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Evaluation of Epidermal Growth Factor Receptor Mutation Status in Serum DNA as a Predictor of Response to Gefitinib (IRESSA)

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In a previous study, we showed that *EGFR* mutation status in serum DNA was useful as a predictor of response to gefitinib (IRESSA). The aim of this study was to assess the feasibility of detecting EGFR mutations in serum DNA and to evaluate the usefulness of *EGFR* mutation status in serum DNA as a means of predicting a benefit from gefitinib therapy in Japanese patients with NSCLC. We obtained pairs of tumor and serum samples from 42 patients treated with gefitinib and examined them for *EGFR* mutations. *EGFR* mutation status was determined by a direct sequencing method and by Scorpion Amplification Refractory Mutation System (ARMS) technology. *EGFR* mutations were detected in the tumor samples of eight patients and in the serum samples of seven patients. *EGFR* mutation status in the tumors and serum samples was consistent in 39 (92.9%) of the 42 pairs. *EGFR!* mutations were more frequent in women and non-smokers, and there were strong correlations between both *EGFR* mutation status in the tumor samples and serum samples, and objective response to gefitinib ($p<0.001$, Fisher's exact test). Median progression-free survival time was significantly longer in the patients with *EGFR* mutations than in the patients without *EGFR* mutations (194 vs. 55 days, $P=0.016$, in tumor samples; 174 vs. 58 days, $P=0.044$, in serum samples, Log-rank test). Median survival time was longer in the patients with *EGFR* mutations detected by either of the two methods than in the patients without *EGFR* mutations, but the difference was not statistically significant. The results suggest that it is feasible to use serum DNA to detect *EGFR* mutations, and that it's potential as a predictor of response to, and survival on gefitinib is worthy of further evaluation.

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Epidermal growth factor receptor (EGFR) gene mutational status and response to gefitinib in patients with non-small cell lung cancer: A prospective study

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Background: Somatic EGFR gene mutations are reported to be associated with clinical responses to gefitinib and erlotinib in patients with non-small cell lung cancer (NSCLC). Retrospective studies have shown around 75% response rate in patients with tumors that have EGFR gene mutations compared with a response rate of less than 10% in those with wild-type EGFR. We prospectively examined the status of EGFR gene mutations in patients with NSCLC and their response to treatment with gefitinib.

Methods: Clinical samples (formalin-fixed paraffin-embedded tumor tissue, pleural effusion, and sputum) were obtained with informed consent from patients with advanced NSCLC at Toranomon Hospital, and were examined for EGFR mutations by direct sequencing or the peptide nucleic acid-locked nucleic acid PCR clamp method (Cancer Res. 2005;65:7276). Patients who received gefitinib therapy after examining EGFR mutations were then evaluated for their response to gefitinib according to RECIST criteria.

Results: Tumor samples from 60 patients who were enrolled in the study from June 2006 to January 2007 were analyzed. EGFR mutations were detected in 17 of 60 patients (28.3%) (13 females/4 males; 16 never-smokers/ 1 former-smoker; all adenocarcinomas). Detected mutations included 9- to 18-base deletion in exon 19 in 12 patients (70.6%), L858R in exon 21 in 4 (23.5%) and an 18-base insertion in exon 19 in 1 (5.9%), respectively. Ten of 17 patients with EGFR mutations were given gefitinib 250 mg daily (median age: 67 years; 9 females/1 male; all never-smokers; performance status 0-1/2-4=6/4; stage IIIB/IV/postoperative recurrence=2/3/5). Four patients were treated with gefitinib as the first-line therapy. Nine patients had measurable lesions, and the response to gefitinib was PR in four patients, SD in three, and PD in two, respectively. The response rate and disease control rate were 44.4% and 77.8%, respectively. On the other hand, four of 43 patients with wild-type EGFR received gefitinib, but none of these patients achieved CR or PR. No significant adverse events (>grade 3) including acute lung injury/interstitial pneumonia were observed.

Conclusion: EGFR mutations were found in the tumors of 28% of Japanese patients with NSCLC. The disease control rate of gefitinib therapy was extremely good in those who had EGFR mutations. Thus, routine evaluation for the EGFR mutation status is desirable in patients with NSCLC before treatment of gefitinib.

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Response to erlotinib in the neoadjuvant setting for early stage non-small cell lung cancer (NSCLC): a case report

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Background: Erlotinib as single agent is associated with objective response rates of about 12% in unselected patients with NSCLC stage IIIB/IV. Much higher response rates were observed in selected groups of patients selected on the basis of EGFR mutations. To investigate whether erlotinib is able to make an extra contribution to surgical treatment of early stage NSCLC, a phase II study was initiated in the Netherlands. This study is meant to provide a proof of principle if erlotinib is a worthwhile induction therapy option and if erlotinib may be advised as induction regimen for a selected group of patients. We report a remarkable response in one of our first patients.

Case Presentation: A 58-year old woman presenting with a clinical stage I adenocarcinoma in the right upper lobe was asked to participate in the study. After written informed consent, she received erlotinib for

3 weeks according to protocol and consecutively underwent surgical resection. Radiological and metabolic response was measured by [18F]-FDG-PET/CT after 3 and 21 days, and postoperatively the pathological response was assessed in the resection specimen.

