Phase II Trial of Gefitinib 250 mg Daily in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

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Abstract Purpose: An objective response rate of 11% was reported in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) treated with 500 mg daily gefitinib although the recommended dose in lung cancer is 250 mg daily. This study evaluated the efficacy and toxicity of 250 mg daily gefitinib in patients with recurrent and/or metastatic SCCHN.

Experimental Design: Phase II trial with objective response rate as the primary end point. Measurements of quality of life and levels of serum vascular endothelial growth factor and transforming growth factor–α were assessed before and during therapy.

Results: In 70 patients, 1 (1.4%) partial response was observed. Median progression-free survival and overall survival were 1.8 and 5.5 months, respectively. Quality of life scores improved transiently during the first weeks of therapy before returning to baseline. Median vascular endothelial growth factor and transforming growth factor–α levels were above the normal range but were not predictive of outcome. Four patients experienced grade 3 drug-related adverse events. Rash of any grade was observed in 64% of subjects. Correlation between disease control (partial response + stable disease), progression-free survival, and overall survival and grade of cutaneous toxicity was observed (P = 0.001, 0.001, and 0.008 respectively).

Conclusions: Gefitinib monotherapy at 250 mg in recurrent and/or metastatic SCCHN seems to have less activity than was previously observed for 500 mg daily. A dose-response relationship may exist for this agent in SCCHN and grade of cutaneous toxicity attributable to gefitinib is a clinical predictor of better outcome.

Early in the development of epidermal growth factor receptor (EGFR)–targeted therapy, SCCHN seemed to be suitable for this strategy because expression of this receptor and/or its ligands is almost universal and increased expression has been linked with poor outcome. SCCHN affects ~40,000 people in the United States annually with up to 50% of patients succumbing to the disease due to recurrence or development of metastases (1). Preclinical studies using a variety of EGFR inhibitors suggested that these agents would be clinically efficacious and EGFR targeted agents have shown reproducible activity in SCCHN (2). For patients with few therapeutic options, the response and survival rates reported were encouraging especially in light of the favorable tolerability of these agents.

In a phase II trial involving 52 patients, the objective response rate using the small molecule EGFR tyrosine kinase inhibitor (TKI) gefitinib at a dose of 500 mg daily was 10.6% with a median time to progression and overall survival of 3.4 and 8.1 months, respectively (3). A significant positive correlation between development of skin toxicity and these outcome measures was also observed. Just before that report, results of two randomized phase II trials in non–small cell lung cancer (NSCLC) comparing gefitinib 250 to 500 mg daily showed similar efficacy for both doses, whereas the lower dose was better tolerated (4, 5). Symptom intensity measured with validated indices has been incorporated into previous EGFR TKI trials to explore whether there were potential benefits beyond observed objective responses.

Preclinical data have also suggested that EGFR modulates the level of vascular endothelial growth factor (VEGF) and can be influenced by levels of its ligand, transforming growth factor–α (TGF–α). A number of in vivo experiments have suggested that EGFR TKIs have antiangiogenic effects by inhibiting VEGF production (6, 7). We hypothesized that serum levels of VEGF...
would be decreased in patients treated with gefitinib and that the extent of reduction would correlate positively with outcome (i.e., patients with the greatest decrease in circulating VEGF levels would experience the greatest benefit).

Conversely, TGF-α has been implicated as the principal ligand for EGFR in the human system, has been shown to promote tumor growth through autocrine mechanisms, and has been negatively correlated with outcome in SCCHN (8, 9). TGF-α activation of EGFR signaling can be inhibited by EGFR-targeted therapy and TGF-α production per se is reduced upon exposure to gefitinib in preclinical models (7, 10, 11). We hypothesized, therefore, that TGF-α serum levels would reflect the tumor microenvironment, that these levels would indicate a tumor that is dependent on TGF-α/EGFR signaling, and that patients with higher pretreatment TGF-α levels would be more likely to benefit from EGFR TKI therapy. In addition, because TGF-α in SCCHN is produced by tumor cells themselves, a reduction in tumor burden should be reflected as lower levels of circulating TGF-α.

