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Erlotinib in the Treatment of Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single Arm Phase II Clinical Trial

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Abstract

Background—Cutaneous squamous cell carcinoma (CSCC) is a very common malignancy. Most patients present with localized disease. Recurrent and metastatic disease is rare, and there is no standard therapy for these patients. These tumors frequently overexpress the epidermal growth factor receptor (EGFR). We conducted a phase II trial to determine the response rate to therapy with erlotinib, an EGFR tyrosine kinase inhibitor (TKI), in patients with locoregionally recurrent or metastatic CSCC that was not amenable to curative treatment.

Methods—Eligible patients had CSCC not amenable to curative intent therapy. Patients who had previously received anti-EGFR targeted therapy were excluded. All patients received therapy with erlotinib 150 mg PO daily. Response was assessed every eight weeks, and treatment continued until progression, unacceptable toxicity, or withdrawal of consent. Primary endpoint was overall response rate (ORR) by RECIST 1.1.

Results—39 patients received treatment on trial; 29 of these patients were evaluable for response. ORR was 10% (3/29); all responses were partial responses (PRs). Disease control rate (PR + stable disease) was 72% (21/29). Median progression free survival was 4.7 months (95% CI: 3.5, 6.2 months); median overall survival was 13 months (95% CI 8.4, 20.5 months). No unexpected toxicities were seen.

Conclusions—Erlotinib therapy was feasible for the majority of patients with incurable CSCC and associated with expected toxicities. However only a modest response rate of 10% was

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observed. Further study of EGFR TKIs in this patient population is not warranted. (NCT01198028)

Keywords

Squamous Cell Carcinoma; Skin Cancer; Erlotinib; Epidermal Growth Factor Receptor; Anti-Neoplastic Agents

Introduction

In the United States, over three million non-melanoma skin cancers are diagnosed yearly, and the incidence is increasing.[1] Cutaneous squamous cell carcinoma (CSCC) represents about one-fifth of these cases, and is the second most common human cancer, after basal cell carcinoma.[2] In the majority of cases, these tumors can be effectively managed with local therapy, but about 4% of patient develop nodal disease and 1.5% die of their disease.[3] Increasing tumor bulk, depth of invasion, poorly differentiated or variant histology, perineural spread, and involved surgical margins predict for tumor recurrence and disease-specific mortality.[4] Moreover, CSCCs arising in a burn site, or from severely injured or chronically diseased skin, have a high rate of metastases; approaching 40% at 5 years.[2] Patients who are chronically immunosuppressed, from either a disease such as chronic lymphocytic leukemia or on immunosuppressive medications after organ transplant, are at higher risk of developing aggressive CSCC.[5]

For patients with disease not amenable to curative intent therapy, treatment options are limited. Cisplatin based regimens have relatively high response rates;[6–8] however, therapy is often poorly tolerated in this population of patients who are often elderly and suffer from comorbid illnesses. Targeted therapies have been studied, especially those targeting the epidermal growth factor receptor (EGFR), which is frequently overexpressed in cutaneous squamous cell carcinoma.[9] Our previous research studied gefitinib, a small molecule tyrosine kinase inhibitor (TKI) with activity against EGFR, in patients with locally advanced cutaneous CSCC.[10] Twenty three patients received gefitinib 250 mg PO daily for up to 60 days prior to definitive treatment with surgery, radiation, or a combination of the two. The response rate was 45%, and four patients (18%) had a complete response. Treatment was well tolerated – rash and diarrhea were the most common adverse effects. In unresectable disease, response rates to gefitinib were low (11%), but 38% of patients had stable disease after 8 weeks of therapy.[11] Cetuximab, an anti-EGFR antibody, has also been studied in this disease in a phase II trial.[12] Thirty-six patients with unresectable CSCC were treated with cetuximab weekly. Response rate in this study was 28%. Cetuximab is listed in the NCCN compendium as a therapy for recurrent/metastatic CSCC.

