Response of Some Head and Neck Cancers to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors May Be Linked to Mutation of *ERBB2* rather than *EGFR*

Ezra E.W. Cohen,[1] Mark W. Lingen,[1,2,3] Leslie E. Martin,[2] Patricia L. Harris,[4] Brian W. Brannigan,[4] Sara M. Haserlat,[4] Ross A. Okimoto,[4] Dennis C. Sgroi,[4,5] Sonika Dahiya,[4,5] Beth Muir,[4,5] John R. Clark,[4] James W. Rocco,[4,6] Everett E. Vokes,[1,3] Daniel A. Haber,[4] and Daphne W. Bell[4]

Abstract

Purpose: Small-molecule tyrosine kinase inhibitors (TKI) of the epidermal growth factor receptor (EGFR) have shown modest yet reproducible response rates in patients with squamous cell carcinoma of the head and neck (SCCHN). Somatic mutations in *EGFR* have recently been shown to be predictive of a clinical response in patients with non–small cell lung cancer (NSCLC) treated with these inhibitors. The objective of this study was to determine if such mutations, or recently reported mutations in *ERBB2*, also underlie EGFR-TKI responsiveness in SCCHN patients.

Experimental Design: We sequenced the kinase domain of *EGFR* and exon 20 of *ERBB2* in tumor specimens from eight responsive patients. In addition, mutational analysis was done on tumor specimens from nine gefitinib nonresponders and 65 unselected cases of SCCHN.

Results: None of eight TKI-responsive specimens had mutations within the kinase domain of *EGFR*. *EGFR* amplification was also not associated with drug responsiveness. However, a single responsive case had a somatic missense mutation within exon 20 of *ERBB2*.

Conclusion: Our data indicate that unlike NSCLC, *EGFR* kinase mutations are rare in unselected cases of SCCHN within the United States and are not linked to gefitinib or erlotinib responses in SCCHN. Alternative mechanisms, including *ERBB2* mutations, may underlie responsiveness in this tumor type.

Squamous cell carcinoma of the head and neck (SCCHN) is diagnosed annually in ~40,000 individuals in the United States (1). Despite current therapeutic modalities, as many as half these will recur, or develop metastases, and eventually succumb to their disease, highlighting the need for alternative forms of therapeutic intervention. Because epidermal growth factor receptor (EGFR: ERBB1 and HER1) is almost universally expressed in SCCHN and high levels of expression have been correlated with a poor clinical prognosis (2–6), clinical trials were undertaken to assess the efficacy of kinase inhibitors that target this growth factor, including gefitinib and erlotinib (7), reporting significant responses in up to 11% of patients refractory to other therapies (8).

Although the response rate of SCCHN to gefitinib and erlotinib is comparable with that seen in non–small cell lung cancer (NSCLC), the demographic and histologic variables associated with responsive cases differ remarkably. In lung cancer, drug responses are characteristically seen in adenocarcinomas arising in nonsmokers, with an increased frequency among women and Asians (9, 10). In contrast, responsive cases of SCCHN were indistinguishable from nonresponsive cases in terms of their histology or associated history of tobacco exposure (8).

In NSCLC, clinical responses to gefitinib or erlotinib have recently been ascribed to the presence of activating mutations within the kinase domain of *EGFR* (11–16). Experimentally, cells expressing these mutant receptors seem dependent upon altered survival signals transduced by these receptors, which themselves also display increased sensitivity to inhibition by gefitinib (17). Thus, at least in a subset of NSCLC, somatic mutations in *EGFR* seem to drive tumorigenesis and provide a biologically relevant target for therapeutic intervention. Clinically, these mutations are associated with dramatic responses to EGFR tyrosine kinase inhibitors (TKI) and may define a biological subset of NSCLC patients. To determine if this molecular mechanism extends to SCCHN, we sequenced the kinase domain of *EGFR* (exons 18-24) in tumors from gefitinib or erlotinib responsive cases as well as untreated cases from the United States.