The current study evaluated the objective response rate, progression-free survival, and overall survival in patients with recurrent or metastatic SCCHN treated with 250 mg gefitinib daily. In addition, the effects of gefitinib on quality of life (QoL), serum TGF-α, and serum VEGF were measured.

Materials and Methods

Patient enrollment. The protocol and informed consent document were reviewed and approved by the Institutional Review Board at each participating institution. Eligibility criteria included patients over the age of 18 with pathologically confirmed, recurrent or metastatic SCCHN not amenable to curative intent therapy, with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (12). Eastern Cooperative Oncology Group performance status of ≤2, leukocyte count ≥3,000/μL, absolute neutrophil count ≥1,500/μL, platelet count ≥100,000/μL, total bilirubin within institutional normal limits, aspartate amino transferase and amino alanine transferase ≤2.5 times the institutional normal limit, and creatinine ≤1.5 mg/dL. Patients were not allowed to have undergone any radiotherapy or chemotherapy within 28 days of entering study and were not allowed any prior EGFR-directed therapy. All patients were required to understand and sign the informed consent document before treatment.

Treatment plan and dose modifications. All patients received gefitinib 250 mg daily orally starting from day 1 of therapy without planned interruptions. Feeding tube administration was allowed as there is documented bioequivalence when compared with oral administration (13). Each cycle was defined as 28 days in length. Dose interruption was allowed for a maximum of 14 days in the event of grade 3 or 4 toxicity or unacceptable grade 2 toxicity. In the event of grade 3 or 4 cutaneous or gastrointestinal toxicity, gefitinib was interrupted until resolution to grade 1 or less. Control of diarrhea using over-the-counter antidiarrheal medication was allowed. Antiemetic and other supportive care agents, including remedies for skin toxicity, were allowed. Patients were continued on study until objective progression of disease, an adverse event necessitating discontinuation, voluntary patient withdrawal, or the physician investigator felt it necessary to discontinue therapy.

Response, toxicity, and quality of life assessment. Response Evaluation Criteria in Solid Tumors (12) were used for objective tumor response assessment. Computed tomography scanning was the preferred baseline and reevaluation technique. Patients were seen by a physician every 4 weeks and reevaluated radiographically every 8 weeks. In addition to a baseline scan, confirmatory scans were obtained 4 weeks following initial documentation of an objective response. For metastatic skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, was recommended. The National Cancer Institute Common Toxicity Criteria version 2.0 was used to grade toxicity.

QoL was measured using a recently developed abbreviated instrument, the Functional Assessment of Cancer Therapy–Head and Neck Symptom Index-10 (FHNSI-10). This brief symptom index, designed by David Cella et al. (14) is a more symptom-focused index specifically for use with patients with advanced and/or recurrent/refractory SCCHN. Disease-related symptoms and concerns from the functional assessment of cancer therapy for head and neck cancer were presented to 65 experts in treating advanced head and neck cancer. These experts then selected the five most important symptoms/concerns to assess in treating advanced SCCHN. The 10 items included in the FHNSI-10 represent those items endorsed by 20% or more of the medical experts (15). They are scored on a five-point scale from 0 (not at all) to 4 (very much). This index was selected for use in the current study based on its brevity and feasibility in an ill patient population as well as the fact that it captures the most likely range of symptoms and limitations experienced by this group of patients. In consultation with Dr. Cella, an additional item from the Functional Assessment of Cancer Therapy–General Scale asking patients how bothersome their side effects were was added to more globally describe their experience of treatment. The QoL index was completed by patients before receiving gefitinib at days 7, 14, 21, and 28 of cycle 1, and then on day 28 of every cycle beginning with cycle 2. A higher score reflects fewer symptoms and better QoL with a maximum possible score of 44.

