Effects of Gefitinib on Serum Epidermal Growth Factor Receptor and HER2 in Patients with Advanced Non–Small Cell Lung Cancer

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ABSTRACT

Purpose: The aim of this study was to assess serum extracellular binding domains of epidermal growth factor receptor (EGFR) and HER2 as surrogate markers of Gefitinib (Iressa, ZD1839, AstraZeneca, London, United Kingdom) activity in patients with non–small cell lung cancer.

Experimental Design: Serum EGFR and HER2 levels were monitored in blood samples taken within 1 week of starting Gefitinib at day 28 and at every computed tomography scan evaluation. EGFR and HER-2 were assayed in duplicate using commercial sandwich enzyme-linked immunosorbent assay kits (Oncogene Science Bayer Corporation, Cambridge, UK). A logistic regression analysis was performed to evaluate: (1) the relationship between best overall tumor response and basal EGFR and HER2 levels, and (2) the association between best overall tumor response and the differences of EGFR and HER2 levels obtained at the best overall tumor response and at baseline.

Results: Forty-six pretreated patients were evaluated, including F/M:11/35, Eastern Cooperative Oncology Group performance status 0–1/2:39/7, IIIB/IV:11/35, and adenocarcinoma/nonadenocarcinoma 29/17. Five partial responses (11%) and 14 stable disease responses (30%) were observed. Median pretreatment EGFR and HER2 were 83.3 ng/ml and 13.7 ng/ml. For baseline EGFR and HER2, the odds ratio of progression was 0.95 [95% confidence interval (CI), 0.91–0.98; P = 0.01] and 0.87 (95% CI, 0.74–1.03; P = 0.11), respectively. The difference between the best overall tumor response and basal EGFR value was predictive for response with a 6% increase in the odds of progression for an increase of 1 ng/ml (odds ratio, 1.06; 95% CI, 1.01–1.11; P = 0.009) and for progression-free survival with a hazard ratio of 1.03 (95% CI, 1.01–1.04; P = 0.003).

Conclusion: Modifications of EGFR serum values during treatment seem to reflect Gefitinib activity.

INTRODUCTION

Gefitinib (Iressa, ZD1839, AstraZeneca, London, United Kingdom) is an orally active tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). Gefitinib inhibits the growth of human cell line cultures that express high levels of EGFR (1). It induces complete regression in xenograph models of colon, prostate, and non–small cell lung cancer (2). Phase I trials in patients with solid tumors refractory to standard chemotherapy agents have shown antitumor activity and good tolerability profile with skin rash and diarrhea as dose-related toxicities (3, 4). Two large Phase II studies conducted in pretreated patients affected by non–small cell lung cancer achieved a response rate of 18% and 11.8%, respectively, and a symptomatic improvement in 40% and 43% of patients (5, 6). These trials confirmed that Gefitinib has promising activity as second- or third-line treatment in a subgroup of heavily pretreated patients, but the biological phenotype of patients who might benefit from this targeted therapy has not yet been defined (7). In cell lines expressing EGFR, Gefitinib inhibits autophosphorylation of this receptor (1), resulting in the inhibition of downstream signaling molecules by formation of inactive unphosphorylated EGFR/HER2 and EGFR/HER3 heterodimers. HER-2, the preferred coreceptor of EGFR, decreases ligand dissociation from EGFR, with which it forms stable heterodimeric complexes on the cell surface (8). Recent preclinical data also suggest that HER2-overexpressing tumors are particularly sensitive to Gefitinib (9). However, the degree of EGFR and HER2 expression in human tumor tissues does not seem to influence response to Gefitinib (10, 11). These predictive studies were conducted in tissue samples obtained at the time of diagnosis, before chemotherapy treatments could have changed tumor population. The extracellular binding domains of EGFR and HER2 are proteolytically released from cell surface and are detectable in conditioned media of carcinoma cell cultures (12, 13) and in serum of patients with cancers overexpressing these proteins (14, 15). The predictive role of serum EGFR and HER2 in relation to Gefitinib therapy has not yet been explored.