Authors' Affiliations: Departments of [1]Medicine, [2]Pathology, and [3]Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois; [4]Cancer Center and [5]Department of Pathology, Massachusetts General Hospital, Charlestown, Massachusetts; and [6]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts
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Requests for reprints: Daniel A. Haber, Massachusetts General Hospital Cancer Center, CNY7, 149 13th Street, Charlestown, MA 02129. Phone: 617-724-7805; Fax: 617-724-6919; E-mail: haber@helix.mgh.harvard.edu.

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Materials and Methods

Tissue samples. Tissue samples were collected from patients treated at the University of Chicago or Massachusetts General Hospital. Three groups of patient samples were analyzed: those with tumors responding to EGFR-TKI, those with tumors not responding to EGFR-TKI, and randomly selected patients not previously treated with EGFR-TKI. Samples from patients who were treated with EGFR-TKI were collected before therapy with either gefitinib (500 or 250 mg) or erlotinib (150 mg in combination with 15 mg/kg bevacizumab; Table 1). The Response Evaluation Criteria in Solid Tumors were used to evaluate response in all cases. Consent to obtain, store, and analyze tissue was obtained on all patients according to institutional review board guidelines.

Mutational analysis of EGFR and ERBB2. H&E-stained sections of formalin-fixed, paraffin-embedded tissue or of snap-frozen tissue were reviewed by a pathologist to estimate the overall tumor cell content. In cases where tumor cells comprised <70% of the tissue, laser capture microdissection was employed to isolate a homogenous tumor cell population. DNA was isolated by standard phenol-chloroform extraction and ethanol precipitated using glycogen as a carrier followed by resuspension in 30 μL TE buffer.

Exons 18 to 24 of *EGFR* and exon 20 of *ERBB2* were amplified using nested PCR consisting of an initial primary PCR followed by a secondary PCR. Primer pairs (sense and antisense) used in the initial amplification of *EGFR* were as follows: exon 18, CAAGTGCCGTGTCCTGGCACCCAAGC and CCAAACACTCAGTGAAACAAAGAG; exon 19, GCAATATCAGCCTTAGGTGCGGCTC and CATAGAAAGTGAACATTTAGGATGTG; exon 20, CCATGAGTACGTATTTTGAAACTC and CATATCCCCATGGCAAACTCTTGC; exon 21, CTAACGTTCGCCAGCCATAAGTCC and GCTGCGAGCTCACCCAGAATGTCTGG; exon 22, GAGCAGCCCTGAACTCCGTCAGACTG and CTCAGTACAATAGATAGACAGCAATG; exon 23, CAGGACTACAGAAATGTAGGTTTC and GTGCCTGCCTTAAGTAATGTGATGAC; exon 24, GACTGGAAGTGTCGCATCACCAATG and GGTTTAATAATGCGATCTGGGACAC. The primer pair (CTGTGGGCCATGGCT GTGGTTTG and GGAATGGGAAGCACCCATGTAGACC) was used in an initial amplification of exon 20 of *ERBB2*. Primary reactions contained 2 μL genomic DNA as a template in a 25-μL reaction consisting of 1× buffer, 50 μmol/L deoxynucleotide triphosphate, 200 nmol/L sense primer, 200 nmol/L antisense primer, and 0.8 unit Expand Taq (Roche Diagnostics, Mannheim, Germany).