Results: Our patient had developed grade 2 skin toxicity in the third week of erlotinib treatment. Evaluation after 3 days and 21 days with [18F]-FDG-PET showed no appreciable metabolic response and stable disease on CT. A lobectomy of the right upper lobe with lymph node dissection was carried out. Pathological evaluation showed strong fibrotic degeneration of the original tumor, with a vital rest of less than 10%. All lymph nodes were free of tumor. The low percentage of tumor cells did not allow for EGFR mutation analysis. There were no postoperative complications, and skin toxicity dissolved spontaneously after cessation of erlotinib.

Conclusions: In this patient with stage I adenocarcinoma of the right lung, receiving 3 weeks of preoperative erlotinib resulted in near complete pathologic response. This result shows that erlotinib could be a potent agent in neoadjuvant and/or adjuvant setting in the treatment of non-small cell lung cancer.

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Analysis of the relationship between the mutations of the *EGFR* and response to gefitinib treatment in patients with recurrent lung cancer after pulmonary resection; updated analysis

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Background: Somatic mutations in the epidermal growth factor receptor (*EGFR*) gene have been reported to be present in non-small-cell lung cancer, and associated with sensitivity of tumors to EGFR tyrosine kinase inhibitors. We previously reported on positive correlation of *EGFR* mutations with effectiveness of gefitinib treatment in 59 patients with recurrence after pulmonary resection (JCO, 23: 2513-2510, 2005). Here, we report the result of updated analysis based on 103 patients, adding 44 patients, with longer follow-up.

Methods: We sequenced exons 18-21 of the *EGFR* gene using total RNA extracted from 103 patients with lung cancer who were treated with gefitinib for their recurrent disease. Because this study was a retrospective analysis of clinical practice, the evaluation of tumor response could not be performed strictly according to Response Evaluation Criteria in Solid Tumors. Therefore tumor response to gefitinib treatment was evaluated by both the imaging studies and the change in serum carcinoembryonic antigen (CEA). Gefitinib treatment was judged as effective when the tumors showed at least a 30% decrease in tumor diameter or when the elevated serum CEA level decreased to a level less than half of the baseline level.

Results: *EGFR* mutations were detected in 61 of 103 tumors (59%). Of them, 31 were exon 19 deletions, 22 were L858R, three were G719X, three were insertions in exons 19 or 20, and two were other types of point mutations. Mutations were significantly frequent in female (72% in female, 48% in male) (P=0.0131, χ^2 test), never-smokers (73% in never-smokers, 48% in former or current smokers) (P=0.0082), and the patients with adenocarcinomas (65% in adenocarcinomas, 17% in non-adenocarcinomas) (*P*=0.0031). The response to gefitinib treatment was assessable in 88 patients, and 51 patients were evaluated as effective (the response rate (RR) was 58%). The RR in the patients with *EGFR* mutations was 83% (45 of 54 patients was effective), whereas the RR in those without mutation was 18% (6 of 34 patients was effective). Logistic regression analysis using various factors (sex, age, smoking status, histology, existence of prior chemotherapy, pathological stage, status of *EGFR* mutation) showed that *EGFR* mutation (odds ratio 53.666, P<0.0001) and absence of prior chemotherapy (odds ratio 5.979, P=0.0143) were significant factors contributing to the response. Patients with *EGFR* mutation survived for a significant longer period than those without mutations after gefitinib treatment (MST, 30.1 versus 10.6 month; P=0.0038, log-rank test). When the patients with *EGFR* mutation were divided to subgroups according to the types of *EGFR* mutations, the RRs of each group were differed (93% in exon 19 deletions, 75% in L858R, 67% in G719X, and 0% in exon 19 insertion). However, there was no difference in overall survival after gefitinib treatment between the patients with two major types of mutation (MST, 36.0 month in exon 19 deletions versus 33.1 month in L858R; P=0.7247).

Conclusions: We confirmed that the tumors with *EGFR* mutations showed good correlation with clinical response to gefitinib treatment in patients with recurrent lung cancer after pulmonary resection in this updated analysis. Furthermore, we found that there were differences in the RR among the classes of mutations.

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Safety of gemcitabine and carboplatin plus bevacizumab for advanced stage non-small cell lung cancer (NSCLC): pooled preliminary safety data from two ongoing studies

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Background: The current standard of care for advanced stage NSCLC is platinum-based doublet chemotherapy. Bevacizumab (BV) is a recombinant, humanized anti-vascular endothelial growth factor monoclonal antibody with proven efficacy in cancer therapy. In advanced NSCLC, the addition of bevacizumab 15 mg/kg every 3 weeks to paclitaxel/carboplatin (PC) prolonged survival and progression-free survival (PFS), and improved PFS (survival data pending) when combined with cisplatin/gemcitabine (Sandler N Engl J Med. 2006, Genentech press release).

Methods: In the present studies, we are using BV 15 mg/kg day 1 in combination with gemcitabine (G) 1000 mg/m^2 days 1 and 8, and carboplatin (C) AUC5 day 1 for the treatment of NSCLC. Eligible pts with stage IIIB-IV NSCLC, PS 0-1, and adequate hematologic, renal and hepatic function, have been enrolled. Pts with squamous cell carcinoma, tumor in the central airways, baseline hemoptysis, or brain metastases are excluded; IIIB pts had malignant effusion. GC/BV treatment was given in q 3-weekly cycles for 4- 6 cycles, with BV continued in stable and responding patients until progression. One of the studies was amended after 7 pts were enrolled to reduce the dose of G from 1250 to 1000 mg/m^2 on days 1 and 8 due to unacceptable neutropenia. Only data from patients treated after the dose reduction is presented. To date, 17 pts in one trial and 12 pts in the other have received at least 2 cycles of combination therapy; we report here the hematologic and non-hematologic toxicity of these pts.