Circulating EGFR and HER2 may provide a convenient indicator for response to Gefitinib. This study aimed to assess...
serum EGFR and HER2 levels as surrogate markers of Gefitinib activity.

**PATIENTS AND METHODS**

**Patient Selection.** All of the patients had to have histologically or cytologically confirmed, measurable, locally advanced or metastatic pretreated non-small cell lung cancer. Patients were ≥ 18 years of age, had a Eastern Cooperative Oncology Group performance status ≤ 2, white blood cell count ≥ 3.5 × 10^9/L with absolute granulocyte count > 2.0 × 10^9/L, platelets ≥ 100 × 10^9/L, hemoglobin ≥ 9 g/dL, bilirubin < 1.5-fold the upper limit of normal, prothrombin time or activated partial thromboplastin time < 1.5 × control, alanine aminotransferase or aspartate aminotransferase < 3-fold upper limit of normal (could be elevated to 5-fold upper limit of normal in patients with known hepatic metastases), and a calculated creatinine clearance rate of > 45 mL/minute. Patients with an active infection, other serious concomitant disorders, or uncontrolled brain metastases were ineligible. Written informed consent was obtained from each patient before entering the study. The study was conducted after the approval of the appropriate ethical review boards. Recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed.

**Study Design and Treatment.** Consecutive patients admitted to the Department of Oncology, Scientific Institute University Hospital San Raffaele with pretreated non-small cell lung cancer received Gefitinib at the daily dose of 250 mg given until disease progression. Gefitinib was taken once daily in the morning. The drug was provided by AstraZeneca, as part of the "Iressa" Expanded Access Programme, on a compassionate use basis. Baseline evaluation was performed within 4 weeks before the study entry and included a complete history and physical examination, a complete blood cell count, serum chemistry analysis, urinalysis, and a total body computed tomography scan. Other imaging modalities were performed according to specific clinical indications. Blood cell count, biochemical screening, physical examination with clinical symptoms, and toxic effects evaluation were also performed as close as possible to day 28 ± 2 of treatment and concomitantly to every computed tomography scan evaluation.

Patients were evaluated by computed tomography scan at baseline and every 2 months for tumor response according to Response Evaluation Criteria in Solid Tumors (16). Adverse events were assessed using National Cancer Institute Common Toxicity Criteria, version 2.0 (17). The blood samples were collected as follows: within 1 week before the first dose of Gefitinib, as close as possible to day 28 ± 2 (steady-state plasma Gefitinib concentrations achieved; ref. 18), and at every computed tomography scan evaluation (every 2 months) to determine the EGFR and HER2 levels at best overall tumor response. The differences between serum concentrations of EGFR and HER2 obtained at day 28 and at the time of best overall tumor response compared to baseline were determined. For patients who progressed before computed tomography scan evaluation, a determination for serum EGFR and HER2 was performed in blood samples obtained as close as possible to day 28 ± 2 of therapy. Patients who died or stopped treatment for any cause before the first on-treatment serum evaluation (as close to day 28 ± 2) were included as progressive disease in predictive analysis.

**Detection of EGFR and HER2.** Five milliliters of peripheral venous blood samples were collected after overnight fasting with Vacutainer glass without additive. The serum was then separated by centrifugation at 3000 rpm for 10 min at 4°C and stored in aliquots at −80°C until the time of analysis.

Serum aliquots were assayed for the extracellular binding domain level of EGFR by a sandwich quantitative enzyme-linked immunosorbent assay using mouse monoclonal capture antibody against EGFR precoated onto a microtiter plate and an alkaline phosphatase-labeled mouse monoclonal antibody as detector specific for the electron capture detection of human EGFR, according to the manufacturer’s instructions (Oncogene Science, Bayer Corporation, Cambridge, UK) (19).

All of the samples and standards were assayed in duplicate at the Laboratory of Medical Oncology, Policlinico Monteluce, Perugia, Italy. One hundred microliters of the standards and samples diluted at 1:50 with sample diluent, respectively, were added to the microtiter wells and incubated for 1.5 hours at 37°C. After washing, 100 μL of alkaline phosphatase-labeled mouse monoclonal detector antibody was added for 30 minutes at room temperature. After several washes to remove any unbound antibody-enzyme reagent, a substrate solution (containing bluephos Substrate) was added for 1 hour at room temperature. One hundred microliters of stop solution were added to each well.

