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A Phase II Trial of Erlotinib in Patients with Previously Treated Squamous Cell and Adenocarcinoma of the Esophagus

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Abstract

Purpose—Tyrosine kinase inhibitors (TKI's) of the epidermal growth factor receptor (EGFR) have activity in solid tumors. We evaluated an oral EGFR TKI, erlotinib, in patients with previously treated esophageal cancer.

Experimental Design—Thirty patients with measurable, metastatic esophageal and gastroesophageal junction cancer were treated with 150 mg of erlotinib daily. EGFR negative (6, 20%) and EGFR overexpressing (24, 80%) tumors were treated. The majority were male (70%) with adenocarcinoma (57%) and had received prior chemotherapy (97%).

Results—Two partial responses were seen in the EGFR+ cohort (2/24, 8%), and no responses in the EGFR- cohort (0/6). Reponses were limited to squamous cell cancer (2/13, 15%, duration 5.5–7 months). Time to tumor progression was greater in squamous cell (3.3 months, range 1–24 months) compared to adenocarcinoma (1.6 months, range 1–6 months, p = 0.026). Therapy was tolerable with the expected toxicity of skin rash (grade 1–2, 67%, grade 3, 10%).

Conclusions—Erlotinib has limited activity in esophageal cancer, with responses and some protracted stable disease observed in squamous cancer. Efficacy by EGFR status could not be assessed given the rarity of EGFR- tumors. Further evaluation of this agent in squamous cell carcinoma is warranted.

Keywords

Esophageal cancer; squamous cancer; erolotinib

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INTRODUCTION

Esophageal cancer is a leading worldwide cause of cancer mortality and accounts for the eighth most common cause of cancer related death (1). Adenocarcinoma of the esophagus and gastroesophageal junction is increasing at an alarming rate in Western countries and is now the most common histology seen in Western Europe and the United States (2). Squamous cell carcinoma remains the predominant histology worldwide, although in the United States squamous cancer is decreasing in all populations including African Americans (3). Despite modest improvements in survival with either preoperative chemotherapy or combined chemoradiotherapy in conjunction with surgery (4), the majority of patients with localized disease will develop metastatic disease. Systemic chemotherapy in metastatic esophageal cancer has limited effectiveness, with responses seen in 20–40% of patients resulting in a median survival of 8–10 months (5). After disease progression on first line chemotherapy, there is no standard second line treatment. The low activity and brief duration of benefit for chemotherapy to palliate metastatic disease, and the limited impact of systemic therapy in the preoperative setting, make clear the need to identify new active agents.

The epidermal growth factor receptor pathway (EGFR) is an important transmembrane signal transduction pathway for many solid tumors, including esophageal cancer (6). Over expression of EFGR is common in both esophageal squamous cell and adenocarcinoma. EGFR expression correlates with a more advanced tumor stage and reduction in overall survival in esophageal cancer (7,8). Activation of the EGFR results in downstream activation of other growth promoting pathways, including the RAS/mitogen-activated protein kinase, pI-3-kinase/AKT, JAK/STAT, and protein kinase C (6). Oral agents that inhibit the EGFR tyrosine kinase (TKI's), including erlotinib, have been reported to have anti tumor activity in non small cell lung cancer and head and neck cancer, with acceptable toxicity (9,10).

In this study, we report the results of a phase II trial of the EGFR TKI erlotinib in patients with esophageal cancer with prior chemotherapy treatment. The primary endpoint was antitumor response rate. Patients with EGFR negative and over expressing tumors, and adenocarcinoma and squamous cancer histology, were enrolled.

PATIENTS AND METHODS

This was a single center, single arm phase II study conducted at the Memorial Sloan-Kettering Cancer Center. The protocol and consent form were approved by the Memorial Hospital institutional review board, and all patients provided signed informed consent

Eligibility

Patients had a histologic diagnosis of metastatic or surgically unresectable adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction, confirmed at Memorial Hospital. Tumors extending into the stomach had to have at least 50% involvement of the distal esophagus (Siewert types I and II). Prior radiotherapy was permitted. Up to one prior chemotherapy regimen for the treatment of metastatic disease, and up to two if one was administered as adjuvant or neoadjuvant treatment, were allowed. Measurable disease was required, defined as at least one lesion measurable in one dimension, either ≥20 mm with conventional techniques, or ≥10 mm with spiral CT scan. Eligibility also included a Karnofsky performance status ≥70%, and organ function defined by an absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, bilirubin less than 2 times the upper limit of normal, AST less than 2 times the upper limits of normal, serum calcium ≤ 12 mg/dl, and creatinine ≤ 1.5 mg/dl. All patients' tumor tissue was tested for

EGFR expression prior to initiating therapy. Exclusion criteria included known brain or central nervous system metastases, uncontrolled intercurrent illness including active infection, symptomatic congestive heart failure, unstable angina pectoris, and ventricular arrhythmia. Pregnant women were excluded. No concurrent malignancy was allowed except for treated carcinoma in-situ of the cervix, superficial transitional cell carcinoma of the bladder, or basal/squamous cell skin cancer.

