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Clinical characteristics of non-small cell lung cancer patients who experienced acquired resistance during gefitinib treatment

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ABSTRACT

Background: The NSCLC patients who experienced good clinical responses to an EGFR-TKI will inevitably develop acquired resistance. A great deal of research is being carried out to discover the molecular mechanisms underlying this resistance. In comparison, few studies have been conducted to find out about the clinical characteristics of acquired resistance in the patients who had responded to an EGFR-TKI. Herein we investigated clinical characteristics of NSCLC patients who experienced acquired resistance during gefitinib therapy.

Patients and methods: We reviewed NSCLC patients who showed a clinical benefit from initial gefitinib therapy. All clinical data were obtained from 11 centers of Korean Molecular Lung Cancer Group (KMLCG). The clinical manifestations of acquired resistance, time to progression (TTP), and post-progression survival (PPS) after gefitinib failure were analyzed retrospectively.

Results: A total of 417 patients were recruited. Median TTP was 10.2 months (95% CI, 9.5–10.9). TTP showed a significant longer duration in female, non-smoker, and patients with adenocarcinoma. At the time of acquired resistance, 63.3% of the patients showed symptomatic deterioration. Sites of disease progression were as follows: primary lung lesion in 58.4%, previous metastasis in 38.3%, and new metastasis in 54.2%. Patients with *EGFR* wild type showed a tendency of higher frequency in symptomatic deterioration and newly development of CNS metastasis compared with patients with *EGFR* mutation. There was a significant difference in newly development of lung metastasis between patients with exon 19 deletion and those with L858R mutation (41.4% vs. 6.3%, $p = 0.02$). PPS was 8.9 months (95% CI, 7.4–10.4). Smoking history, PS, new CNS lesion and subsequent chemotherapy were independent factors for PPS.

Conclusion: This study suggests that clinical manifestations of acquired resistance may be different according to *EGFR* mutation status and *EGFR* mutation genotype. In addition, subsequent chemotherapy confers clinical benefit in terms of PPS in NSCLC patients who experienced acquired resistance after gefitinib therapy.

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality, with an estimated 1.4 million deaths in 2008 globally [1]. The main reason for the high mortality is that most patients are diagnosed with advanced stage disease. At the time of initial diagnosis, more than 80% of all lung cancer cases are non-small cell lung cancer (NSCLC) and approximately 70% of patients with NSCLC are affected by advanced disease, stage IIIB or IV [2].

A few years ago, platinum-based doublet chemotherapy was best treatment option for patients with advanced NSCLC, who have a good performance status (PS) [3,4]. However, traditional chemotherapy provides the limited gains as it prolongs overall survival (OS) by only a few months in these patients compared with supportive care [4]. Because phase III randomized trials have shown that many of the platinum-doublet combinations have similar objective response rates and survival, the benefit of standard chemotherapy would appear to have reached a plateau [5–8]. In order to overcome this problem, recent research efforts have focused on the development of targeted agents and the integration of targeted agents into the treatment algorithm.

Given the importance of epidermal growth factor receptor (EGFR) in the development and progression of NSCLC [9], EGFR-targeted agents have been developed, including the small molecule, selective and reversible EGFR-tyrosine kinase inhibitor (EGFR-TKI), gefitinib (IRESSA, AstraZeneca). Gefitinib have been widely used for patients with NSCLC, especially Asians. Higher response of gefitinib was associated with certain clinical characteristics – never smokers, women, Asian ethnicity and adenocarcinoma histology [9,10]. Activating EGFR mutations were also more prevalent in these groups, suggesting they may determine sensitivity to gefitinib [11–13]. In the Iressa Pan-Asia Study (IPASS), a phase III trial conducted in chemo-naïve Asian patients with advanced adenocarcinoma of the lung who were either never smokers or light smokers, subgroup analysis confirmed that these predictive factors, especially EGFR mutation status were important in deciding gefitinib treatment [14].