Nested primers pairs used in secondary amplification of *EGFR* were exon 18, GCACCCAAGCCCATGCCGTGGCTGC and GAAACAAAGAGTAAAGTAGATGATGG; exon 19 CCTTAGGTGCGGCTCCACAGC and CATTTAGGATGTGGAGATGAGC; exon 20, GAAACTCAAGATCGCATTCATGC and GCAAACTCTTGCTATCCCAGGAG; exon 21, CAGCCATAAGTCCTCGACGTGG and CATCCTCCCC TGCATGTGTTAAAC; exon 22, GACGGGTCCTGGGGTGATCTGGCTC and CTCAGTACAATAGATAGACAGCAATG; exon 23, GTAGGTTTCTAAACATCAAGAAAC and GTGATGACATTTCTCCAGGGATGC; exon 24, CATCACCAATGCCTTCTTTAAGC and GCTGGAGGGTTTAATAATGCGATC. Exon 20 of ERBB2 was amplified using nested primers CTGTGGGCCATGGCTGTGGTTTG and GGAAGCACCCATGTAGACCTTCTGG. Nested reactions contained 2 μL primary PCR product as a template in a 25-μL reaction consisting of 1× buffer, 50 μmol/L deoxynucleotide triphosphate, 200 nmol/L sense primer, 200 nmol/L antisense primer, and 0.8 unit Expand Taq (Roche Diagnostics). Cycling conditions for both primary and secondary PCR reactions were 95°C for 15 minutes followed by 40 cycles consisting of 95°C for 30 seconds, 58°C for 30 seconds, 72°C for 45seconds followed by 72°C for 5 minutes. PCR amplicons were purified using exonuclease I (U.S. Biochemical, Cleveland, OH) and shrimp alkaline phosphatase (U.S. Biochemical) and diluted in water before bidirectional capillary sequencing, which was done using BigDye Terminator v1.1 chemistry (Applied Biosystems, Foster City, CA) in combination with an ABI3100 instrument according to the manufacturer's instructions. Electropherograms were aligned and reviewed using Sequence Navigator software.

Determination of EGFR copy number. *EGFR* copy number was determined by Taqman real-time quantitative PCR with Taqman Universal PCR mastermix and an ABI Prism 7900HT sequence detection system (Applied Biosystems). The primers (5′-3′) and fluorogenic probe used for *EGFR* were CAATTGCCAGTTAACGTCTTCCTT (sense primer), TTTCTCACCTTCTGGGATCCA (antisense primer), and TCTCTCTGTCATAGGGAC (probe). For the control gene, *PCDH7*,

Table 1. Characteristics of patients on EGFR inhibitor clinical trials who demonstrated an objective response

Case no	Age at start of therapy	Sex	Race	Primary site	Histology*	Smoking history†	Prior therapy	Treatment‡	Response	Duration of response (mo)	Overall survival (mo)
1	50	F	W	OC (tongue)	VC	4	CRT, CT	G 500 mg	PR	11.0	18
2	51	M	W	OP (pharynx)	PD	3	CT	G 500 mg	PR	3.1	3.2
3	53	M	W	OC (buccal)	PD	2	CRT	G 500 mg	CR	4.7	6
4	64	M	W	OP (BoT)	PD	1	CRT	G 500 mg	PR	8.5	20
5	72	M	W	SGL	MD	5	CRT	G 500 mg	Minor	9.0	37.4
6	62	M	W	OP (pharynx)	WD	4	CRT	G 250 mg	PR	5.5	5.5
7	75	F	W	OC (buccal)	MD	4	CRT	E 150 mg + B 15 mg/kg	CR	>8.0§	>8.0
8	59	M	W	OP (tonsil)	MD-PD	3	CRT, CT	G 500 mg	PR	4	7

NOTE: Response was assessed using the Response Evaluation Criteria in Solid Tumors in all patients, and all responses were verified by independent review. Duration of response is defined from first evidence of response until first evidence of disease progression measured in months. Overall survival is defined from start of therapy until death measured in months.

Abbreviations: M, male; F, female; W, White; OC, oral cavity; OP, oropharynx; AR, alveolar ridge; BoT, base of tongue; SGL, supraglottic larynx; VC, verrucous carcinoma; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; CRT, chemoradiotherapy; CT, chemotherapy alone; G, gefitinib; E, erlotinib; B, bevacizumab; PR, partial response; CR, complete response.

*Only patients with squamous cell carcinoma were eligible to participate in the clinical trials.

†1, never used tobacco products; 2, used pipe, cigar, or chewing tobacco; 3, <20 pack-years cigarette use; 4, 20-40 pack-years cigarette use; 5, >40 pack-years cigarette use. Pack years is defined as the number of packs smoked per day multiplied by the number of years smoked.

‡All EGFR-TKIs were administered orally once daily without interruption. Bevacizumab was administered intravenously every 3 weeks.

§This patient remains on therapy at time of article submission.