Gefitinib was initially approved by the Federal Drug Administration for advanced non-small cell lung cancer in 2003, but approval was withdrawn in 2005 after postmarketing studies failed to confirm the clinical benefit seen in initial studies.[13, 14] Because gefitinib was no longer commercially available, our study was performed using the closely related EGFR tyrosine kinase inhibitor erlotinib. Erlotinib 150 mg daily was more effective than gefitinib 250 mg daily in patients with non-small cell lung cancer not selected for *EGFR* mutation

and is thought to be more active against wild type EGFR.[13, 15] Thus, we believed it was important to establish the efficacy of erlotinib monotherapy with a phase II single arm trial in patients with CSCC not amenable to curative-intent therapy.

Materials and Methods

Study Design and Objectives

This trial was an open-label, uncontrolled, single-center phase II study conducted at University of Texas MD Anderson Cancer Center. The primary endpoint was to determine the overall response rate (ORR) (complete response [CR] or partial response [PR]) to treatment with erlotinib in patients with locoregionally recurrent or metastatic CSCC.

Secondary endpoints were duration of response, duration of stable disease, progression free survival (PFS), overall survival (OS), and safety and tolerability.

Patient Eligibility

Eligible patients had histologically or cytologically confirmed CSCC that was not amenable to curative intent therapy, with either distant metastases or locoregional disease for which curative resection or definitive radiation were not feasible. Measurable disease, age of at least 18 years, ECOG performance status 0–2, and adequate organ and marrow function were required. One prior systemic therapy was allowed. Patients who had received prior EGFR inhibitor therapy and those with other invasive malignancy within the past 3 years were excluded. Patients with pulmonary fibrosis, chronic liver disease, or active disorders affecting gastrointestinal motility or absorption were also excluded. Patients with a history of organ transplantation and those on immunosuppression for autoimmune disease were eligible as long as they met criteria for organ function and were not receiving cytotoxic treatment (e.g., methotrexate). Patients with chronic lymphocytic leukemia were excluded. All patients gave written informed consent, and the protocol was approved by the MD Anderson Clinical Research Committee and Institutional Review Board.

Study Treatment

All patients received erlotinib 150 mg PO daily on continuous 28 day cycles. Patients could continue treatment until disease progression. Dose reductions and management of expected toxicities were specified in the protocol. Therapy was discontinued if patients were unable to recover from toxicities despite dosing interruption up to 14 days or if patients were unable to tolerate erlotinib at a 50 mg/day dose.

Study Assessments

All patients underwent pretreatment screening within 14 days prior to starting therapy including medical history, physical examination, assessment of performance status, and laboratory testing. Baseline imaging was performed within 28 days prior to the start of treatment. Tumor response was assessed according to RECIST 1.1 criteria every 8 weeks until progression.[16]

Toxicity was evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). Serious adverse events were reported to the MD Anderson IRB and to the sponsor.

Statistical Analyses

Descriptive statistics including mean, standard deviation, median, and range for continuous variables, such as age, were provided. Frequency counts and percentages for categorical variables, such as gender and race were provided. Kaplan-Meier method was used for time-to-event analysis including progression free survival and overall survival. Median time to event in months with 95% confidence interval was calculated. Statistical software SAS 9.3 (SAS, Cary, NC), S-Plus 8.2 (TIBCO Software Inc., Palo Alto, CA) and R were used for all the analyses.

Results

A total of 39 patients were enrolled and treated on the study between April 2011 and June 2014. Ten patients received less than 4 weeks of therapy and were not re-imaged. They were deemed not evaluable for response. Five patients discontinued due to toxicity, two by patient/investigator choice, and three due to early death not thought to be related to study drug. These 10 patients were included in toxicity and survival analyses only.

