Clinical Significance of Heterogeneity in Response to Retreatment With Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Lung Cancer Acquiring Secondary Resistance to the Drug

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Abstract

To elucidate clinical significance of heterogeneity in response to retreatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), tumor response to second EGFR-TKIs was assessed per patient and per organ in 68 patients. Of 35 cases of progressive disease, 22 (62.8%) showed mixed response. The organ type and prior drug sensitivity at the failure time of first EGFR-TKIs may predict the efficacy of second EGFR-TKIs in organs.

Background: In patients with lung cancer acquiring resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), an intrapatient heterogeneity in response to retreatment with EGFR-TKIs remains to be elucidated. **Patients and Methods:** Records were retrospectively reviewed for 68 patients with advanced non–small-cell lung cancer who received second EGFR-TKIs after systemic progression that followed durable response to the first EGFR-TKIs. All tumor lesions identified on radiologic images before second EGFR-TKIs were categorized into organs. Tumor response to EGFR-TKIs was assessed per patient and per organ. Mixed response (MR) was defined as the coexistence of at least 2 responsive and progressive organs. **Results:** Tumor lesions were detected in 244 organs. The response rate (RR) and median time to progression (TTP) to second EGFR-TKIs for patients were 26.5% and 11.6 weeks (95% CI, 8.5-14.7 weeks), and the RR and median TTP for organs were 38.8% and 17.3 weeks (95% CI, 14.8-19.8 weeks). Of 35 patients categorized to progressive disease, 22 (62.8%) showed MR. Among organs, the RR was highest for the central nervous system (CNS) and lowest for the liver (CNS vs. others vs. liver: 77.8%, 36.9%, 17.6%; $P < .001$). Multivariate analysis confirmed the organ type and prior drug sensitivity at the time of stopping first EGFR-TKIs as predictors for the risk of progression to second EGFR-TKIs in organs. **Conclusions:** Intrapatient heterogeneity in response to second EGFR-TKIs is not a rare event. The organ type and prior drug sensitivity at the failure time of first EGFR-TKIs may predict the efficacy of second EGFR-TKIs in individual organs.

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have good efficacy in patients with non–small-cell lung cancer (NSCLC) harboring sensitizing *EGFR* mutations.[1] Several randomized controlled clinical studies found that the first-generation EGFR-TKIs as first-line treatment had response rates of 60% to 80%, median progression-free survival (PFS) of 9 to 13 months, and median overall survival (OS) of 19 to 31 months; these values were superior to those of standard chemotherapy in patients with advanced *EGFR*-mutant or mutation-enriched NSCLC.[2-7] However, most patients with *EGFR*-mutant lung cancer who initially benefit from EGFR-TKI therapy eventually acquire secondary resistance to the drug and experience progressive disease

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(PD). Appropriate therapies after progression on EGFR-TKIs have not yet been established.

As an alternative treatment in such patients acquiring secondary resistance to EGFR-TKIs, retreatment with the same class of drugs has been tried in several clinical studies. Although some studies reported that a few patients respond again to EGFR-TKIs,[8-10] other studies questioned the effectiveness of retreatment in the tumors having already acquired genomic alterations, such as *EGFR* T790M mutations or *MET* (met proto-oncogene) amplification, which make them resistant to these drugs.[11,12] Vasile et al[8] found that 8 patients with advanced NSCLC previously responding to gefitinib had a 25% response rate to retreatment with gefitinib, whereas Costa et al[12] reported that 18 patients with lung cancer having *EGFR* mutations had only a 6% response rate to erlotinib after gefitinib failure. Moreover, the authors have sometimes encountered patients who had mixed responses to retreatment with EGFR-TKIs in actual practice. This phenomenon may contribute to the inconsistent results of the prior studies.

The aim of this study was to assess the occurrence of heterogeneity in responses to retreatment with EGFR-TKIs in patients with advanced NSCLC who received second EGFR-TKIs after systemic progression that followed durable response to the first EGFR-TKIs. Additionally, this study tried to identify clinical markers to predict which tumor lesions will be responsive or progressive on second EGFR-TKI treatment in this patient population.