Study assessments

Prior to treatment, patients underwent a complete history and physical, a complete blood count, serum and liver chemistries including phosphorus and magnesium, prothrombin and partial thromboplastin time, and urinalysis. Patient tumor biopsies were tested for EGFR over expression by immunohistochemistry (as described below). Baseline imaging included either MRI or CT scan of the chest and abdomen. Patients were seen once weekly for the first 5 weeks of therapy, then once every 2 weeks. A complete blood count was obtained at each physician clinic visit, and serum and liver chemistries were obtained once every 4 weeks. Repeat imaging was performed at 4 weeks, and then once every 8 weeks. Response was defined by the RECIST criteria (11). Partial responses had to be confirmed with at least one follow up imaging study, or on physical exam, at 4 weeks. Stable disease had to be maintained for a minimum of 8 weeks from the initiation of protocol therapy. Toxicity was evaluated using the CTC version 3.0 criteria.

Treatment

Erlotinib (OSI-774, NSC 71871) was supplied by the National Cancer Institute/DCTD in 25, 100, or 150 mg tablets. Patients self administered 150 mg erlotinib orally once daily, one hour before or two hours after a meal. Patients could also dissolve the tablets in 100 ml of distilled water, and administer orally, or through a feeding tube. Patients were required to take either an H-2 receptor antagonist or a proton pump inhibitor for ulcer prophylaxis. Patients continued therapy until disease progression, or until the development of unacceptable toxicity. Dose reductions for toxicity, or therapy delay due to toxicity, were permitted to 100, 50, or 25 mg. Therapy was held for grade 3 or 4 toxicity including skin rash, diarrhea, nausea/vomiting, fatigue, or neutropenia/thrombocytopenia. Therapy was held until toxicity was ≤ grade 1, and treatment was resumed at one level dose reduction. Patients could continue therapy for up to grade 2 diarrhea or skin rash if manageable with supportive medications; if therapy were held for grade 2 skin rash or diarrhea, treatment could be resumed at the same dose level. For treatment delay due to recurrent grade 2 skin rash or diarrhea, one dose level reduction was made. Therapy delay beyond two weeks for toxicity mandated withdrawal from the study, unless clinical benefit from therapy (response or stable disease) could be demonstrated.

EGFR expression analysis

Immunohistochemistry for EGFR was performed using the DAKO EGFR Immunohistochemistry Detection System (EGFR PharmDxTM) and standard immunohistochemical techniques, as previously reported (12). Immunoexpression was graded based on the percentage of tumor cells showing strong membranous staining as 0 (<10%), 1+ (10–35%), 2+ (35–65%), or 3+ (>65%). For purposes of data analysis, tumors showing 1+ to 3+ or greater staining were regarded to be positive.

Evaluation of EGFR Mutation

With the publication of results in non small cell lung cancer indicating the potential impact of EGFR mutation on effectiveness of EGFR TKI's (13), during the course of the study an attempt was made to retrieve additional tissue to study for EGFR mutation. This was

possible in only 5 of 30 patients treated on study, given that patients had expired, were lost to follow up, or tissue was no longer available. Formalin fixed, paraffin embedded tumor specimens were obtained from institutional repositories. Routinely stained tissue sections were used to determine the area of highest tumor cellularity for DNA preparation. Tumor tissue was then microdissected and genomic DNA was isolated from these tissues using standard techniques. Using PCR primers previously specified, exons 18, 19 and 21 of *EGFR* were sequenced directly using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems) and an ABI 3730 automated capillary sequencer (13).

Study Design and Statistical Analysis

The primary endpoint was to determine the response rate (partial or complete response) to treatment with erlotinib in two cohorts of patients studied separately: EGFR negative and EGFR positive by immunohistochemistry. Twelve patients per cohort were entered in the first stage, and accrual to a cohort was stopped if no response were observed. If one response was observed, accrual of an additional 12 patients to a total of 24 patients per cohort was permitted. Further study was to be recommended if two or more patients out of 24 responded per cohort. If the true response rate for erlotinib was 20%, there was a 90% chance that this trial design would lead to recommendation of erlotinib for further study.