Patient Characteristics

The demographics for the 39 patients treated on this study are shown in table 1. The majority of patients were male (87%) and were non-Hispanic whites (95%). Most patients (72%) were over age 65. Primary sites were in heavily sun-exposed areas (scalp, face, lip, distal extremity) in 90% of patients; three patients had primary sites on the trunk and one patient on the thigh. No organ transplant recipients enrolled on trial. All but one patient had prior surgery for CSCC, and most patients (82%) had also received prior radiation therapy. The predominant pattern of recurrent disease was locoregional. Of 16 patients who had received prior chemotherapy, 12 had platinum agents with radiation, 1 had neoadjuvant therapy, and 3 had chemotherapy for recurrent disease.

Exposure to Erlotinib

The median number of days on erlotinib treatment was 98 (range 1–526 days). The most common reason for discontinuation was clinical or radiographic progression (28 patients, 72%). Five patients (13%) discontinued therapy secondary to toxicity, three patients (8%) withdrew consent.

Response to Therapy

Twenty-nine patients completed 4 weeks of therapy and were considered evaluable for response. Of those patients – 3 (10%) had a confirmed partial response, 18 (62%) had stable disease, and 8 (28%) had progressive disease as the best overall response by RECIST 1.1 criteria. Disease control rate was 72%. All three patients with PR had prior chemotherapy: two received carboplatin with radiation and one had paclitaxel and carboplatin front-line for recurrent disease. The three patients who responded to treatment remained on therapy for

4.6, 5.3, and 13.2 months before developing progression. The median duration of stable disease was 7.2 months (range: 1.6 to 41.4 months).

Progression Free and Overall Survival

For the 39 patients who received treatment on study, median progression free survival was 4.7 months (95% CI 3.5, 6.2 months). 14% of patients were alive and without progression at 1 year. Median overall survival was 13 months (95% CI 8.4, 20.5 months). One year OS rate was 53% and three year OS rate was 19% (Figure 1).

Safety and Tolerability

Adverse events (AEs) were reported for all 39 patients who enrolled on study (Table 2). The most common toxicities were acneiform rash (64%) and fatigue (46%). Most toxicities were grade 1 and 2. There were no grade 4 or 5 treatment related AEs; grade 3 AEs were fatigue (10%, 4 patients), acneiform rash (8%, 3 patients), dehydration (3%, 1 patient) and syncope (3%, 1 patient). AEs were consistent with those seen in prior trials with erlotinib.

Seven patients died during therapy or within 30 days after the final dose of erlotinib. None of these deaths were thought to be related to treatment; underlying disease was thought to be a major factor in all deaths.

Discussion

In our phase II study of erlotinib in patients with recurrent or metastatic CSCC, modest response rates (10%) were seen. Overall response rate and median PFS (4.7 months) were similar to that seen in similar patients treated with gefitinib.[11] Cetuximab had a higher response rate in a phase II study (28%) but a similar median PFS (4.1 months); however, this trial did not allow patients with prior systemic therapy.[12] In our study, no unexpected toxicities were seen, though 13% of patients discontinued therapy due to toxicity, suggesting that systemic therapy, even with generally well-tolerated EGFR TKIs, can be toxic in this patient population, where many patients are elderly and have significant comorbidities.

Novel therapies are urgently needed for these patients. Our group has shown that these tumors tend to have a high mutational burden;[17] and increasing mutational burden has been linked to responsiveness to immunotherapy in other malignancies.[18, 19] Case reports suggest that patients with incurable CSCC may benefit from checkpoint inhibitors such as nivolumab or pembrolizumab.[20, 21] In 26 patients with CSCC in an expansion cohort of a phase I trial of PD-1 inhibitor REGN2810, a response rate of 52% was observed.[22] Phase II trials are currently ongoing with PD-1 inhibitors pembrolizumab (NCT 02964559) and REGN2810 (NCT02760498) in unresectable or metastatic CSCC.[20, 21] Immunotherapy is likely to play a major role in treatment of this disease in the future.

In conclusion, our study demonstrates that erlotinib has modest activity in incurable CSCC, similar to prior results with gefitinib. The activity of immune checkpoint inhibitors in early phase trials is encouraging, supporting further research with these agents for patients with aggressive high risk CSCC.