Although gefitinib treatment leads to a significant clinical benefit in select patients with NSCLC, all responders will ultimately suffer disease progression. Several resistant mechanisms have been identified, such as T790M, MET amplification, activation of alternative pathways (IGF-1, HGF, PI3CA, AXL), and transformation to mesenchymal cells or small cell features [15–21]. The secondary mutation in EGFR (T790M) accounts for approximately half of acquired resistances to EGFR-TKI, and the next is MET amplification in 20% of patients. Many researches on acquired resistance were focused on molecular mechanisms and method to overcome resistance, while a few researches showed the clinical data of acquired resistance to gefitinib [22–26].

In this study, we evaluated the clinical patterns of acquired resistance, time to progression (TTP), and post-progression survival (PPS) after gefitinib failure in Korean NSCLC patients who respond to gefitinib therapy.

2. Patients and methods

2.1. Patients

We conducted a retrospective multicenter study at Chonnam National University Hwasun Hospital; Chungnam National University Hospital; Hallym University Medical Center; Inha University Hospital; Konkuk University Medical Center; Konyang University Hospital; Korea Cancer Center Hospital; Korea University Guro Hospital; Kosin University Gospel Hospital; Pusan National University Hospital; and Yeungnam University Medical Center, from April 2002 through November 2009. Candidates were carefully screened for eligibility using the following criteria: (1) histological or cytological confirmation of advanced NSCLC, (2) objective clinical benefit from gefitinib monotherapy, and (3) experienced progression of disease despite the maintenance of gefitinib. Using the criteria for acquired resistance proposed by Jackman et al. [27], objective clinical benefit was defined by either: complete or partial response (CR or PR), or durable stable disease ($\geq$6 months) after initiation of gefitinib. Cases were excluded by any of the following criteria: (1) treatment with gefitinib or erlotinib before enrollment of this study, (2) combined systemic therapy with gefitinib, and (3) cessation of gefitinib without identifying progressive disease (PD). We reviewed clinical, pathological, and radiological data, and follow-up information obtained until May 2010. The study protocol was approved by the Ethical Review Committees of the local institutions.

2.2. Evaluation of treatment response

Baseline assessment including a history and physical examination, complete blood count, comprehensive blood chemistries, chest radiography and chest computed tomography (CT), was performed before starting treatment. The patients received routine chest radiography every 1–2 months, and chest CT every 2–3 months to assess the tumor response, according to the Response Evaluation Criteria in Solid Tumors (RECIST) [23]. To evaluate extra-pulmonary symptoms and to detect any change in pre-existing metastatic lesions, additional procedures such as CT, magnetic resonance imaging (MRI), bone scintigraphy (BS) and positron emission tomography/CT (PET/CT) were performed.

2.3. Statistical analysis

TTP was defined as time until PD after initial gefitinib therapy. PPS was defined as the period from PD to death. Data are expressed as median values. Comparisons of categorical variables between the different groups were made with the Pearson's chi-square test or Fisher exact test. The independent t test for continuous variables was performed for means between different groups. Clinical evaluation of TTP and PPS was estimated by the Kaplan–Meier method. The log-rank test was used to compare the survival outcome with different potential factors. Cox proportional hazard analysis using the forward stepwise method was performed to explore the effect of each variable on PPS. All P values reported are the results of two-sided tests, and values less than 0.05 were considered significant. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

From April 2002 to November 2009, 417 patients were enrolled in the study. Patients' characteristics are summarized in Table 1. The median age was 63 years (range 26–87 years). Patients included 258 (61.9%) female, 276 (67.5%) never-smokers, 333 (81.4%) with PS 0–1, 325 (82.7%) with adenocarcinoma, 332 (79.6%) with stage IV disease. In addition, metastases to multiple organs were found in 134 patients (32.2%). Metastases to the lung, bone, central nervous system (CNS), pleura, liver, and adrenal gland were found in 165 (39.7%), 157 (37.7%), 87 (20.9%), 24 (5.8%), 23 (5.5%), and 24 (5.8%) patients, respectively. Forty-five patients (11.6%) received gefitinib as the first-line therapy, 147 (37.9%) second-line, 136 (35.1%) third line, and 60 (15.5%) further lines. Best responses to gefitinib therapy were as follows: CR in 2 patients (0.4%), PR in 273 (65.5%), and stable disease (SD) in 142 (34.1%).