Spotlight on Clinical Response

Molecular Cancer Therapeutics

Response to Erlotinib in Patients with *EGFR* Mutant Advanced Non–Small Cell Lung Cancers with a Squamous or Squamous-like Component

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Abstract

We previously reported that although *EGFR* mutations are not a feature of pure squamous cell carcinomas (SCC) of the lung, these mutations do occur in adenosquamous carcinomas (AD-SCC) and in rare solid adenocarcinomas, both of which can mimic SCC in small samples. Here we present an expanded series of these cases with a focus on sensitivity to erlotinib. The study included 13 patients with *EGFR* mutant lung carcinomas, which after detailed pathologic review were classified as AD-SCC ($n = 11$) or solid adenocarcinoma ($n = 2$). The majority received a diagnosis of SCC in at least 1 sample. All patients were treated with erlotinib. Eight of 11 patients with AD-SCC were evaluable for response. Their overall response rate was 88% (7/8; 95% CI, 47% to 99%). One of 2 solid adenocarcinoma patients responded to erlotinib. As a group, median progression-free survival was 12 months (95% CI, 8 to not reached); median overall survival was 29 months (95% CI, 27 to not reached). In conclusion, *EGFR* mutant AD-SCC and solid adenocarcinoma show a response to erlotinib that is comparable to that seen in patients with conventional adenocarcinoma. These tumors can mimic SCC in small samples. We propose an approach to increase the capture of these rare histology patients for *EGFR* mutation testing. *Mol Cancer Ther; 11(11); 2535–40. ©2012 AACR.*

Introduction

The sensitivity of a subset of non–small cell lung cancers (NSCLC) to EGFR TKIs is firmly linked to the presence of activating *EGFR* mutations (1). *EGFR* mutations occur almost exclusively in conventional adenocarcinomas of lung. The majority of the data on tyrosine kinase inhibitors (TKI) sensitivity is thus derived from mutations that arise in this histology, with radiographic response rates ranging from 55% to 91% and progression-free survival (PFS) ranging from 7 to 13 months (1, 2).

In contrast to TKI sensitivity in conventional adenocarcinomas, TKI sensitivity in *EGFR*-mutant carcinomas of unusual histology is not well established. Recent data suggest that histology can modify the sensitivity of *EGFR*-mutant tumors to TKIs. For example, carcinomas with epithelial–mesenchymal transition and small cell carcinomas may be inherently TKI-resistant despite the presence of activating *EGFR* mutations (3–5). The impact of other non-adenocarcinoma histologies, particularly squamous, on determining response to EGFR TKIs is not well established.

Whether *EGFR* mutations do arise in squamous cell carcinomas (SCC) of the lung is itself a controversial topic. Although several large series of surgically resected SCC tumors found no *EGFR* mutations (6, 7), a number of reports, primarily from small biopsy/cytology samples, have found *EGFR* mutations in a small proportion of SCCs. We have recently shown that the 2 main settings in which clinical small biopsy/cytology samples with a diagnosis of SCC are found to harbor *EGFR* mutations include (1) undersampling of adenosquamous carcinoma (AD-SCC), and (2) morphologic mimicry by solid adenocarcinoma (8). We ourselves have found no *EGFR* mutations among 95 surgically resected and pathologically verified SCCs at our institution (8). This suggests that when abundant primary tumor is available for rigorous pathologic evaluation, the low rate of *EGFR* mutations collapses.

AD-SCC is a rare type of lung cancer, representing 0.4% to 4% of NSCLCs, which consists of a mixture of both adeno and squamous components. *EGFR* mutations occur in AD-SCCs with a similar frequency as in adenocarcinoma, and with a similar predilection for never-smokers. Notably, *EGFR* mutations are present in both the adeno and squamous components of these tumors (9–11). The well-known diagnostic limitation inherent to small

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biopsy/cytology specimens is that such samples may contain only a single component of AD-SCC. This may result in a detection of *EGFR* mutations in a sample diagnosed as SCC.

The second, less common, explanation for the detection of *EGFR* mutations in SCC is an unusual morphologic variant of adenocarcinoma marked by a solid growth pattern. This can closely mimic SCC (we termed this squamous-like variant of adenocarcinoma "pseudosquamous" or "squamoid"; ref. 8). Despite a morphologic similarity to SCC, immunohistochemistry (IHC) can readily distinguish between these 2 histologies. Given the increasing usage of IHC to characterize poorly differentiated NSCLCs, this morphologic mimic is unlikely to appear under the guise of SCC in the future.