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References

1. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol. 2010; 146:283–287. [PubMed: 20231499]
2. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001; 344:975–983. [PubMed: 11274625]
3. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013; 68:957–966. [PubMed: 23375456]
4. Clayman GL, Lee JJ, Holsinger FC, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005; 23:759–765. [PubMed: 15681519]
5. Thomas, VD., Aasi, SZ., Wilson, LD., Leffell, DJ. Cancer of the Skin. In: DeVita, VT.Lawrence, TS., Rosenberg, SA., editors. Cancer: Principles and Practice of Oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
6. Denic S. Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin. Amer J Clin Oncol. 1999; 22:32–34. [PubMed: 10025376]
7. Guthrie TH, McEleveen LJ, Porubsky ES, Harmon JD. Cisplatin and doxorubicin: an effective chemotherapy in the treatment of advanced basal cell and squamous carcinoma of the skin. Cancer. 1985; 55:1629–1632. [PubMed: 4038911]
8. Sadek H, Azli N, Wendling JL, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer. 1990; 66:1692–1696. [PubMed: 1698529]
9. Maubec E, Duvillard P, Velasco V, Cricks B, Avril MF. Immunohistochemical analysis of EGFR and HER-2 in patients with metastatic squamous cell carcinoma of the skin. Anticancer Res. 2005; 25:1205–1210. [PubMed: 15865067]
10. Lewis CM, Glisson BS, Feng L, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. Clin Cancer Res. 2012; 18:1435–1446. [PubMed: 22261807]
11. William WN, Feng L, Ferarrotto R, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single arm phase II clinical trial. J Am Acad Dermatol. 2017 in press.
12. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011; 29:3419–3426. [PubMed: 21810686]
13. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005; 366:1527–1537. [PubMed: 16257339]
14. Stinchcombe TE, Socinski MA. Gefitinib in advanced non-small cell lung cancer: does it deserve a second chance? Oncologist. 2008; 13:933–944. [PubMed: 18784157]
15. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353:123–132. [PubMed: 16014882]
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228–247. [PubMed: 19097774]
17. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res. 2014; 20:6582–6592. [PubMed: 25303977]
18. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348:124–128. [PubMed: 25765070]
19. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014; 371:2189–2199. [PubMed: 25409260]

20. Winkler JK, Schneiderbauer R, Bender C, et al. Anti-PD-1 therapy in nonmelanoma skin cancer. Br J Dermatol. 2016

21. Borradori L, Sutton B, Shayesteh P, Daniels GA. Rescue therapy with anti-programmed cell death protein 1 inhibitors (PD-1) of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in 5 cases. Br J Dermatol. 2016

22. Papadopoulos K, Owonikoko T, Johnson M, et al. REGN2810: A fully human anti-PD-1 monoclonal antibody, for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—Initial safety and efficacy from expansion cohorts (ECs) of phase I study. J Clin Oncol ASCO Annual Meeting 2017. 2017; 35:9503–9503.

