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Aberrations in the epidermal growth factor receptor gene in 958 patients with diverse advanced tumors: implications for therapy

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Background: Epidermal growth factor receptor (*EGFR*) mutations are associated with the response to EGFR inhibitors in patients with non-small-cell lung cancer (NSCLC). We sought to investigate *EGFR* aberrations in patients with diverse advanced cancers.

Patients and methods: Patients referred to the phase I clinic were evaluated for the presence of *EGFR* mutations and response to therapy.

Results: *EGFR* aberrations were detected in 34 of 958 patients (3.5%). Though *EGFR* mutations were most frequent in NSCLC (21 of 131, 16%), they were also present in a variety of other solid tumors (13 of 827 patients, 1.6%) including adrenocortical (1/10 patients), skin (1/24), breast (1/55), carcinoid (1/8), cholangiocarcinoma (1/20), head and neck (1/61), ovarian (1/84), parathyroid (1/1), salivary gland (1/20), renal (1/17), sarcoma (2/38), and thymic carcinomas (1/7). Of the 13 *EGFR* aberration-positive non-NSCLC patients (median number of prior systemic therapies = 3), 6 had treatment with an EGFR inhibitor. Two patients (diagnosis = parathyroid tumor and basal cell carcinoma) achieved stable disease (SD), lasting 6 and 7 months, respectively.

Conclusion: We found *EGFR* aberrations in 1.6% of a large group of patients with diverse tumors other than NSCLC, and treatment with an EGFR inhibitor could be associated with prolonged SD.

Key words: *EGFR* mutation, non-NSCLC, phase I trials, response, time-to-treatment failure

introduction

The emergence of a personalized medicine paradigm supports the treatment of cancer according to an individual's molecular profile [1–5]. This treatment strategy is validated by recent 'success stories' in cancer: Bcr-Abl kinase inhibitors in *BCR-ABL*-positive chronic myelogenous leukemia, Kit kinase inhibitors in *KIT* mutation-positive gastrointestinal stromal tumors, BRaf inhibitors in *BRAF* mutation-positive melanoma, and an ALK tyrosine-kinase inhibitor in *ALK*-positive non-small-cell lung cancer (NSCLC) [1–3, 6]. Targeting the specific molecular characteristics of these subtypes results in increased response rates [1–8].

The epidermal growth factor receptor (EGFR) signaling pathway is activated in many different cancers [9, 10]. Activation may be mediated by mutations in four exons (18 through 21), which encode part of the tyrosine-kinase domain and are clustered around the ATP-binding pocket of the enzyme [10–13]. There is a broad literature on the efficacy of EGFR inhibitors in lung cancer [12, 14–17], but less is known about the presence and significance of *EGFR* mutations in other solid tumors [18–29]. The success of treatment of *EGFR* mutation-positive NSCLC with EGFR inhibitors prompted us to investigate aberrations in this gene in a group of patients with diverse advanced tumors.

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patients and methods

patients

We reviewed the electronic records of 958 consecutive patients with advanced solid tumors referred to the Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program) at The University of Texas MD Anderson Cancer Center beginning 1 January 2009 to determine the *EGFR* mutation status in this patient population and their clinical outcomes. The study and all treatments were conducted in accordance with the guidelines of the MD Anderson Institutional Review Board.

tissue samples and mutation analyses

EGFR mutations were investigated in archival formalin-fixed, paraffin-embedded tissue blocks or material from a fine needle aspiration biopsy

obtained from diagnostic and/or therapeutic procedures. All histologies were centrally reviewed at MD Anderson. *EGFR* mutation testing was done in the Clinical Laboratory Improvement Amendment––a certified molecular diagnostic laboratory within the Division of Pathology and Laboratory Medicine at MD Anderson.