Secondary endpoints were to evaluate the response rate by tumor histology (adenocarcinoma versus squamous cell carcinoma), toxicity, time to progression, and overall survival. Overall survival and progression-free survival probabilities were estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test. Fisher's exact test was used to assess the associations between EGFR expression and histology with response.

RESULTS

Patients

From July 2002 through September 2005, 40 patients were screened for protocol therapy and had testing for EGFR over expression; 30 patients tested positive for over expression (75%), including 17/26 patients with adenocarcinoma (65%), and 13/14 patients with squamous cell carcinoma (93%). Ten patients never initiated protocol therapy, either due to ineligibility or to rapid clinical decline prior to protocol entry. A total of 30 patients were accrued on study and all are evaluable for toxicity and response. Because one response was observed in the EGFR over expressing cohort, the sample was expanded to a total of 24 patients. Accrual to the EGFR negative cohort was slow given the rarity of EGFR negative patients, and accrual was terminated after no responses were observed in 6 patients treated in this cohort.

Patient demographics are summarized in Table 1. The majority of patients were male (70%) with adenocarcinoma (57%), and most adenocarcinomas were located in the gastroesophageal junction (59%). Over expression of EGFR was observed in 24 patients (80%), including 12 patients with adenocarcinoma (71%) and 12 patients with squamous cancer (92%). The majority of patients had nodal metastases (87%) followed by liver (27%) and lung metastases (23%). All but one patient had received prior chemotherapy, either in the adjuvant setting (70%), for advanced disease (40%), or both (13%). The majority had received prior combined chemoradiotherapy (67%), and 50% had undergone prior esophagectomy. The median performance status was Karnofsky 80%. The majority were current or former smokers (90%).

Treatment Outcome

Two responses were observed in the EGFR over expressing cohort (8%), and no responses were observed in the 6 patient EGFR negative cohort (p=0.6). The two responses observed were in the 13 patients with squamous carcinoma (15%, 95% confidence intervals 0–34%) and there were no responses observed in the 17 patients with adenocarcinoma(p = 0.20), with a duration of response of 7 and 5.5 months. The responses were observed in patients with nodal disease involving the neck and the mediastinum. The responses occurred in one patient treated with prior preoperative chemoradiotherapy, surgery, and chemotherapy for recurrent disease, and one patient with prior chemoradiotherapy for unresectable disease. Both responders were former smokers, one male and one female, although in one patient the smoking history was remote. Although an equal number of patients with squamous cancer had stable disease (7/13 patients, 54%) compared to patients with adenocarcinoma (8/17, 47%), the duration of stable disease in squamous cancer (median 5 months, range 2–24 months) was longer compared to adenocarcinoma (median 3.5 months, range 2–6 months).

Time to progression was greater in squamous cell carcinoma (median 3.3 months) compared to adenocarcinoma patients (median 1.6 months, p = 0.026). Five patients had protracted stable disease, including one patient with adenocarcinoma (6 months) and four patients with squamous cell carcinoma (8, 9, 12 and 24 months). There was no correlation with skin toxicity and either the achievement of stable disease or partial response, with the two partial responses seen in patients with grade 1 rash. There was also no correlation between degree of EGFR expression (negative versus positive, or 1 versus 2 versus 3+) and the achievement of response or stable disease (data not shown), although the two responders were seen in the EGFR + cohort.

The median survival in all patients was 10.3 months, 8.2 months for squamous cell cancer and 11.2 months for adenocarcinoma (p = 0.75).

Toxicity

Most toxicities were grade 1 or 2, with the exception of dermatologic toxicity or skin rash (grade 3 in 10% of patients, grade 1–2 in 67%). Diarrhea was at worst grade 2 in 13%. Six patients (20%) required a dose reduction to 100 mg daily, five for skin rash and one for diarrhea. No patients were taken off therapy due to drug toxicity, only to progressive disease.

EGFR Mutation Analysis

No mutations in exons 18, 19 and 21 of the EGFR were observed in the 5 patient tumor samples tested, including one patient with squamous cell carcinoma with a partial response.

DISCUSSION

In the current trial, we observed partial responses to the oral EGFR TKI erlotinib in patients with metastatic esophageal cancer with EGFR overexpression. Response was observed in 15% of squamous cancers of the esophagus, and we observed that nearly a third of patients with squamous cancers had protracted stable disease ranging from 8–24 months. No clear conclusion can be made about the impact of EGFR expression, as only 6 patients with EGFR negative tumors were treated on study. No responses were observed in 17 patients with adenocarcinoma, with nearly half of these patients progressing at the time of the first CT scan. EGFR over expression occurred to a lesser degree in adenocarcinoma (70%) compared to squamous cancer (92%). In the limited analysis in 5 patients for mutation of the EGFR, no mutations were observed, including one squamous cancer that achieved a partial response. No correlation of either response or stable disease with skin rash was observed.