In this study, we expanded on data from our initial series of *EGFR*-mutant carcinomas with squamous and pseudosquamous histologies. Because the sensitivity to EGFR TKIs in carcinomas with these unusual histologies is not established, we sought to retrospectively determine the response of these tumors to erlotinib.

Materials and Methods

Study design, patients, and radiographic response

We identified 13 patients with *EGFR*-mutant NSCLCs that had a true squamous component ($n = 11$) or solid/pseudosquamous adenocarcinoma histology ($n = 2$). On the basis of our recent study (8), we refer to all *EGFR*-mutant samples that had a true squamous component (as confirmed by morphology and IHC) as representative of AD-SCC, irrespective of whether a glandular component could ($n = 9$) or could not ($n = 2$) be found on pathologic re-review. All pathologic samples were re-reviewed by 2 thoracic pathologists (N. Rekhtman and A.L. Moreira) using light microscopy and IHC, as described in our recent publication (8). All patients were diagnosed with recurrent or metastatic disease and treated with erlotinib. Where available, baseline and follow-up CT scans were reviewed to determine radiographic response to erlotinib as per RECIST 1.1. The study was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board.

Genotype analysis

Briefly, *EGFR* exon 19 deletions were identified through a PCR-based assay (12). *EGFR* exon 21 mutations, including secondary T790M mutations, as well as mutations in *AKT1*, *BRAF*, *ERBB2*, *KRAS*, *MEK1*, *NRAS*, and *PIK3CA* were assayed by Sequenom (Sequenom, Inc.), as described previously (8).

Statistical analysis

PFS was measured from the date at which treatment with erlotinib began to the date at which there was evidence of radiographic progression. Overall survival (OS) was measured from the date of diagnosis of stage IV disease until the date of death. Survival probabilities were calculated using the Kaplan–Meier method. Group comparison was carried out with log-rank tests and Cox proportional hazards methods. Statistical analyses were done using SAS statistical software (SAS Institute, Inc.).

Results

Patient and tumor characteristics

Clinicopathologic characteristics for the 11 patients with *EGFR*-mutant AD-SCC are summarized in Table 1. Details of the pathologic review of samples from patients 1 to 7 are provided in our recent publication (corresponding patient IDs are indicated in Table 1; ref. 8). An analogous pathologic review was carried out for patients newly identified in this series (patients 8 to 11). Overall, 9 of 11 patients had at least 1 sample with a pathologic diagnosis of SCC, highlighting the difficulty in the diagnosis of AD-SCC in small samples. Clinicopathologic characteristics for the 2 patients with solid/pseudosquamous adenocarcinoma are summarized in Table 2; their detailed morphologic and IHC characteristics are described in reference (8). Eleven of 13 (85%) patients in the cohort were never smokers.

EGFR mutation status

As shown in Tables 1 and 2, *EGFR* mutations included exon 19 deletions ($n = 9$) and exon 21 L858R substitutions ($n = 4$). No other mutations were detected. Eight patients with AD-SCC (patients 1 to 8) had paired biopsies from other sites or time-points that were used to show the presence of both squamous and glandular components in different samples from the same patient. Of these 8 patients, 5 had sufficient material for genotyping in both biopsies, which revealed identical *EGFR* mutations in all paired samples, supporting their clonal relationship despite the heterogeneous histology.

Of note, 3 samples in this series (from patients 1, 2, and 3) were biopsies taken at the time of acquired resistance (AR) to erlotinib. Two of the AR samples were entirely squamous (patients 1 and 2) and 1 was adenosquamous (patient 3). Notably, a squamous histology was also present in 2 of 3 pretreatment biopsies (patients 1 and 3). None of the 3 AR samples harbored a secondary T790M mutation, whereas the original sensitizing *EGFR* mutation was detected in all 3 samples.

Response to erlotinib

Of the 11 patients with AD-SCC, 8 were evaluable for response. Their overall response rate (ORR) was 88% (7/8 partial responses; 95% CI, 47% to 99%). One of 8 patients had stable disease. Of the 2 patients with solid adenocarcinoma, 1 patient had a partial response to erlotinib and the other, stable disease. A waterfall plot of response is shown in Fig. 1.