DNA was isolated from formalin-fixed, paraffin-embedded tissue by using a QIAmp DNA Minikit (Qiagen Inc., Valencia, CA) according to the manufacturer's instructions. *EGFR* exons 18–21 sequence were analyzed in both sense and antisense directions for the presence of mutations using nested PCR followed by direct sequencing of the nested PCR amplicons. The nested PCR was done using the primers and under annealing conditions as described by Lynch et al. [11]. The nested PCR amplicons were purified using the Qiagen QIAquick PCR purification kit, followed by cycle-sequencing using the BigDye Terminator Kit v1.1 (ABI, Foster City, CA) on an ABI Prism 3130 genetic analyzer, according to the manufacturer's instructions. Whenever possible, in addition to *EGFR*, we tested for other mutations such as *PIK3CA* (codons 532–554 in exon 9 and codons 1011–1062 in exon 20), *KRAS* (codons 12, 13, and 61), and *TP53* (exons 4–9).

treatment and evaluation

Patients who received an EGFR inhibitor may have received erlotinib or cetuximab, either alone or in combination with other drugs or each other [30, 31]. The treatment efficacy was assessed from computed tomography scans, magnetic resonance imaging and/or positron emission tomography scan at baseline before treatment initiation and then every two cycles (6–8 weeks). All radiographs were read in the Department of Radiology at MD Anderson and reviewed in the Department of Investigational Cancer Therapeutics tumor measurement clinic. Responses were categorized as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [32] criteria and were reported as best response.

statistical analysis

Patient characteristics, including demographics, tumor type, *EGFR* mutation status, and EGFR inhibitor use, were summarized using frequencies and percentages.

results

patient characteristics

A total of 958 consecutive patients with advanced tumors were analyzed for the presence of *EGFR* mutations. Thirteen of the 34 (38.2%) patients with *EGFR* mutations had advanced cancers other than NSCLC. Of the 13 patients, 9 (69%) were men and their median age was 57 years (range 41–75 years). The median number of prior therapies was 3 (range 2–11). Patient characteristics are summarized in Table 1.

EGFR aberrations

EGFR aberrations were detected in 34 of the 958 (3.5%) patients. *EGFR* aberrations were present in 21 of the 131 (16%) patients with NSCLC and in 13 of the 827 (1.6%) patients with advanced cancers other than NSCLC (see Table 1). Five patients had *EGFR* aberrations in exon 19; six, in exon 20; and three, in exon 21 (Table 2). One patient had two aberrations (exons 19 and 20). Of the 14 aberrations noted, there were two deletions (both in exon 19) and 12 point mutations. Among the aberrations, three were considered sensitive mutations, three were resistant, and the others were unknown (Table 2).

Table 1. Baseline characteristics of 13 *EGFR* mutation-positive patients with tumors other than NSCLC

Age (years)	
Median	57
Range	41–75
Gender, *n* (%)	
Male	9 (69.2)
Female	4 (30.8)
Ethnicity, *n* (%)	
Caucasian	12 (92.3)
Hispanic	1 (7.7)
Tumor type [*n*/patients tested; (%)]	
Sarcoma	2/38 (5.3)
Ovarian	1/84 (1.2)
Head and neck: squamous cell	1/61 (1.6)
Breast	1/55 (1.8)
Skin[a]	1/24 (4.2)
Salivary gland[b]	1/20 (5.0)
Cholangiocarcinoma	1/20 (5.0)
Renal	1/17 (5.9)
Adrenocortical	1/10 (10.0)
Carcinoid	1/8 (12.5)
Thymic	1/7 (14.3)
Parathyroid	1/1 (100.0)
EGFR mutation, *n* (%)	
Sensitive mutation	2 (15.4)
Resistant mutation	2 (15.4)
Sensitivity is unclear	8 (61.5)
Two mutations	1 (7.7)
KRAS mutation, *n* (%)	
Positive	0 (0)
Negative	12 (92.3)
Unknown	1 (7.7)
PIK3CA mutation, *n* (%)	
Positive	1 (7.7)
Negative	11 (84.6)
Unknown	1 (7.7)
TP53 mutation, *n* (%)	
Positive	2 (15.4)
Unknown	11 (84.6)
History of smoking, *n* (%)	
Ex-smoker	4 (30.8)
Never	9 (69.2)
Number of prior therapies	
Median	3
Range	2–11

EGFR, epidermal growth factor receptor; *KRAS*, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small-cell lung cancer; *PIK3CA*, phosphatidylinositol-3-kinase, catalytic, alpha polypeptide; *TP53*, tumor protein p53.
[a]Skin: *EGFR* mutation-positive patient had basal cell carcinoma of the skin.
[b]Salivary gland: *EGFR* mutation-positive patient had parotid carcinoma.