Serum concentrations of HER2 were determined using an ELISA kit (Oncogene Science, Bayer Corporation, Cambridge, UK) based on the same test principle as the EGFR assay. The kit uses a mouse monoclonal antibody recognizing the extracellular domain of HER2 protein. The detection antibody was a biotinylated mouse monoclonal anti-HER2 protein antibody. The amount of detector antibody bound to antigen was measured by binding it with a streptavidin-horseradish peroxidase conjugate, which catalyzes the conversion of the cromogenic substrate O-phenylenediamine into the colored product.

Colorimetric quantification was performed using a multitester spectrophotometer at 490 nm for HER2 and 620 nm for EGFR. A standard curve was created using Software 990-CBV by plotting of the mean absorbance of each standard versus the concentrations of the EGFR and HER2. The results were expressed in nanograms per milliliter by reading directly from the standard curve.

The lower detection limit of the method for EGFR and HER2 was 0.25 ng/ml and 1.5 ng/ml, respectively.

For each analysis, serum samples of known concentration with low, mid, and high levels were used as internal quality control; the intra- and interassay coefficients of variation were below 6% for EGFR and below 8% for HER2.

Laboratory and clinical data were collected independently.

**Statistical Considerations.** This study was designed as a prospective trial. This pilot study was to explore the biological hypothesis in a clinical setting that serum EGFR may be a surrogate marker of Gefitinib activity. The relationship between EGFR and HER2 and best overall tumor response was evaluated by means of a logistic regression model. In such a model, the best overall tumor response (stable disease versus partial re-
response versus progressive disease) was considered as the response variable and the remaining factors, included the use of a continuous scale, as predictors. The same model was used having as predictors the difference between EGFR and HER2 levels at day 28 and best overall tumor response (partial response versus stable disease versus progressive disease) compared to baseline. Results are reported as odds ratio, their 95% confidence interval (95% CI), and $P$ value at Wald’s test. An odds ratio of 1 denotes the absence of difference in the odds of progression for an increase of 1 ng/mL in EGFR or HER2 levels, whereas an odds ratio >1 or <1 denotes increased or decreased odds, respectively.

Progression-free survival and overall survival were estimated using the Kaplan-Meier method (20). Progression-free survival was computed from the date of the first Gefitinib assumption to the date of first appearance of progressive disease or death from any cause; patients known to be alive and without progressive disease at the time of analysis were censored at the time of their last follow-up. Cox’s multivariate analysis was performed to investigate any correlation between serum markers and progression-free survival.

Overall survival was calculated from the day of first Gefitinib assumption to the date of death from any cause; patients known still to be alive at the time of the analysis were censored at the time of their last follow-up. With respect to the sample size, all of the multivariate analysis included four factors (performance status 0–1 versus 2, stage, histology, adenocarcinoma versus other, and serum EGFR). The best cut-off levels were defined by receiver operating characteristic curves.

All of the $P$ values were two-sided. Analyses were carried out using the SAS System, version 8.20.

RESULTS

Patient Characteristics. From June 2002 to January 2003, a total of 46 consecutive patients were treated with Gefitinib. The majority of the patients were male (76%), with a median age of 65 years (range, 36–90) and a good Eastern Cooperative Oncology Group Performance Status (performance status 0–1: 85%). There were 63% adenocarcinomas (including 3 cases of bronchiolar-alveolar carcinomas). Most of the patients (76%) had metstatic non-small cell lung cancer with bone representing the main metastatic site. Fifty seven percent of patients were pretreated with a first-line platinum-based chemotherapy, and 53% with at least two lines of chemotherapy, including platinum, gemcitabine, and taxanes. All of the patients with locally advanced unresectable disease were pretreated with mediastinal radiotherapy as part of a chemoradiation integrated approach.