Vascular endothelial growth factor and transforming growth factor-α levels. After obtaining separate informed consent, blood samples were collected from patients in 7 mL heparinized tubes before and after 8 weeks of therapy with gefitinib. Triplicate samples were analyzed for serum VEGF and TGF-α using commercially available ELISA kits (R&D Systems, Minneapolis, MN). Briefly, plates were coated overnight with anti-VEGF (1 μg/mL) or anti-TGF-α (0.4 μg/mL) antibodies and then blocked with 1% bovine serum albumin. Samples were added followed by anti-VEGF (50 ng/mL) and anti-TGF-α (300 ng/mL) biotinylated antibodies. Streptavidin peroxidase, substrate solution, and stop solution were added in sequence and plates were read immediately using the Synergy HT Multi-Detection Microplate Reader (Bio-Tek, Winooski, VT) at dual wavelengths of 450 to 540 nm.

Statistical analysis. The primary end point of the study was objective response rate (complete response plus partial response) based on Response Evaluation Criteria in Solid Tumors. A single-stage phase II study design was used to test the null hypothesis that the true response rate was ≤5% against the alternative that it was at least 15%. A sample size of 63 evaluable patients was planned. If seven or more objective responses were observed, the null hypothesis would be rejected and the study would conclude that 250 mg gefitinib is an effective treatment for SCCHN. With this scenario, the probability of one-sided type 1 error was 0.037 and the study power was 0.853.

To consider the effect of gefitinib on disease control rate (a secondary end point defined a priori as the addition of complete response, partial response, and stable disease), an interim analysis was conducted. Based on a previous study with 500 mg gefitinib, the rate of disease progression at first evaluation was 8 weeks was expected to be 50% and an 85% rate of disease progression was felt to be the maximum acceptable. If 23 or more of the first 30 evaluated patients had disease progression as their best objective response, the trial would be stopped. The probability of stopping thus was 0.0026 if the true rate of progression was 50% and 0.93 if the true rate of disease progression was 85%.

The secondary end points of progression-free and overall survival were measured from date of registration and summarized by computing Kaplan-Meier curves. Median survival and/or the percentage surviving at specific time points are reported together with corresponding 95% confidence intervals (95% CI). Factors associated with progression-free survival and overall survival were examined using log-rank tests. All efficacy and toxicity end points were assessed and reported for all registered patients (eligible or not). The primary efficacy analysis
included all registered patients who met the eligibility criteria. All registered patients who met the eligibility criteria and received any study drug were included in the analysis of toxicity. A Wilcoxon rank-sum test was used to examine the relationship between disease control rate and cutaneous toxicity and a Fisher's exact test was used to examine the relationship between disease control rate and prior palliative chemotherapy.

The feasibility of using the FHNSI-10 in a group of severely ill recurrent disease patients was explored by calculating the percentage of evaluable patients who completed the questionnaire at each time point. FHNSI-10 items were summed to create an overall QoL summary score. First, change over time for the entire cohort of patients was examined using a random effects linear regression model (16). Second, change in subjects who benefited (partial response and stable disease) and subjects who did not benefit (progressive disease) was examined separately by adding a time-by-response interaction term to the model.

The distribution of VEGF and TGF-α were found to be skewed to the right and thus a median and interquartile range was used to describe central tendency and variation. Wilcoxon signed-rank test was used to compare changes in serum markers between baseline and week 8.

**Results**

**Patient demographics and eligibility.** From June 2002 to March 2004, 71 patients were enrolled at four participating sites. The characteristics of all patients enrolled are presented in Table 1. Seventy percent had metastatic disease. Thirty-four (48%) patients received gefitinib via an enteral feeding tube. Sixty-one percent had received one or more courses of palliative chemotherapy. All but one patient had received definitive radiotherapy. Only seven patients did not have a history of prior chemotherapy exposure as part of palliative or initial curative intent treatment.