Simultaneous mutations were noted in three patients (Table 2). Twelve of the 13 *EGFR*-mutant patients with advanced cancers other than NSCLC were tested for *PIK3CA* proto-oncogene mutation and 1 of the 12 (8%) had simultaneous *PIK3CA* and *EGFR* mutations (H1047R mutation

Table 2. Characteristics of 13 patients with *EGFR* mutation-positive tumors other than NSCLC

Case No.	Tumor type	Histology	*EGFR* aberration (exon)	*EGFR* mutation sensitive/ resistant [10, 12, 39]	Concomitant mutations	EGFR therapy	Best response by RECIST	TTF (months)
1	Adrenocortical	Adrenal cortical carcinoma	Deletion in exon 19	Sensitive	*PIK3CA*: no *KRAS*: no *TP53*: H214Y (exon 6)	–	–	–
2	Breast	Infiltrating ductal carcinoma	G857E (exon 21)	Sensitive	*PIK3CA*: not done *KRAS*: no *TP53*: not done	–	–	–
3	Parathyroid	Parathyroid carcinoma	G796S (exon 20)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	Erlotinib	SD	6
4	Carcinoid	Carcinoid tumor	A859T (exon 21)	Possibly resistant	*PIK3CA*:H1047R (exon 20) *KRAS*: no *TP53*: not done	–	–	–
5	Cholangiocarcinoma	Moderately differentiated cholangiocarcinoma	E804K (exon 20)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	–	–	–
6	Salivary gland	Poorly differentiated carcinoma of parotid gland	D770N (exon 20)	Resistant	*PIK3CA*: no *KRAS*: no *TP53*: not done	Erlotinib, cetuximab, and bevacizumab	PD	1
7	Epiglottis	Poorly differentiated squamous cell carcinoma	H835L (exon 21)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: V157F (exon 5)	Cetuximab, carboplatin, and paclitaxel	SD	3
8	Ovarian	High-grade papillary serous carcinoma	T751I (exon 19)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	Erlotinib, cetuximab, and bevacizumab	PD	4
9	Renal	Undifferentiated adenocarcinoma	H773Y (exon 20); deletion in exon 19	Possibly resistant; sensitive	*PIK3CA*: no *KRAS*: not done *TP53*: not done	–	–	–
10	Thymic	High-grade thymic carcinoma	T785I (exon 20)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: Not done	–	–	–
11	Sarcoma	Unclassified sarcoma	V769M (exon 20)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	–	–	–
12	Sarcoma	Unclassified spindle cell sarcoma	T751I (exon 19)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	Erlotinib	PD	2
13	Skin	Basal cell carcinoma	P741S (exon 19)	Sensitivity is unclear	*PIK3CA*: no *KRAS*: no *TP53*: not done	Cetuximab, carboplatin, paclitaxel; cetuximab, and sirolimus	SD; SD	7; 2

EGFR, epidermal growth factor receptor; *KRAS*, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small-cell lung cancer; PD, progressive disease; *PIK3CA*, phosphatidylinositol-3-kinase, catalytic, alpha polypeptide; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTF, time-to-treatment failure; *TP53*, tumor protein p53.

in exon 20 of the *PIK3CA* gene in addition to the A859T *EGFR* mutation in exon 21). Similarly, 12 of the 13 patients were tested for *KRAS* mutations and all were wild-type. Two of the 13 patients were assessed for *TP53* mutation and both (100%) had simultaneous *TP53* and *EGFR* mutations (one patient with H214Y mutation in exon 6 and the other with V157F mutation in exon 5 of the *TP 53* gene in addition to the *EGFR* mutation).