Response to Therapy and Toxicity Profile. All of the patients were evaluated for response and toxicity. We observed 5 (11%) partial responses, 14 (30%) stable disease, and 27 (59%) progressive disease. Side effects were generally mild and consisted of grade 1–2 skin toxicity reported in 17% of patients and grade 1–2 diarrhea reported in 15% of cases. After a median follow-up time of 6.7 months (95% CI, 5.2–8.1), 30 (65.2%) patients progressed with a median progression-free survival of 2.3 months. Fig. 1 shows the progression-free survival and overall survival curves. Median survival for the whole population has not been reached. Twenty patients (43.5%) have died, with a median time to death of 1.8 months (95% CI, 0.8–4.6).

EGFR and HER2 Detection, Pharmacodynamics, and Predictive Evaluations. Eleven patients who died within 28 days from the beginning of treatment were included as progressive disease in predictive analysis. Full data of EGFR and HER2 levels at each time point for each patient are provided in Table 1 and Fig. 2, A and B. Higher levels of baseline EGFR predicted for response (odds ratio, 0.96; 95% CI, 0.93–0.99; $P = 0.035$). No meaningful cut-off level predicting response was determined for basal EGFR in this study group. No association with progression-free survival was detected (odds ratio, 0.98; 95% CI, 0.97–1.00; $P = 0.09$). A multivariate logistic analysis for response, including performance status, histology, stage, and baseline EGFR was performed. Higher baseline serum EGFR was associated with response (odds ratio, 0.95; 95% CI, 0.91–0.99; $P = 0.01$; Table 2).

Increasing EGFR serum levels at day 28 with respect to
Fig. 2. A, difference between EGFR and HER2 serum levels at best tumor response and EGFR and HER2 serum levels at baseline. B, difference between EGFR and HER2 serum levels at day 28 and EGFR and HER2 serum levels at baseline. PD, progressive disease, SD, stable disease, PR, partial response.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>28th day</th>
<th>Best response</th>
</tr>
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<tr>
<td></td>
<td>No. of patients</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Whole population</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EGFR</td>
<td>46</td>
<td>83.3</td>
<td>55.3–156.4</td>
</tr>
<tr>
<td>HER2</td>
<td>46</td>
<td>13.7</td>
<td>6.9–85.5</td>
</tr>
<tr>
<td>Responders EGFR</td>
<td>5</td>
<td>75.3</td>
<td>60.2–96.5</td>
</tr>
<tr>
<td>HER2</td>
<td>5</td>
<td>16</td>
<td>9–85.5</td>
</tr>
<tr>
<td>Stable EGFR</td>
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<td>113.75</td>
<td>60.8–155.2</td>
</tr>
<tr>
<td>HER2</td>
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<td>14</td>
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<tr>
<td>Progressive EGFR</td>
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<td>82.3</td>
<td>55.3–156.4</td>
</tr>
<tr>
<td>HER2</td>
<td>27</td>
<td>13</td>
<td>6.9–57</td>
</tr>
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</table>

Note. Median and range values are expressed as ng/ml.
baseline were an indicator of disease progression (odds ratio, 1.04; 95% CI 1.004–1.07; P = 0.02) and shorter progression-free survival (odds ratio, 1.02; 95% CI, 1.01–1.03; P = 0.005).

No meaningful cut-off was found. A multivariate analysis, including performance status, histology, stage, and delta EGFR at day 28 confirmed that increasing serum EGFR levels were associated with disease progression (odds ratio, 1.04; 95% CI, 1.005–1.07; P = 0.02) and shorter progression-free survival (odds ratio, 1.02; 95% CI, 1.002–1.03; P = 0.02).