One patient was not included in evaluation of response and four patients were not included in the toxicity evaluation. The reason for excluding a patient from response evaluation was due to discovery of brain metastases on computed tomography scan at 8 weeks of therapy. A prestudy head computed tomography was not obtained and, thus, it was not possible to evaluate whether the lesions represented progressive disease. All other sites of disease were stable and the patient was asymptomatic. All other patients, including seven that were nonevaluable (Table 2), were included in the response assessment. The four patients not included in toxicity assessment all received less than one cycle of therapy and were either lost to follow-up (two patients) or had progressive disease and were taken off study before toxicity assessment (two patients).

**Response.** In the intent-to-treat analysis of the 70 patients, there was 1 (1.4%) and 23 (33%) patients with partial response or stable disease as their best observed response, respectively. Excluding the seven nonevaluable patients from the analysis yields an objective response rate of 1.6%. Therefore, the null hypothesis that the overall response rate of gefitinib in this setting is <5% is not rejected. The disease control rate, defined a priori as the addition of complete response, partial response, and stable disease, was 34% (95% CI, 23-47%).

The primary difference in eligibility between the current study and the 500 mg single-agent trial was the number of allowable prior therapies. The current study did not restrict patients with respect to the number of prior therapies, whereas the 500 mg trial allowed a maximum of one prior therapy for recurrent and/or metastatic disease. A subset analysis was done on the current study examining only those patients who had received one or no prior regimens for recurrent and/or metastatic disease. Excluding patients who were nonevaluable, the disease control rate in this group was numerically higher at 44% compared with patients who had received two or more prior regimens (15%, \(P = 0.11\)). The subject with responding disease received prior chemotherapy (cisplatin and tirapazamine) with concomitant reirradiation for locally recurrent disease.

A correlation between the development of a rash during EGFR-targeted therapy and therapeutic outcome was reported in previous studies in SCCHN. In the present study, the correlation between disease control rate and cutaneous toxicity showed that partial response or stable disease was significantly associated with grade of skin toxicity: The higher the grade, the more likely were patients to have partial response or stable disease (\(P = 0.001\)).

**Progression-free and overall survival.** At the time of this analysis, with a median follow-up of 18 months, all patients have either experienced progressive disease or died. The median progression-free survival and overall survival for the entire cohort were 1.8 months (95% CI, 1.7-3.1) and 5.5 months (95% CI, 4.0-7.0), respectively (Fig. 1). The 6-month and 1-year survival rates were 47% (95% CI, 35-58%) and 19% (95% CI, 11-29%), respectively.
respectively. Grade of skin toxicity positively correlated with both progression-free survival \((P = 0.001)\) and overall survival \((P = 0.008)\). The 13 subjects who developed grade 2 or greater skin toxicity experienced median progression-free survival and overall survival of 4.4 and 7.6 months, respectively. These outcome measures were not associated with number of prior therapies \((P = 0.67\) for progression-free survival and 0.61 for overall survival) or prior chemoradiotherapy \((P = 0.17\) for progression-free survival and 0.77 for overall survival).

**Toxicity.** Sixty-seven patients were included in the toxicity analysis presented in Table 3. Most toxicities encountered were grade 1 or 2 in severity. Cutaneous adverse events were most frequent with an incidence of 64% overall. Except for the one patient who voluntarily withdrew from the study due to grade 2 skin rash, no patients were removed from study due to gefitinib toxicity. All grade 2 or greater respiratory toxicity was attributable to either disease progression or an intercurrent pulmonary illness.

**Quality of life.** QoL assessment was added to the protocol as a secondary end point after the start of enrollment. Fifty-two of the 71 patients on study were enrolled on the QoL component. Figure 2A presents the percent of on-study patients who completed QoL assessments at each of the indicated time points and reveals that ≥75% of patients were captured at every time point. Patients were no longer followed for QoL after stopping gefitinib treatment.