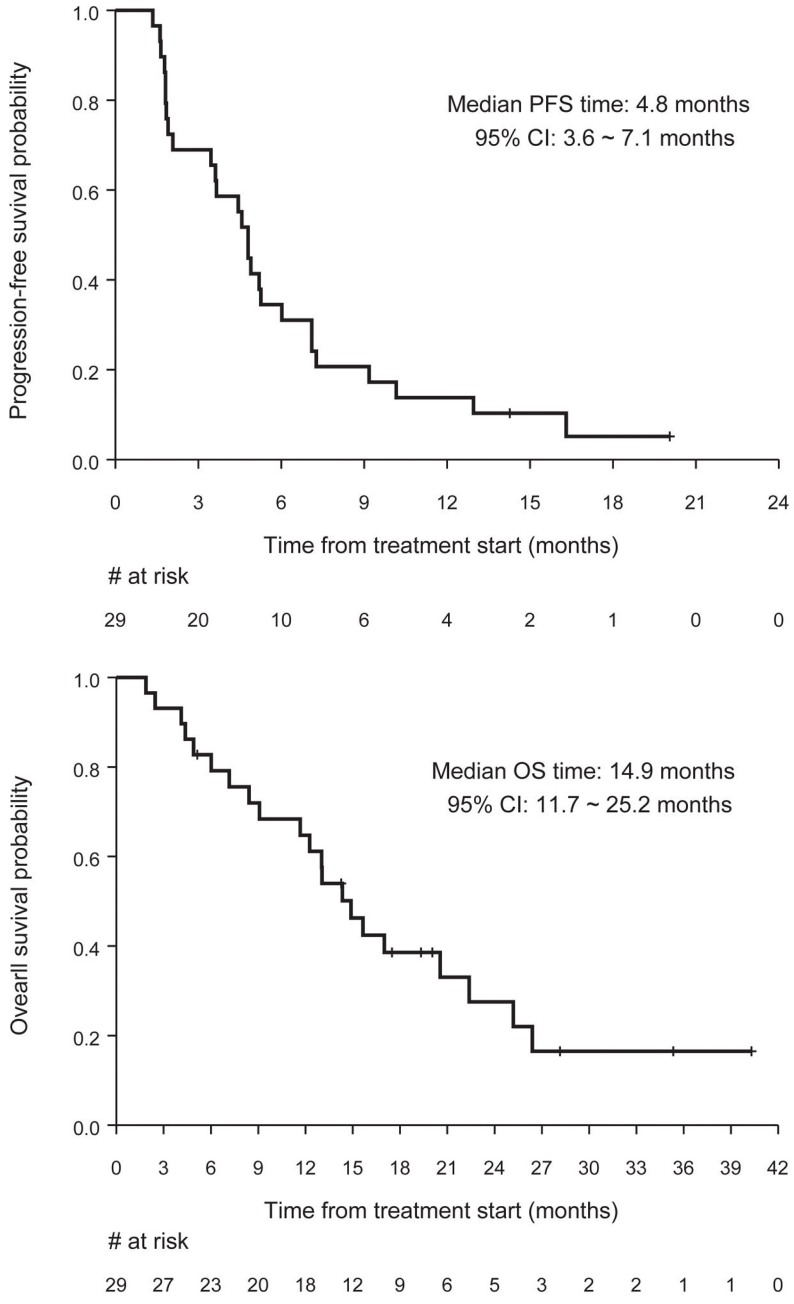

FIGURE 1.
Kaplan Meier curves for progression free survival and overall survival

TABLE 1

Patient Characteristics

Characteristics	Number of patients	%
Age		
Median	68	
Range	45–88	
>65	28	72%
Sex		
Male	34	87%
Female	5	13%
Race		
Non-Hispanic White	37	95%
Hispanic	1	3%
Black	1	3%
Primary Site		
Skin of head or neck	31	79%
Skin of extremity	5	13%
Skin of trunk	3	8%
Prior Therapy		
Chemotherapy	16	41%
Neoadjuvant/Concurrent	13	32%
Recurrent disease	3	8%
Surgery	38	97%
Radiation	32	82%
ECOG Performance Status		
0	11	28%
1	23	59%
2	5	13%

TABLE 2

Treatment Related Adverse Events

	Grade 1–2 (%)	Grade 3 (%)	Total (%)
Acneiform rash	22 (56%)	3 (8%)	25 (64%)
Fatigue	14 (36%)	4 (10%)	18 (46%)
Diarrhea	14 (36%)		14 (36%)
Nausea/vomiting	10 (26%)		10 (26%)
Watering eyes	10 (26%)		10 (26%)
Oral mucositis	8 (21%)		8 (21%)
Constipation	5 (13%)		5 (13%)
Dry eye	4 (10%)		4 (10%)

All grade AEs seen in greater than ≥10% of the study population are included