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Table 2. Number of cases analyzed from each clinical cohort

Clinical cohort	No. cases
EGFR-TKI Responders	8
EGFR-TKI Nonresponders	9
Unselected SCCHN	
Smokers	50
Never smokers	15

these were GCTGCAATCTCCTCCCTGAA (sense primer), TGCCTTTTCTCACCTGCATTC (antisense primer), and CCACTGCTCCGACATG (probe).

Results

The kinase domain of *EGFR* (exons 18-24) was sequenced in tumors from eight gefitinib or erlotinib responsive cases of SCCHN (Table 1) treated at the University of Chicago (seven cases) or at Massachusetts General Hospital (one case). Of these, two cases had a complete response, and others had partial responses. We also sequenced the *EGFR* kinase domain in nine tumors from gefitinib nonresponders. No somatic mutations were detected in any of these TKI-treated cases of SCCHN (Table 2). To determine whether such mutations are present in unselected cases of SCCHN, we genotyped 50 cases of characteristic SCCHN cancers from the Massachusetts Eye and Ear Infirmary tumor bank and an additional 15 cases of SCCHN arising in never smokers (Table 2). None of these cases had detectable mutations within the kinase domain of *EGFR*. Given the recent report of *EGFR* gene amplification in some NSCLC cases responsive to gefitinib (18), as well as the occurrence of *EGFR* amplification in a subset of untreated cases (19, 20), we also determined the copy number of *EGFR* in treated SCCHN cases using quantitative PCR. No amplification of *EGFR* was detected among five responsive cases, whereas a single nonresponsive case had low level (2- to 4-fold) amplification (data not shown).

In addition to specific mutations in the kinase domain of *EGFR*, similar mutations have recently been reported in the related growth factor *ERBB2* (*HER2*) within a subset of NSCLC (21, 22). ERBB2 heterodimerizes with EGFR, such that inhibition of EGFR kinase activity by TKI is expected to reduce ERBB2-dependent signaling. Furthermore, although both gefitinib and erlotinib have high specificity for EGFR, they also exhibit some *in vitro* activity towards ERBB2 (gefitinib IC_{50} = 3,700 nmol/L; erlotinib IC_{50} = 350 nmol/L). We therefore tested for mutations in the reported *ERBB2* hotspot (exon 20) in our cohort of TKI-responsive cases of SCCHN. Of four evaluable cases of responsive SCCHN, one (case 2, treated with gefitinib 500 mg oral dose) harbored a heterozygous mutation within *ERBB2*, which was not present in surrounding normal stromal tissue (Fig. 1). The variant resulted in a nucleotide alteration from T to C at position 2318 leading to an amino acid substitution of alanine for valine at codon 773. Importantly, this residue forms part of the recurrent insertions (ins774AYVM and ins776YVMA) previously described in untreated NSCLC (21, 22), raising the possibility that such mutations may be linked to EGFR-TKI responsiveness. No somatic mutations of *ERBB2* were identified in tumors from nine unresponsive SCCHN cases (P = 0.307) or among 56 untreated cases resected from smokers (50 cases) or never smokers (six cases).

Discussion

We have found that neither *EGFR* kinase domain mutations nor gene amplification explain the response of a subset of SCCHN to erlotinib and gefitinib, and that *EGFR* mutations are rare among cases of SCCHN within the U.S. population. While this work was in progress, Lee et al. reported the presence of *EGFR* kinase domain mutations in ~7% of unselected cases of SCCHN from Korea (23). The fact that we did not observe such mutations among 65 cases of unselected SCCHN from the United States, 17 cases of patients treated with EGFR-TKI, nor among seven SCCHN cell lines reported previously (11), suggests that the frequency of *EGFR* mutations in SCCHN cancer may differ among ethnic groups. Such a difference in the prevalence of *EGFR* mutations between East Asian and European populations is now well established for NSCLC (12, 14–16, 24–26), and its extension to SCCHN is of