Patients and Methods

Patients and Data Collection

The authors identified 119 patients with advanced NSCLC who had been re-treated with gefitinib or erlotinib at the National Cancer Center Hospital (Goyang, South Korea) between July 2003 and March 2009 by using pharmacy disposition records. Among them, 68 patients were selected who fulfilled the following criteria: (1) clinical benefits from first EGFR-TKIs treatment (responder or PFS $\geq$ 6 months), (2) systemic progression while on first EGFR-TKIs, and (3) treatment with chemotherapy between first and second EGFR-TKIs. The Institutional Review Board at the National Cancer Center Hospital approved this study. As this was a retrospective study, the Institutional Review Board waived the requirement for informed consent.

Tumor Response Assessment

Tumor responses were generally assessed every 8 weeks by computed tomography and other imaging techniques. Tumor lesions were identified on radiologic images including computed tomography, magnetic resonance imaging, whole-body bone scan, or positron emission tomography scans. All tumor lesions were categorized according to the affected organ such as primary lesions (primary lung tumor and locoregional lymph nodes), lung, central nervous system (CNS), liver, bone, pleura, distant lymph nodes, and other organs. Tumor response was assessed per organ longitudinally from initial use to reuse of EGFR-TKIs. For each organ individually, a sum of the longest diameters of 1 to 5 target lesions was calculated, and tumor response was determined on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[13] Mixed response (MR) was defined as at least 2 organs within a patient with a different response (response vs. progression).

EGFR *Mutation Analysis*

Tests for mutations of the *EGFR* gene were performed in tumor biopsy specimens retrieved from 14 patients. Nucleotide sequencing of the kinase domain of the *EGFR* gene (exons 18, 19, 20, and 21) was done by using nested polymerase chain reaction amplification of the individual exons. The details of the sequencing procedure are described elsewhere.[14]

Statistical Analyses

The association between 2 categorical variables was analyzed by the χ^2 test or the Fisher exact test. Time to progression (TTP) was measured from the first day of starting second EGFR-TKIs treatment until the identification of PD. If new systemic chemotherapy had been administered or any cause of death had been observed without documented disease progression on the given tumor lesion, it was censored at the date of the last imaging evaluation. OS was calculated from the first day of starting second EGFR-TKIs treatment until death or the most recent follow-up. Survival time was estimated using the Kaplan-Meier method and was compared between groups using the log-rank test. The Cox proportional hazards model was used for univariate and multivariate survival analyses. Two-sided values of $P < .05$ were considered statistically significant.

Results

Patient and Treatment

Among 68 patients, the proportions who were female, had adenocarcinoma histology, and had never-smoker status were 79.4%, 95.6%, and 83.8%, respectively (Table 1). Among 14 available to *EGFR* mutation test, sensitive *EGFR* mutations were detected in 13 patients (exon 19 deletion mutation [n = 7] and L858R mutation in exon 21 [n = 6]). The patients had a complete response (CR) (n = 1) or partial response (PR) (n = 67) to first EGFR-TKIs, with a median PFS of 8.9 months (95% confidence interval [CI], 6.2-11.6 months). The median time from initial EGFR-TKI failure to restarting was 9.8 months (range, 2.1-22.4 months). The median number of chemotherapy regimens administered during the TKI-free period was 3 (range, 1-6). Survival data were evaluated until the end of July 2012. The median duration of follow-up from diagnosis was 38.9 months (95% CI, 34.7-44.5 months). The median OS was 38.4 months (95% CI, 33.4-43.4 months) from diagnosis and was 7.8 months (95% CI, 5.4-10.2 months) from the start of second EGFR-TKIs.

Incidence of MR

Tumor lesions were detected in 179 organs of 68 patients at the baseline evaluation before first EGFR-TKIs were started. In 107 organs having measurable tumor lesions, CR, PR, and stable disease (SD) were 3 (2.8%), 96 (89.7%), and 8 (7.5%), respectively. On the other hand, tumor lesions were detected in 244 organs before second EGFR-TKIs. The median number of affected organs per patient was 4 (range, 2-6). Of 244 organs, 65 (26.6%) were primary lesion, 50 (20.5%) were lung, and 36 (14.8%) were CNS. Among 134 organs with measurable lesions, the response rate and disease control rate were 38.8% and 79.9%, respectively. The response rate and disease control rate for patients were 26.5% and 48.6%, respectively. Among 35 patients whose best overall response to second EGFR-TKIs was PD, 22 (62.8%) had MR. An example of