How do these results compare with other recent trials of EGFR TKI's in esophageal cancer? Our results are in close agreement with the study reported by Janmaat (14). Gefitinib 500 mg daily was given to 36 patients all with prior chemotherapy treatment, including 26 patients with adenocarcinoma and 9 patients with squamous cancer. A response was seen only in squamous cancer, and a higher degree of response or stable disease was seen in females, in squamous cancers, and in patients with higher (3+) EGFR expression. K-ras mutation, recently identified as a potential marker of EGFr therapy resistance (15), was tested and found in only 2 of 23 patients (9%), both of whom had early progressive disease on therapy. No EGFR mutations were found in 26 patients studied. High EGFR copy number was observed in two patients, one responder and one non responder.

In contrast to our study, Dragovich (16) observed significant responses in 43 patients with adenocarcinoma of the GE junction treated with erlotinib 150 mg daily. Patients on this trial had no prior treatment for metastatic disease, in contrast to 53% of patients on our study receiving prior chemotherapy for advanced disease. Four responses were seen (9%) and stable disease was seen in 5 patients (12%). However, the median time on study was only 2 months, indicating that the majority of patients had rapid disease progression. These authors do not comment on characteristics of the responding patients. Potential predictive molecular markers of response were assessed, including EGFR mutation (none found) and amplification of EGFR (none found). Positive immunohistochemical staining for EGFR, pAKT, and TGF-alpha was observed in the majority of samples tested and there was no correlation with response. Another positive trial reported by Ferry (17) evaluated gefitinib 500 mg daily in 26 patients with adenocarcinoma of the esophagus or gastroesophageal junction. Three responses were observed (12%), including one patient without prior therapy, and one patient each with prior adjuvant or prior advanced disease chemotherapy. Most patients, however, also had rapid disease progression (median time 1.9 months). In a separate report (18), these authors reported the evaluation EGFR mutations in a cohort of 17 patients with adenocarcinoma and identified 2 with mutations (12%); both of these patients were treated with gefitinib and failed to respond. One patient with EGFR amplification treated on study responded to treatment.

Collectively the data for EGFR TKI's suggest limited single agent activity in esophageal cancer, with most patients experiencing early disease progression. The median survival of 11.2 months for adenocarcinoma patients on our trial, despite rapid progression of disease on erlotinib, indicates a benefit from salvage treatment with further chemotherapy, and our patient survival exceeded reports of the other trials with median survivals of only 4.5–6.7 months. While the data for adenocarcinoma of the distal esophagus and GE junction for EGFR TKI's appear to be conflicting, the data from our trial and others suggest a consistent signal of activity for EGFr TKI's in esophageal squamous cancer. Our observation not only of responses but of protracted stable disease extending out 1–2 years supports the study of erolotinib as a potential adjuvant therapy in squamous cancer. Combining erlotinib with chemotherapeutic agents, however, to date has failed to improve outcome compared to chemotherapy alone in non small cell lung cancer (19,20). Some investigators are now evaluating alternative dosing and scheduling of these agents with chemotherapy in non small cell lung cancer.

From the trials of TKI's in esophageal cancer, there also is no clear molecular marker predictive of response to therapy, including K-ras or EGFR mutation, with the possible exception of either amplification of, or increased copy number of, the EGFR gene, which was observed in two responding patients. In our series, tissue study was limited to EGFR expression, and the majority of squamous cell and adenocarcinoma patients were over expressors; the limited number of EGFR negative patients accrued on our trial limits any conclusions about the efficacy of erlotinib in this patient subset. In other series, both K-ras

mutation and EGFR mutations were rarely if ever observed in esophageal cancer; it is unlikely, therefore that these markers will have any significant application in this disease. This contrasts with the important role of K-ras mutation in identifying resistance to EGFR targeted agents in colorectal and non small cell lung cancers, and EGFR mutation in determining benefit for treatment with EGFR TKI's in non small cell lung cancer. More promise in targeting the EGFR pathway in esophageal cancer may come from monoclonal antibodies blocking the binding of ligands to the receptor. Encouraging response rates and time to tumor progression reported for phase II trials in esophageal cancer combining antibodies such as cetuximab with combination chemotherapy (21).