response in six *EGFR* mutation-positive patients treated with EGFR inhibitors

Of the 13 *EGFR* aberration-positive patients with non-NSCLC, 6 have been treated with an EGFR inhibitor. No patient achieved a partial or complete response. However, two of the six patients attained prolonged stable disease (SD). One patient with parathyroid cancer and a mutation of unknown sensitivity (G796S mutation in exon 20) achieved SD for 6 months with erlotinib (EGFR kinase inhibitor) therapy. Another patient with basal cell carcinoma and a mutation of unknown significance (P741S in exon 19) attained SD for 7 months after treatment with cetuximab (EGFR antibody) along with carboplatin and paclitaxel (Taxol). The contribution of the chemotherapy versus cetuximab to the prolonged SD is unclear.

discussion

The identification of molecular aberrations and the selection of therapy to 'match' these aberrations are gaining momentum as a treatment approach, even in the clinical trials setting [33–35]. There is now a wealth of data that suggest that *EGFR* mutations are associated with the response in NSCLC [12, 14–17, 36]. Less is known about these mutations in other patient groups.

EGFR mutations increase the kinase activity of EGFR, leading to upregulated activation of downstream survival pathways [37, 38]. The presence of *EGFR* mutations in solid tumors other than lung cancer is uncommon, <5% across disease types. In our study, *EGFR* aberrations in exons 19–21 were present in 34 of 958 (3.5%) consecutive patients with advanced cancers. Though the incidence of *EGFR* mutations was higher in patients with NSCLC (16%, 21 of 131 patients), they were also found in 13 patients (1.6%; 13 out of 827 patients) with a variety of other tumor types including 2 patients with sarcoma, and 1 each with parathyroid, thymic, carcinoid, adrenocortical, renal, parotid/salivary gland, cholangiocarcinoma, skin, breast, squamous cell of head and neck, and ovarian cancers (Table 1). These results are consistent with previous reports that have documented these mutations across a range of disease types including [39] peritoneum (18%), prostate (7%), gastric (6%), central nervous system (6%), adrenocortical (5%), ovary (4%), thyroid (4%), salivary gland (4%), eye (3%), breast (2%), head and neck (2%), urinary tract (2%), bone (1%), renal (1%), colorectal (1%), esophageal (1%), skin (1%), soft tissue (1%), and thymic carcinomas (1%). Though it is possible that *EGFR* germline mutations may exist among these patients with non-NSCLC, none have previously been reported in the literature. *EGFR* germline mutations have been reported as occurring rarely in patients with NSCLC [40, 41]. It is also conceivable that other techniques such as the reverse transcription-PCR (RT-PCR) method in RNA might detect additional mutations.

In our study, out of the six *EGFR* mutation-positive patients with advanced, heavily pretreated cancer other than NSCLC who were given an EGFR inhibitor, one patient with parathyroid cancer achieved SD for 6 months on erlotinib alone; another patient with basal cell cancer attained SD for 7 months on cetuximab combined with chemotherapy. In the latter patient, the contribution of the EGFR inhibitor versus the chemotherapy to the prolonged SD is not clear.

In conclusion, we demonstrated the presence of an *EGFR* aberration in many different types of solid tumors. With the shifting paradigm of individualized cancer treatment, the identification of molecular aberrations and their sensitivity to a targeted therapy will be critical. This is challenging since many aberrations are found in only a small subset of patients, as seen with *EGFR* aberrations in the current study. Therefore, the multi-gene assay technology will be needed to characterize patient tumors. One of our patients achieved prolonged SD on an EGFR inhibitor alone despite having failed two prior systemic treatments. Anecdotal responses to EGFR inhibitors have also been reported in *EGFR* mutation-positive patients with ovarian and pancreatic cancers as well [19, 22]. These results suggest that the role of *EGFR* mutations and EGFR inhibitors should be investigated more thoroughly in patients who have cancers other than NSCLC.

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disclosure

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