Only 1 patient (patient 4) had evidence, by outside report, of a divergent response to erlotinib at 2 histologically distinct biopsy sites, where a parenchymal lung tumor shrank (adenocarcinoma) while a sacral metastasis (SCC) increased in both size and FDG-avidity. Other patients in this group had no evidence of heterogeneous

Table 1. Clinicopathologic findings for patients with *EGFR*-mutant adenosquamous carcinomas

Patient[a]	Age	Gender	Race	Smoking status	Stage[b]	Biopsy #1[c]	Biopsy #1 mutation	Biopsy #2[c]	Biopsy #2 mutation	Lines of therapy	EGFR TKI line	Best response to EGFR TKI	TTP on TKI (months)	OS (months)
1 (1)	61	M	White	Never	IV	Squamous (L1)[d]	exon 19 del	Adenosquamous (LLL lung)	exon 19 del	3	2nd line	PR	12.1	27.5
2 (2)	71	F	White	Never	IV	Squamous (RLL lung)[d]	exon 19 del	Adenocarcinoma (RLL lung)	exon 19 del	2	1st line	Unavailable	19.6	32.9+
3 (3)	58	F	White	Never	IV	Squamous (RUL lung)	exon 19 del	Adenosquamous (LLL lung)†	exon 19 del	3	2nd line	SD	23.6	32.2+
4 (4)	45	F	Hispanic	Never	IV	Squamous (sacrum)	exon 19 del	Adenocarcinoma (pleural fluid)	exon 19 del	2	2nd line	Unavailable	Unavailable	15.3
5 (5)	46	M	Asian	Never	IV	Squamous (R lung)	exon 19 del	Adenocarcinoma (SC LN)	exon 19 del	1	1st line	PR	5.0+	6.6+
6 (6)	73	M	White	Former (25 PY)	IV	Squamous (adrenal)	exon 19 del	Adenocarcinoma (SC LN)	insufficient	2	3rd line	Unavailable	Unavailable	29.8
7 (10)	58	M	Asian	Never	IV	Squamous (bronchus)	L858R	Squamous (T8)	insufficient	1	1st line	PR	1.9	2.5
8 (new)	76	M	White	Never	IV[e]	Squamous (R lung)[d]	insufficient	Adenocarcinoma (L lung)	exon 19 del	1	1st line	PR	5.3	5.3+
9 (new)	68	M	White	Never	IV	Squamous (L lung)	L858R	None	N/A	4	4th line	PR	2.8+	24.0+
10 (new)	30	F	Asian	Never	IV	Adenosquamous (R lung)	L858R	None	N/A	2	1st line	PR	8.4	10.9+
11 (new)	50	M	White	Never	IV	Adenosquamous (L lung)	exon 19 del	None	N/A	1	1st line	PR	9.2+	9.6+

NOTE: The majority of patients were diagnosed with squamous cell carcinoma in at least 1 sample.

Abbreviations: SC LN, supraclavicular lymph node; PR, partial response; SD, stable disease; PY, pack years; TTP, time to progression.

[a]In parentheses are corresponding patient IDs in reference 8.

[b]Stage at the time of TKI treatment.

[c]Biopsy numbers are not chronological: biopsy #1 represents the index case (*EGFR* mutant SCC).

[d]Acquired resistance biopsy.

[e]Previous stage IIA treated with induction cisplatin + pemetrexed followed by LLL lobectomy, with subsequent development of bilateral pulmonary nodules and a recurrent parenchymal lesion at the lobectomy site.

Table 2. Clinicopathologic findings for patients with *EGFR*-mutant solid pseudosquamous adenocarcinomas

Patient[a]	Age	Gender	Race	Smoking status	Stage[b]	Initial diagnosis (site)	Mutation	Re-review	Lines of therapy	EGFR TKI line	Best response to EGFR TKI	TTP on TKI (months)	OS (months)
12 (11)	89	F	Asian	Never	IV	Squamous (lung)	L858R	Adenocarcinoma	1	1st line	SD	7.6	16.5
13 (12)	53	F	White	Former (31)	IV[c]	Squamous (lung)	exon 19 del	Adenocarcinoma	1	1st line	PR	12.4	20.6+

NOTE: Both patients were initially diagnosed with squamous cell carcinomas.

Abbreviation: TTP, time to progression.

[a]In parentheses are corresponding patient IDs in reference 8.

[b]Stage at the time of TKI treatment.

[c]Previous stage IB s/p adjuvant cisplatin + docetaxel followed by RLL lobectomy, which was subsequently followed by a metastatic recurrence.

