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Association of pharmacokinetics and pharmacogenomics with safety and efficacy of gefitinib in patients with *EGFR* mutation positive advanced non-small cell lung cancer

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ABSTRACT

Objectives: Gefitinib is a potent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and is a key drug for patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC). The pharmacokinetics of orally administered gefitinib varies greatly among patients. We prospectively evaluated the association of pharmacokinetics and pharmacogenomics with the safety and efficacy of gefitinib in patients with *EGFR* mutation-positive advanced NSCLC.

Patients and methods: Pharmacokinetics was evaluated with samples of peripheral blood obtained on day 1 before treatment and 1, 3, 5, 8, and 24 h after gefitinib (250 mg per day) was administered and on days 8 and 15 as the trough values. The plasma concentration of gefitinib was analyzed with high-performance liquid chromatography. The genotypes of *ABCG2, ABCB1, CYP3A4, CYP3A5,* and *CYP2D6* genes were analyzed with direct sequencing.

Results: The subjects were 35 patients (21 women; median age, 72 years; range, 53 to 90 years) with stage IV adenocarcinoma harboring *EGFR* mutations. The median peak plasma concentration (C_{max}) was 377 (range, 168–781) ng/mL. The median area under the curve (AUC) of the plasma concentration of gefitinib from 0 to 24 h was 4893 (range, 698–13991) ng/mL h. The common adverse events were skin toxicity (68% of patients), diarrhea (46%), and liver injury (63%). One patient died of drug-induced interstitial lung disease (ILD). The overall response rate was 82.9% (95% confidence interval, 66.4%–93.4%). The median progression-free survival time was 10 months, and the median survival time was 25 months. The pharmacokinetics and pharmacogenomics were not associated with significantly different toxicities, response rates, or survival times with gefitinib. However, the AUC and C_{max} were highest and the trough value on day 8 was the second highest in one patient who died of drug-induced ILD.

Conclusion: Elevated gefitinib exposure might be associated with drug-induced ILD.

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1. Introduction

Somatic mutations of the epidermal growth factor receptor (EGFR) gene, *EGFR*, were first discovered in 2004 as a predictive marker for treatment with EGFR tyrosine kinase inhibitor (TKI) in patients with advanced non-small cell lung cancer (NSCLC) [1,2]. Phase III trials in patients with *EGFR* mutation-positive advanced NSCLC have found that EGFR-TKI is superior to platinum doublet cytotoxic chemotherapy [3–6]. Thus, for such patients EGFR-TKI is now globally considered the standard first-line treatment.

Gefitinib is a potent EGFR-TKI that is metabolized in the liver, mainly by cytochrome P450 (CYP) 3A4/3A5, and, to lesser extent, by CYP2D6 and CYP1A1. After being metabolized, gefitinib is transported by the active efflux pumps *P*-glycoprotein (ATP-binding cassette [ABC], sub-family B, member 1 [ABCB1]) and breast cancer resistance protein (BCRP, ABC, sub-family G, member 2 [ABCG2])

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[7–9]. After oral absorption of gefitinib, its pharmacokinetics shows large variability among patients [10]. These pharmacokinetics differences might be attributed to polymorphisms of the genes of CYPs, ABCB1, and ABCG2.

After being administered for treatment, gefitinib causes numerous toxicities, the most common of which are skin toxicity, diarrhea, and liver injury [3,4]. The most severe, yet rare, toxicity is a drug-induced interstitial lung disease (ILD) [11]. Such toxicities sometimes cause gefitinib therapy to be discontinued. The severity of these toxicities is different in each patient. The most common toxicities have been suggested, by several previous studies, to be related to the plasma concentration of gefitinib [10,12–14]. However, it remains unclear whether common toxicities are related to the plasma concentration of gefitinib when it has been administration at a dose of 250 mg because large studies have not been reported [10,14]. Additionally, the relationship of the plasma concentration of gefitinib to gefitinib-related ILD has not, to our knowledge, been previously reported.

The association between the toxicity of gefitinib and pharmacogenomics has been controversial. Polymorphism of *ABCG2* is reportedly associated with the occurrence of diarrhea due to gefitinib [15]. On the other hand, other studies have reported no associated between gefitinib-induced toxicities and genetic polymorphisms including those of *ABCG2* [14,16].

Of patients with *EGFR* mutation-positive advanced NSCLC, 20%–30% show intrinsic resistance to EGFR-TKI [3,4]. The mechanisms of intrinsic resistance are poorly understood, despite various mechanisms for acquired resistance having been identified [17,18]. In one study a ratio of plasma trough levels of gefitinib on day 8 and day 3 of administration of gefitinib was reportedly associated with a progression-free survival (PFS) time; however, the results are inconclusive because the study included patients with advanced NSCLC either negative or positive for *EGFR* mutation [19]. Until now, the relationship between the efficacy of gefitinib and its pharmacokinetics and pharmacogenomics in patients with *EGFR* mutation-positive advanced NSCLC has been unclear. The pharmacokinetics and pharmacogenomics might possibly be mechanisms of the intrinsic resistance to EGFR-TKI.