For one patient with stable disease both EGFR and HER2 levels at best overall tumor response were not available. In patients with partial response, the modification of EGFR ranged from −36 to 3 ng/mL; in 4 of 5 patients (80%) a decrease in EGFR was detected. In patients with stable disease, the modification of EGFR ranged from −69.3 to 69.3 ng/mL. In 9 of 13 patients (69%) a decrease in EGFR was detected. In patients with progressive disease the modification of EGFR ranged from −9.2 to 70 ng/mL. Fourteen (88%) of 16 patients with progressive disease had an increase in serum EGFR. An increase in EGFR levels (median 3.6 ng/mL; range, −69.3 to 70.2) at the time of best overall tumor response compared with baseline values predicted for tumor progression. For an increase of 1 ng/mL of EGFR at best overall tumor response, a 5% increase in the odds of progression was calculated (odds ratio, 1.05; 95% CI, 1.01–1.08; P = 0.011). A multivariate analysis for response, including performance status, histology, stage, and delta EGFR at best overall tumor response was performed. Increased EGFR levels were associated with disease progression (odds ratio, 1.06; 95% CI, 1.01–1.11; P = 0.009; Table 2). The median difference of 3.6 ng/mL gave a clinically significant cut-off level to identify patients with disease control (partial response and stable disease) versus patients with progressive disease. Using this cut-off, the odds ratio of progression between the two groups was 35 (odds ratio, 35; 95% CI, 5–242; P = 0.0003).

As shown in Fig. 3, patients with an increase in EGFR levels at best overall tumor response compared with baseline had worse progression-free survival (odds ratio, 3.63; 95% CI, 1.4–9.40; P = 0.005). These data were confirmed in multivariate analysis, including performance status, histology, stage, and delta EGFR (odds ratio, 1.03; 95% CI, 1.01–1.04; P = 0.003; Table 2).

Baseline HER2 was not associated with response (odds ratio, 0.87; 95% CI, 0.74–1.03; P = 0.111). The difference between the HER2 values at the best overall tumor response and baseline (median, −1.0; range, −46.5 to 9.5 ng/mL) was not predictive for response (odds ratio, 1.03; 95% CI, 0.95–1.12; P = 0.471). A decrease of HER2 levels was detected in 4 (80%) of 5 patients with partial response (range of HER2 in this group, −46 to 6.0 ng/mL) and in 8 of 13 (62%)...
patients with stable disease (range of HER2 in stable disease, −18.0 to 9.0 ng/mL). An increase in HER2 was observed in 4 (25%) of 16 patients with progressive disease (range, −6.4 to 4.0 ng/mL).

No correlation between response or serum markers and skin rash was found (odds ratio, 0.7; 95% CI, 0.2–2.6; \( P = 0.5 \)).

DISCUSSION

To our knowledge, this is the first study evaluating the relationship between Gefitinib activity and serum EGFR and HER2 levels in patients with advanced non-small cell lung cancer. Data from this study indicate that serum EGFR values were modified during treatment with Gefitinib. Basal EGFR concentrations and serum modifications in EGFR during therapy were associated with response to Gefitinib and progression-free survival, independently of performance status, stage, and histology. The response rate and toxicity profile in this study were similar to those reported recently in two large Phase II trials (IDEAL 1 and 2), which demonstrated that Gefitinib is an active therapy in pretreated non-small cell lung cancer patients, with a radiologic response rate of about 10–18% (6, 7).

These observations suggest some important information regarding Gefitinib activity and the possible clinical implications of observed phenomena. It is known that the EGFR network plays an important role in multiple tumorigenic processes, contributing to cancer cell proliferation, angiogenesis, and metastasis, as well as protection from apoptosis (21), and that Gefitinib is a selective inhibitor of the EGFR-tyrosine kinase in cell lines with a functional EGFR pathway (1). It has been suggested that differences in expression of EGFR members may explain different responses to EGFR-tyrosine kinase inhibitors, but the degree of EGFR and HER2 expression does not seem to be predictive for response (10, 11, 22). However, because the immunohistochemical analysis was performed in tumor tissue obtained at diagnosis, this analysis might not be representative of EGFR and HER2 status at the time of Gefitinib assumption. EGFRs are composed of an extracellular binding domain, a transmembrane lipophilic segment, and an intracellular tyrosine kinase protein. Because extracellular binding domain is proteolytically released (23, 24) and may be detected in serum of patients with cancers overexpressing EGFR and HER2 (14–15, 25), this pilot study was developed to test whether EGFR and HER2 serum concentrations may be influenced by Gefitinib activity. This biological hypothesis was based on the fact that extracellular binding domains are produced either by proteolytic cleavage of the functionally activated receptors or by alternative transcription of primary mRNA (26–28). This process has been shown to require an active tyrosine kinase (23, 24) suggesting that a decrease of serum EGFR in patients sensitive to Gefitinib is caused by EGFR-tyrosine kinase inhibition, which makes the receptor not susceptible to proteolysis. For the same reasons, increase of circulating EGFR is expected in those patients who do not respond to Gefitinib because tyrosine kinase is not inhibited. Furthermore, a reduction of activated EGFR was observed in tumor tissue of patients responding to Gefitinib (18) suggesting that extracellular binding domain concentrations may also result from proportional modifications in the absolute number of activated receptors.