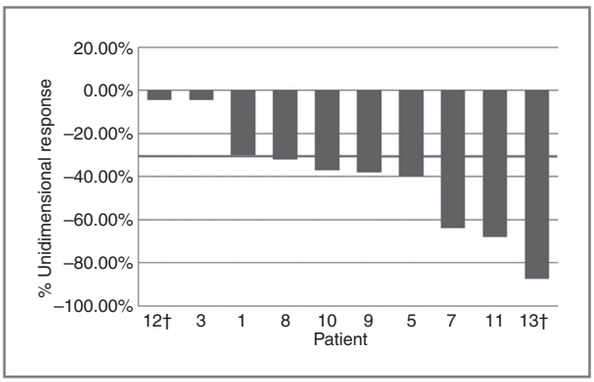

Figure 1. Radiographic response to erlotinib in patients with adenosquamous and solid pseudosquamous adenocarcinomas harboring *EGFR* mutations. †, denotes solid (pseudosquamous) adenocarcinomas; other cases are carcinomas with a squamous component (confirmed or presumed adenosquamous carcinomas).

radiologic responses, although no other patient in this series had distinct histologies at different sites of disease at the time of erlotinib treatment.

The median PFS of all evaluable patients (AD-SCC and solid adenocarcinoma) treated with erlotinib was 12 months [95% CI, 8 to not reached (NR); Fig. 2]. Median OS was 29 months (95% CI, 16 to NR; Fig. 3). For patients with AD-SCC, median PFS was 12 months (95% CI, 8 to NR) and median OS was 29 months (95% CI, 27 to NR).

Discussion

We recently showed that *EGFR*-mutant SCCs of lung usually represent undersampled AD-SCC or, less commonly, a solid variant of adenocarcinoma (8). Here we expand on this observation, and show that these unusual tumors have an overall sensitivity to erlotinib that is similar to that seen in patients with conventional adenocarcinomas.

Previous reports on the sensitivity of *EGFR*-mutant carcinomas with squamous histology (which our study suggests represent, in the majority of cases, undersampled AD-SCC) to EGFR TKIs include only several small case series. On the basis of a pooled analysis of 15 publications, Shukuya and colleagues (13) suggested that SCCs with sensitizing *EGFR* mutations have a diminished sensitivity to EGFR TKIs, with an ORR of 38% ($n = 16$ patients) and median PFS of 3.1 months ($n = 10$ patients). In addition, several studies have described TKI responses in SCCs that harbor atypical or complex *EGFR* mutations—mutations that are thought to have no or uncertain TKI sensitizing potential (13), and SCCs lacking *EGFR* mutations (14, 15), suggesting that TKI responses in some SCCs may be related to factors other than activating *EGFR* mutations.

Our study is the largest single series to report on the response to erlotinib in patients with sensitizing *EGFR* mutations in NSCLCs with a squamous component. In contrast to the lower response seen in aggregate from previous studies, we found that these patients have an ORR of 88% and a median PFS of 12 months. Responses appeared to be uniform at all evaluable sites of disease in

almost all cases. We do note that 1 patient (patient 4) in our series had a divergent radiographic response to erlotinib, with what appeared to be primary resistance at a sacral lesion that was histologically confirmed as squamous carcinoma.

This series also included 3 patients who had a squamous component in samples obtained at the time of AR to erlotinib. Unlike cases of small cell and epithelial–mesenchymal transformation, there have been no reports correlating squamous histology with the development of AR to EGFR TKIs (3, 4). Notably, in 2 of 3 of our patients, a squamous component was also present in a pretreatment sample, suggesting that the squamous histology seen at the time of AR is more likely a manifestation of the patient's underlying AD-SCC than a result of histologic transformation. Selection for the squamous component of the underlying AD-SCC remains a possibility that we cannot exclude, however, particularly given the absence of the most common mechanism of resistance (*EGFR* T790M mutation) in all 3 AR samples with squamous histology.

Given the clinical benefit shown herein, an important practical question is how best to capture these rare unusual-histology patients for *EGFR* mutation testing. As a first step, we recommend using strict morphologic criteria and, if needed, widely advocated IHC markers to establish a diagnosis of SCC and to exclude solid/pseudosquamous adenocarcinoma (8, 16, 17). Cases found to represent solid adenocarcinoma should be tested for *EGFR* mutations and treated with TKI based on the responses shown herein. For pathologically verified SCC in primary resections (where the likelihood of undersampled AD-SCC is low), we do not advocate routine *EGFR* testing, which is supported by the lack of *EGFR* mutations in such samples in several previous studies (6, 7, 8).