Overall, QoL scores improved from baseline to week 1 \((P = 0.002)\) and week 2 \((P = 0.039)\) and then declined to the level of baseline by week 3 onward (Fig. 2B). When examining QoL scores with respect to best response at 8 weeks, the baseline score was 4.05 higher in patients with progressive disease than in those with partial response or stable disease but the difference did not reach statistical significance \((P = 0.066)\). Changes in QoL were then calculated through 8 weeks (Fig. 2C) revealing that, among patients with partial response/stable disease, QoL increased from baseline to weeks 1, 2, 4, and 8 \((P < 0.05)\). In contrast, among patients with progressive disease, QoL scores increased only from baseline to week 1 \((P = 0.048)\). Overall, however, there was no significant response by time interaction \((P = 0.19)\).

**Vascular endothelial growth factor and transforming growth factor-α.** Serum VEGF and TGF-α levels were available at baseline on 61 and 59 patients, respectively. The median VEGF at baseline was 78 pg/mL (interquartile range, 41-167; Fig. 3A). Thirty-nine patients had VEGF measured 8 weeks after baseline with a median level of 68 pg/mL (interquartile range, 17-116). Of 37 patients who had both baseline and follow-up VEGF values, VEGF increased in 15 patients, decreased in 19 patients, and had no change in 3 patients. Overall, there was no significant change from baseline to week 8 \((P = 0.86)\).

The median serum TGF-α level at baseline was 20 pg/mL (interquartile range, 6-194; Fig. 3B). Thirty-eight patients had TGF-α measured at 8 weeks after treatment with a median value of 78 pg/mL (interquartile range, 6-1,101). Of 35 patients who had both baseline and follow-up TGF-α values, TGF-α increased in 21 patients, decreased in 10 patients, and had no change in 4 patients. Overall, there was a significant increase from baseline to week 8 \((P = 0.03)\). Interestingly, patients with stable disease or partial response trended toward a greater increase in TGF-α levels with a median increase of 74 (interquartile range, 0-995) compared with a median increase of 4 (interquartile range, -2-57) in patients with progressive disease (Wilcoxon rank-sum test, \(P = 0.13\)). Disease status \((P = 0.51)\) and gender \((P = 0.70)\) were not associated with changes in serum TGF-α levels.

Neither the baseline levels nor the change from baseline to week 8 were associated with progression-free survival or overall survival for either marker.

**Table 2.** Reason patients were deemed nonevaluable for response

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>7</td>
</tr>
<tr>
<td>Death prior to response evaluation</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2</td>
</tr>
<tr>
<td>Withdrawn from study before response</td>
<td></td>
</tr>
<tr>
<td>Evaluation</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
</tr>
<tr>
<td>VW</td>
<td>2</td>
</tr>
<tr>
<td>VW due to AE</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE: Percentages are rounded to the nearest whole number. These patients were included in the intent-to-treat analysis.

Abbreviations: SAE, serious adverse event; AE, adverse event; VW, voluntary patient withdrawal.
The hypothesis of this study was that in recurrent and/or metastatic SCCHN 250 mg daily gefitinib would have activity comparable with reported results using 500 mg daily as in NSCLC. In fact, the current study was designed to reject a null hypothesis that the overall response rate of 250 mg daily gefitinib is <5%. The previous trial of 500 mg gefitinib daily reported an 11% response rate, 3.4-month time to progression, and 8.1-month median overall survival (Table 4; ref. 3). Although 250 mg gefitinib daily was well tolerated, this dose had minimal activity. In addition, the relatively short 1.8-month progression-free survival would suggest that 250 mg daily gefitinib is of much less benefit to these patients. These results are in direct contrast to the randomized phase II studies in NSCLC that observed almost identical response rates, symptom improvement, and survival between 250 and 500 mg of gefitinib (4, 5).