Therefore, clarifing the association of pharmacokinetics and pharmacogenomics with the toxicity and efficacy of gefitinib is important. In the present study, we aimed to clarify (1) the association of pharmacokinetics with pharmacogenomics, (2) the association of pharmacokinetics and pharmacogenomics with toxicity of gefitinib, and (3) the association of pharmacokinetics and pharmacogenomics with efficacy of gefitinib in patients with *EGFR* mutation-positive advanced NSCLC.

2. Patients and methods

2.1. Study participants and treatment

From October 2009 through December 2012, 35 patients with *EGFR* mutation-positive advanced NSCLC were prospectively enrolled in this study. The eligibility criteria were as follows: histologically or cytologically proven *EGFR* mutation-positive NSCLC, unresectable and ineligible for thoracic radiotherapy, stage IIIB or IV disease, 20 years or older, no prior treatment of EGFR-TKI, Eastern Cooperative Oncology Group performance status of 0–3, a measurable lesion, and adequate bone marrow function (neutrophil count of 1500/μl or more, platelet count of 100,000/μl or more, and hemoglobin level of 8.0 g/dl or more), renal function (serum creatinine levels less than 1.5 mg/dl), and hepatic function (total serum bilirubin level less than 2.0 mg/dl, aspartate aminotransferase and alanine aminotransferase levels less than or equal to 2.5 times the upper limits of the normal ranges). Patients were excluded if they had ILD, active infections, severe heart disease, uncontrolled diabetes mellitus, second malignancy, or taken a medicine that affected CYP3A4, a proton-pump inhibitor, or a histamine H2 receptor antagonists. Gefitinib was administered orally once daily at a dose of 250 mg until disease progressed or severe adverse events occurred. This study protocol was approved by the Ethics Committee of Showa University School of Medicine. We obtained written informed consent from all patients.

2.2. Pharmacokinetics and pharmacogenomics analysis

The evaluation of pharmacokinetics was performed with samples of peripheral blood obtained on day 1 before treatment and 1, 3, 5, 8, and 24 h after the first administration of 250 mg of gefitinib. Additionally, the samples of peripheral blood were obtained before administration of gefitinib on days 8 and 15 to determine the trough value. The samples were centrifuged immediately, and the plasma was stored at −80°C until analysis. The plasma concentration of gefitinib was analyzed with high-performance liquid chromatography following the method of Faivre et al [20]. We determined the plasma concentration-time profiles from 0 to 24 h on day 1 of the first administration of gefitinib. The peak plasma concentrations (C_{max}) and the interval required to reach the peak concentration (Tmax) were obtained directly from the profile. The median area under curve (AUC) of the plasma concentration of gefitinib from 0 to 24 h was calculated with the linear trapezoidal rule.

Genomic DNA was extracted from 200 μL of peripheral blood, which had been stored at −80°C until analysis. The genotypes of *ABCB1 1236C>T, ABCB1 2677G>T or A, ABCB1 3435C>T,* and *ABCG2* 421C>A were analyzed with direct sequencing following the method by Akiyama et al. [21]. The genotypes of *CYP3A4 20230G>A, CYP3A4 15603C>G, CYP3A4 20070T>C, and CYP3A4 20148A>G* were analyzed with direct sequencing following the method by Eiselt et al. [22]. The genotype of *CYP3A5 6986A>G* was analyzed with direct sequencing following the method by Saeki et al. [23]. The genotype of *CYP2D6 *1/*1, 10, or 36* was analyzed with direct sequencing following the method by Soyama et al. [24].

2.3. Clinical evaluation

The evaluation before treatment with gefitinib included a baseline history, physical examination, complete blood count with differential, routine chemistry profiles, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging or CT of the brain, and a radionucleotide bone scan or positron-emission tomography. Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors criteria version 1.1. The toxicity of gefitinib was evaluated according to the National Cancer Institute Common Terminology Criteria for adverse events 4.0.

The association between the pharmacokinetics of gefitinib and the pharmacogenomics was prospectively evaluated in patients with *EGFR* mutation-positive advanced NSCLC. Also evaluated in these patients were the associations of pharmacokinetics and pharmacogenomics with skin toxicity, mucosal toxicity, diarrhea, nausea, liver injury, and the pulmonary toxicity and efficacy of gefitinib.

2.4. Statistical methods

Overall survival time was measured from the start of the present treatment until death or the last follow-up examination. The PFS time was measured from the start of treatment to the identifiable time of progression. The Kaplan–Meier method was used to construct survival curves. Survival differences between patients with lower than median AUC, $_{Cmax}$, or trough values and higher than

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