risk Factors for Their Acute Exacerbation

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Idiopathic interstitial pneumonias (IIPs) are among the most common complications in patients with lung cancer. In such patients, the most serious expression of the toxicity of anticancer treatment in Japan is the acute exacerbation of IIPs. However, there has been no consensus and no evidence presented regarding the optimal treatment for advanced lung cancer with IIP.

The results of our retrospective study of lung cancer with IIPs suggest that combined chemotherapy with carboplatin plus etoposide or carboplatin plus paclitaxel might be used for patients with small-cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) with IIPs. We, therefore, performed a prospective study of carboplatin plus etoposide and of carboplatin plus paclitaxel to assess their safety and potential efficacy for the treatment of advanced lung cancer with IIP.

From July 2002 through October 2008, 35 Japanese patients (28 men and 7 women), including 14 with idiopathic pulmonary fibrosis, were enrolled and treated with carboplatin plus etoposide for SCLC and with carboplatin plus paclitaxel for NSCLC. Two patients with idiopathic pulmonary fibrosis (5.7%), 1 receiving each treatment, had treatment-associated acute exacerbations of IIPs. The overall response rate, median progression-free survival, median survival time, and 1-year survival rate of patients with SCLC were 88%, 5.5 months, 8.7 months, and 29%, respectively. The overall response rate, median progression-free survival, median survival time, and 1-year survival rate of patients with NSCLC were 61%, 5.3 months, 10.6 months, and 22%, respectively. The antitumor efficacy was comparable to that in a randomized phase III study of Japanese patients without IIPs. We observed an incidence of treatment-related acute exacerbation of 5.7%. In previous studies in Japan, the incidence of chemotherapy-related acute exacerbation has ranged from 8.7% to 21%. The regimens carboplatin plus etoposide and carboplatin plus paclitaxel were effective for patients with advanced lung cancer with IIPs and appeared to be safer than suggested by previous reports.

In 2009, a national questionnaire survey for first-line chemotherapy for patients with lung cancer and IIPs was supported by a grant to the Diffuse Lung Diseases Research Group from the Ministry of Health, Labour and Welfare of Japan [The 2009 annual report of the Diffuse Lung Diseases Research Group]. The incidence of acute exacerbation associated with first-line chemotherapy was 13.1%. The main regimens were carboplatin plus paclitaxel and a platinum agent plus etoposide and were used for 100 cases (25%) and 80 cases (15%), respectively. The incidence of treatment-related acute exacerbation was 5% and 6%, respectively. These rates were lower than the mean incidence in this survey and that in previous reports. The results of this survey support our prospective studies.

To further confirm the usefulness of carboplatin plus etoposide and paclitaxel for treating advanced lung cancer, a larger prospective study is necessary.

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cancer with IIP, we are now carrying out a larger-scale clinical trial with detailed evaluation, including proteomic analysis, to identify risk factors for acute exacerbation. Studies of carboplatin plus etoposide for SCLC and paclitaxel for NSCLC were approved by the Institutional Review Board in March 2009. We initially planned to enroll 35 patients in each arm. The primary endpoint is the incidence of treatment-related acute exacerbation, and secondary endpoints include the response rate, progression-free survival, the overall survival rate, and toxic effects.

Proteomics is a powerful tool for investigating the distribution of proteins and small molecules within biological systems through the analysis of different types of sample. To investigate aberrant plasma proteins to predict acute exacerbation, we have planned to compare the proteomic profiles of sera from subjects with or without acute exacerbation. Immunoaffinity chromatography was used to deplete highly abundant plasma proteins, and the resulting plasma samples were separated into 8 fractions by means of anion-exchange chromatography. Quantitative protein profiles of the fractionated samples were generated with two-dimensional difference gel electrophoresis, in which the experimental samples and the internal control samples are labeled with different dyes and co-separated with 2-dimensional polyacrylamide gel electrophoresis. We believe the combination of multidimensional liquid chromatography and two-dimensional difference gel electrophoresis is a valuable tool for serum proteomics in lung cancer with IIPs. Enrollment is proceeding smoothly.

**References**