In fact, during Gefitinib therapy, in 80% of responders, a reduction in EGFR serum concentration was detected. In 88% of patients with progressive disease an increase in EGFR was observed. Baseline levels and modification in HER2 concentrations were not relevant for response and were not influenced by Gefitinib treatment. These seem to confirm our previous observation, which evidenced that the efficacy of Gefitinib in pretreated patients with non-small cell lung cancer seems unrelated to HER2 expression (11). These data suggest that Gefitinib may influence serum EGFR but not serum HER2 and that serum EGFR may be a clinically important surrogate marker of targeted inhibitor. Moreover, patients with higher pretreatment EGFR serum levels were more suitable for response, suggesting that circulating EGFR may reflect the need of functional activation of the EGFR pathway in responding patients. Although baseline EGFR serum levels appeared to be associated with response, a clinically relevant cut-off has not been established, probably due to the small sample size of the study. Therefore, additional study is needed to assess whether determination of basal EGFR could be a useful indicator of early response versus resistance. The modifications of EGFR soluble levels in the study patients evidence that they appear to be composed of two different subgroups: serologic responders and serologic nonresponders. The fact that modification of EGFR serum levels during therapy with Gefitinib is correlated with progression-free survival suggests that this measurement may be a useful predictor of clinical benefit in terms of durable disease control. Moreover, early modifications of EGFR, at day 28 of treatment, appeared to be an early indicator of response versus resistance. These data may have major translational implications in clinical practice and should be additionally investigated.

In previous studies, a performance status of 0–1, prior immuno/hormonal treatment, female gender, adenocarcinoma histology in non-small cell lung cancer (5), and skin rash in patients with head and neck cancer (29) were identified as baseline prognostic factors for response in trials with EGFR-targeted therapies. Gender and performance status have been identified previously as prognostic factors for response and survival after first-line chemotherapy in individuals with non-small cell lung cancer (30). Moreover, it has been shown that patients with non-squamous histology are more likely to respond to second-line chemotherapy (31). Therefore, these factors may not be such specific predictors for response to therapy with EGFR inhibitors. Skin rash was also considered as an outcome in our study, but no correlation with serum markers or response was found. These data fit with the observation that no significant association between HER1/EGFR expression and skin rash was found (29). Development of skin toxicity was a statistically significant predictor of response and improved outcome in patients with head and neck and colon cancer (32, 33) treated with EGFR antibodies and in one study where patients with recurrent or metastatic head and neck squamous cell carcinoma were treated with Gefitinib (34). It should be noted that in our study the observed incidence of rash was quite low in comparison with other reports (5, 6). This could be partially explained by early progression of 11 patients; in fact, the high rate of early withdrawal might have been the cause of underestimation of the skin toxicity. Moreover, two large monotherapy trials in non-small cell lung cancer failed to show a correlation...
between response and skin rash (5, 6). Thus far, skin rash may not be considered a sure predictor of response in patients with non-small cell lung cancer treated with EGFR inhibitors. The differences among reported studies could stem from several factors, including the disease, the kind of drug used (antibodies or tyrosine kinase -inhibitors), and the scoring of toxicities.

In conclusion, in our study, modifications of EGFR serum values during treatment seem to reflect Gefitinib activity in patients with advanced non-small cell lung cancer. This could be of interest in defining a clinically relevant surrogate marker of the activity of this targeted drug.

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