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REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006; 24:2137–2150. [PubMed: 16682732]
2. Blot WJ, Mclaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol. 1999; 26:2–8. [PubMed: 10566604]
3. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol. 2007; 17:2–9. [PubMed: 17185192]
4. Homs MY, v d Gaast A, Siersema PD, et al. Chemotherapy for metastatic carcinoma of the esophagus and gastroesophageal junction. Cochrane Database Sys Rev. 2006; 18:4063.
5. Ku G, Ilson D. Esophageal cancer: adjuvant therapy. Cancer J. 2007; 13:162–167. [PubMed: 17620765]
6. Karamouzis MV, Grandis JR, Argiris A. Therapies directed against epidermal growth factor in aerodigestive cancers. JAMA. 2007; 298:70–82. [PubMed: 17609492]
7. Wang KL, Wu TT, Cho TS, et al. Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinoma: association with poor outcome. Cancer. 2007; 109:658–667. [PubMed: 17211865]
8. Hanawa M, Suzuki S, Dobashi Y, et al. EGFR protein overexpression and gene amplification in squamous cell carcinoma of the esophagus. Int J Cancer. 2006; 118:1173–1180. [PubMed: 16161046]
9. Perez, SolerR; Chachoua, A.; Hammond, LA., et al. Determinants of tumor response and survival with erlotinib in patients with non small cell lung cancer. J Clin Oncol. 2004; 22:3238–3247. [PubMed: 15310767]
10. Soulieres D, Senzer NN, Vokes EE, et al. Multicenter study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. J Clin Oncol. 2004; 22:77–85. [PubMed: 14701768]
11. Therasse P, Arbuck S, Eisenhauer E, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000; 92:205–216. [PubMed: 10655437]
12. Bhargava R, Chen B, Klimstra DS, et al. Comparison of two antibodies for immunohistochemical evaluation of epidermal growth factor receptor expression in colorectal carcinomas, adenomas, and normal mucosa. Cancer. 2006; 106:1857–1862. [PubMed: 16532444]
13. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci. 2004; 101:13306–13311. [PubMed: 15329413]
14. Janmaat ML, Gallegos-Ruis MI, Rodriguez JA, et al. Predictive factors for outcome in phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. J Clin Oncol. 2006; 24:1612–1619. [PubMed: 16575012]

15. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchoalveolar carcinoma and adenocarcinoma, bronchioalveolar subtype, predict response to erlotinib. J Clin Oncol. 2008; 26:1472–1478. [PubMed: 18349398]

16. Dragovich T, McCoy SM, Fenoglio-Preiser, et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J Clin Oncol. 2006; 24:4922–4927. [PubMed: 17050876]

17. Ferry DR, Anderson M, Beddard K, et al. A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. Clin Cancer Res. 2007; 13:5869–5875. [PubMed: 17908981]

18. Kwak EL, Jankowski J, Thayer SP, et al. Epidermal growth factor receptor kinase domain mutations in esophageal and pancreatic adenocarcinomas. Clin Cancer Res. 2006; 12:4283–4287. [PubMed: 16857803]

19. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III trial of erlotinib in combination with cisplatin and gemcitabine in advanced non small cell lung cancer: the tarceva lung cancer investigation trial. J Clin Oncol. 2007; 25:1545–1552. [PubMed: 17442998]

20. Herbst RS, Prager D, Hermann R, et al. Tribute: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non small cell lung cancer. J Clin Oncol. 2005; 23:5900–5909. [PubMed: 16043828]

21. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol. 2007; 18:510–517. [PubMed: 17164226]

Table 1

Patient Demographics

	Number (%)
Patients	30
Male:Female	21:9 (70%:30%)
Median Age	62 (51–78)
Karnofsky Performance Status (range)	80 (70–90)
Adenocarcinoma	17 (57%)
EGFR +	12 (70%)
Squamous Cell	13 (43%)
EGFR +	12 (92%)
Primary Location (Adenocarcinoma)	
Proximal Esophagus	1 (6%)
Mid Esophagus	0
Distal Esophagus	6 (35%)
GE Junction	10 (59%)
Prior Chemotherapy	29 (97%)
Adjuvant	21 (70%)
Advanced Disease	12 (40%)
Both	4 (13%)
None	1 (3%)
Prior Radiotherapy	22 (73%)
Chemoradiotherapy	20 (66%)
Prior Esophagectomy	15 (50%)
Smoking History	
Current	1 (3%)
Former	26 (87%)
Never	3 (10%)
Disease Sites	
Lymph Nodes	26 (87%)
Liver	8 (27%)
Lung	7 (23%)
Peritoneum	3 (10%)
Bone	1 (3%)