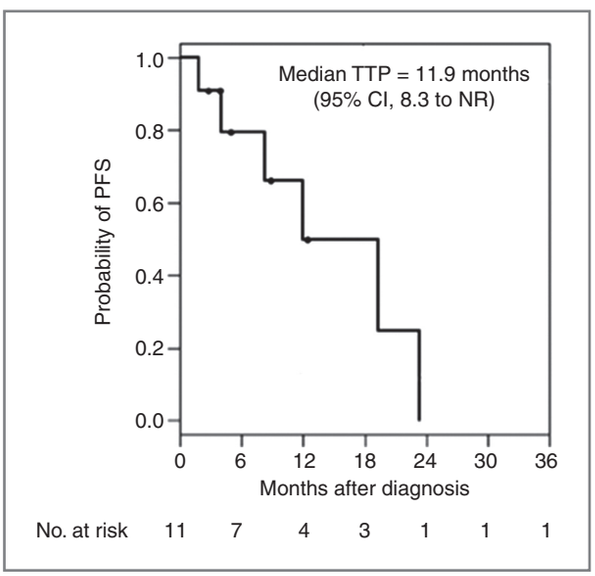

Figure 2. Kaplan–Meier survival curve for progression-free survival (PFS) in patients with *EGFR*-mutant adenosquamous and solid pseudosquamous adenocarcinomas treated with erlotinib. NR, not reached; TTP, time to progression.

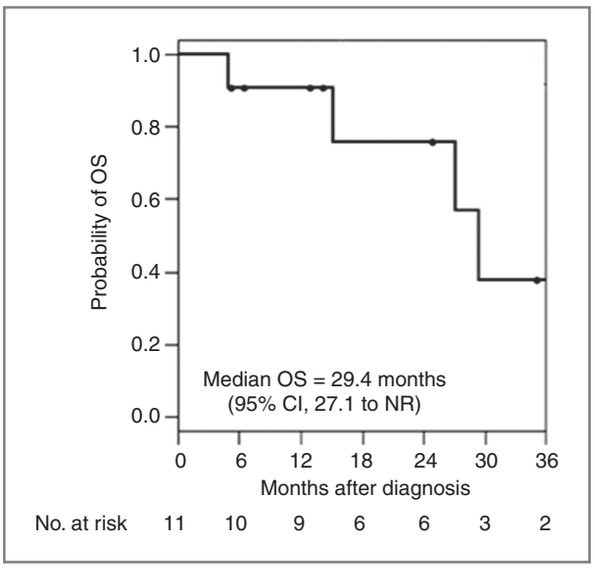

Figure 3. Kaplan–Meier survival curve for overall survival (OS) in patients with *EGFR*-mutant adenosquamous and solid pseudosquamous adenocarcinomas treated with erlotinib. NR, not reached.

In small biopsy samples, however, neither morphology nor IHC can surmount the problem of incomplete sampling of an underlying AD-SCC, where the glandular component may simply not be represented. Although analysis of multiple small samples (as in this retrospective series) increases the likelihood of detecting both components, it does not guarantee it. Thus, in a prospective setting, it may be impossible to distinguish pure SCC from a component of AD-SCC in a single (or even several) small samples. Given this inherent limitation, the only way to ensure capture of all *EGFR* mutations would be to test all small samples with a diagnosis of SCC. This is unlikely to be cost-effective, given the low prevalence of AD-SCC relative to pure SCC. As almost all cases in this series were referred for *EGFR* mutation testing based on the atypical presentation of SCC in a never smoker, we believe that this single clinical factor, which heralds a higher likelihood of finding an underlying AD-SCC than true SCC (based on the low incidence of never smokers with pure SCC seen in our previous series; ref. 8), can be used to guide whether or not these patients should undergo testing. This recommendation stems in part from a prioritization of resources, which may be obviated in the future with the introduction of routine multiplex genotyping of lung SCCs (18).

Disclosure of Potential Conflicts of Interest

M.G. Kris received commercial research grant from Boehringer-Ingelheim, Pfizer Inc., Genentech-Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: P.K. Paik, M.G. Kris, N. Rekhtman
Development of methodology: P.K. Paik, M.G. Kris

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.K. Paik, A.L. Moreira, M. Ladanyi, M.G. Kris, N. Rekhtman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.K. Paik, A.M. Varghese, C.S. Sima, A.L. Moreira, M. Ladanyi, M.G. Kris, N. Rekhtman
Writing, review, and/or revision of the manuscript: P.K. Paik, A.M. Varghese, C.S. Sima, A.L. Moreira, M. Ladanyi, M.G. Kris, N. Rekhtman
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