This disparity in results may be attributed to statistical anomaly or random variation but more likely results from biological differences between NSCLC and SCCHN with respect to the effect of the EGFR TKI gefitinib. Certainly, one must be cautious when comparing phase II trials. Despite the attempt to control variables and biases, all confounding factors that might influence outcome cannot be known or accounted for. The patient characteristics on the two recurrent and/or metastatic SCCHN trials were similar but notable differences included a greater proportion of patients with distant metastasis in the 250 mg trial compared with the 500 mg trial (71% versus 53%, respectively). Moreover, there was a difference in a single eligibility criterion between the studies, specifically the number of allowable prior therapies. Nevertheless, analysis of the patient subset in this study that received one or no prior therapies for recurrent or metastatic disease (Table 4, column 3) does not yield more favorable efficacy variables. This observation also confirms the reported phenomenon that the number of prior regimens a patient receives does not influence the likelihood of response to EGFR TKI (4, 5, 17).

The results reported here suggest that in the setting of recurrent or metastatic SCCHN, 250 mg of daily gefitinib is less active than 500 mg. This observation has significant implications for both this class of agents and this disease, suggesting that a dose-response relationship for these agents exists in the dose range that should achieve target inhibition. In fact, doses higher than 500 mg may be optimal with respect to efficacy and should be further explored in diseases where single-agent activity has been observed. A phase II trial administering the EGFR TKI erlotinib at 150 mg daily to 115 refractory SCCHN patients observed a 4.3% objective response rate and 9.6-week median progression-free survival and could be viewed as an example of dosing an EGFR TKI at the maximum tolerated dose (18). Those results suggest that efficacy will inevitably plateau with these agents but can be greater than that realized using 250 mg gefitinib daily.

The current results also likely reflect a difference in the mechanism of response to EGFR TKI between SCCHN and NSCLC. In NSCLC, the presence of somatic EGFR tyrosine kinase mutations has been described in ~10% of non-Asian and 30%...
of Asian unselected patients (19). These mutations seem to be a predictor of objective response to EGFR TKI and correlate with demographic factors associated with higher response rates. Thus, a molecular and clinical subset of NSCLC patients most likely to derive a benefit from these agents is identifiable. To date, such mutations have been reported in 7% of 41 unselected SCCHN Asian patients (20). In an analysis of samples from eight SCCHN patients in the United States treated with EGFR TKI, no mutations were discovered in the EGFR tyrosine kinase domain (21). If the mutation frequencies in NSCLC between ethnic groups were mirrored in SCCHN, one would expect substantially lower frequencies in the non-Asian population treated in this study. Moreover, because the majority of EGFR mutations occur in the adenocarcinoma subtype of NSCLC, SCCHN tumors would be expected to contain a significantly lower mutation frequency.

It is possible, therefore, that in tumors with predominantly wild-type EGFR, such as SCCHN, a higher level of EGFR TKI is required to achieve tumor response or clinical benefit, thus substantiating a dose-response observation. Another possibility is that, at higher doses, these agents are more promiscuous in their inhibitory profiles and effect kinases besides EGFR. In fact, a patient responding to 500 mg gefitinib has been described with an ERBB2 kinase domain mutation (21).

Interestingly, despite the lack of objective responses in this study, a positive correlation between all outcome measures and skin toxicity was observed. This association has been noted in every trial administering an EGFR inhibitor in SCCHN and in several other disease-specific studies (2). In the present study, the sample size allowed examination of the correlation in relation to grade of cutaneous toxicity and, similar to the single-agent erlotinib trial in SCCHN, patients who developed higher grades of rash had a higher likelihood of achieving disease control, longer progression-free survival, and improved overall survival. The skin toxicity associated with these agents likely represents a mechanistic effect related directly to EGFR inhibition. The lesions seem to be secondary to recruitment of inflammatory cells, eventually producing the characteristic rosacea-like rash (22, 23).

The explanation of the association between outcome and skin toxicity has not been fully elucidated. The simplest argument suggests that this is a pharmacokinetic phenomenon and draws support from data in patients with advanced NSCLC and breast cancer, demonstrating a correlation between trough concentrations of EGFR TKI and the incidence of rash (24, 25). As a result of this observation, a strategy of escalating the dose of EGFR TKI to produce grade 2 or greater cutaneous toxicity is currently undergoing testing in clinical trials.