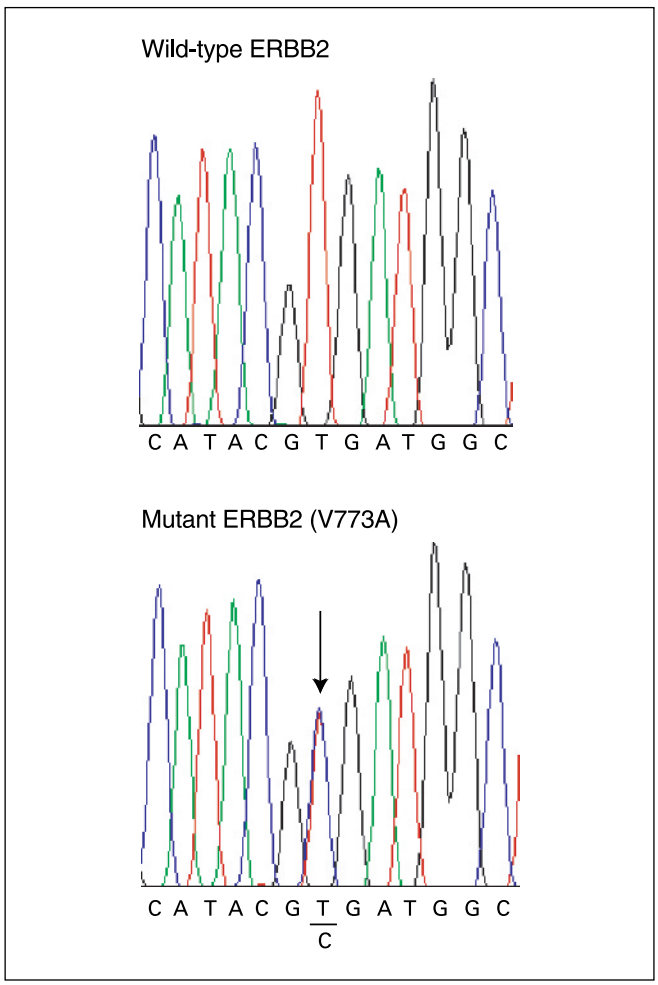

Fig. 1. Mutation of *ERBB2* within a gefitinib-responsive tumor. A single base substitution of C forTat nucleotide 2318 (*arrow*) leads to an amino acid substitution of alanine for valine at codon 773 in the tumor from case 2. A wild-type sequence is shown for comparison.

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considerable interest in searching for genetic and environmental risk factors. It will be important to determine whether *EGFR* mutations in Eastern Asian SCCHN patients are associated with response to EGFR-TKIs.

Our findings further suggest that *ERBB2* mutations may be linked to EGFR-TKI sensitivity in at least some of these responsive cases. Although *ERBB2* mutations within this region of the gene have been described in NSCLC their functional relevance to gefitinib or erlotinib responsiveness, or dual inhibitors of EGFR/ERBB2, such as lapatinib or HKI-272, has not yet been evaluated. This observation has clinical significance, as *EGFR* mutational testing enters the clinical arena as a predictor of therapeutic response to TKI in lung cancer. Alternative mechanisms must be sought to explain the majority of responses in SCCHN.

The absence of *EGFR* mutations in TKI-responsive SCCHN studied here is perhaps not surprising, given the unique subset of lung cancers defined by such mutations (i.e., adenocarcinomas arising in never smokers), with apparent modulation by both sex and ethnic factors (11–16, 24–26). In our study, no such distinct phenotype was evident in responsive cases of SCCHN. In this context, it is interesting to note that a dose-response effect for gefitinib may exist in SCCHN cancers (response rates of 1% in a study using 250-mg daily dosing, versus 11% in a second study using a 500-mg dose; refs. 8, 27). Thus, in contrast to the exquisite sensitivity of tumors with mutant *EGFR* to gefitinib and the absence of different responses at these two doses (9, 10), inhibition of EGFR-dependent signaling even in responsive cases of SCCHN may require higher drug levels.

In conclusion, we note that most SCCHN cases responsive to gefitinib or erlotinib do not seem to have mutations in *EGFR* or *ERBB2*, as does a small subset of responsive NSCLC. Further studies are required to determine whether a unifying molecular mechanism may underlie TKI responsiveness in such cases and potentially in other tumor types where occasional gefitinib and erlotinib responses have been reported.

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