However, there is a weak relationship between EGFR TKI concentration and activity and, clearly, there are patients who develop the characteristic rash at low drug plasma concentrations. Polymorphisms of the EGFR gene have been described that seem to influence expression of the protein (26, 27). Amador et al. (27) observed that one such polymorphism involving the number of CA single sequence repeats in intron 1 was associated with sensitivity to erlotinib in a panel of SCCHN cell lines. Furthermore, in SCCHN patients, the number of CA repeats was equivalent in tumor and genomic DNA and, in colorectal cancer patients, the number of repeats correlated with development of skin toxicity. These findings support a pharmacogenetic hypothesis that certain patients are genetically prone to develop the rash, that the rash is directly related to EGFR inhibition, that epithelial tumors retain identical genetic determinants of toxicity, and that these polymorphisms also render the cancer cells sensitive to EGFR blockade. The exploration of EGFR gene polymorphisms and their relationship to toxicity and outcome is currently being evaluated in prospective clinical trials.

The QoL instrument used in this study was very acceptable to patients as evidenced by the high rate of compliance. In

Table 4. Comparison of outcome measures observed during two sequential phase II trials administering single-agent gefitinib

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>500 mg gefitinib</th>
<th>250 mg gefitinib</th>
<th>250 mg gefitinib, 1 l prior CT for advanced disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>10.6</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>SD (%)</td>
<td>43</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>TTP (median in mo)</td>
<td>3.4</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>OS (median in mo)</td>
<td>8.1</td>
<td>5.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Abbreviations: RR, response rate; SD, stable disease; TTP, time to progression; OS, overall survival; CT, chemotherapy.
addition, whereas there was some suggestion that patients with stable disease showed short-term improvement in QoL, overall there was little change in patients’ scores over the course of the study. These results parallel clinical observations that whereas gefitinib 250 mg daily had little effect on SCCHN, it also did not produce significant toxicity nor lead to decline in QoL.

At the start of the trial, we hypothesized that gefitinib would be most effective in tumors that were dependent on EGFR-regulated growth. As a surrogate of this phenotype, we studied serum levels of VEGF and TGF-α. Serum levels of both these growth factors were increased above the normal range in the patients enrolled. However, gefitinib treatment did not reduce serum levels of these proteins, and, in fact, TGF-α levels rose significantly. Moreover, even in patients whose levels decreased over the interval, there was no evidence of increased efficacy. The lack of effect on VEGF and the increase in TGF-α could result from the overall lack of efficacy of the agent at this dose. However, even in patients without progressive disease at 8 weeks whose tumor burden presumably did not increase substantially, an increase in TGF-α was observed. Interestingly, an increase in circulating TGF-α has been noted in a preclinical model using the monoclonal EGFR antibody, cetuximab (28). This was hypothesized to be secondary to disruption of ligand-receptor interaction caused by cetuximab resulting in greater amounts of free TGF-α. The current study suggests that disruption of EGFR signaling per se could produce a paradoxical rise in TGF-α through a mechanism that might involve a biochemical feedback loop between the ligand and receptor. Hypothetically, inhibition of EGFR signaling could result in increased production and/or secretion of TGF-α.

One must also consider that these proteins are excreted as autocrine and paracrine growth factors that act in the local microenvironment, and circulating levels between baseline and week 8 of therapy do not reflect this. Thus, serum levels of VEGF and TGF-α measured in this study may not be appropriate pharmacodynamic surrogates of gefitinib effect and tumor levels may best serve this purpose.

The present study, therefore, strongly suggests that 250 mg gefitinib daily is not as active as 500 mg daily in recurrent and/or metastatic SCCHN. Reasons for the difference between this observation and NSCLC trials are speculative but are consistent with what is being learned regarding mechanisms of response to EGFR TKI. The need to identify SCCHN patients who are most likely to respond to EGFR TKI continues to be of paramount importance although it seems that higher doses of gefitinib are required for maximal benefit in this disease.

Acknowledgments

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References

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