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Gefitinib for Patients with Incurable Cutaneous Squamous Cell Carcinoma A Single Arm Phase II Clinical Trial

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Abstract

Background—Pre-clinical data demonstrate a key role for the epidermal growth factor receptor (EGFR) in the carcinogenesis of cutaneous squamous cell carcinomas (CSCC). There is, however, limited data on the efficacy of EGFR inhibitors in incurable, recurrent and/or metastatic CSCC.

Objective—To determine the response rate to gefitinib in patients with CSCC not amenable to curative therapy including surgery or radiation.

Methods—This was a single arm, phase II study. Forty patients were treated with gefitinib 250 mg orally daily until disease progression or intolerable toxicities. The pre-specified target response rate of interest was 20%.

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IRB statement: The study was approved by The University of Texas MD, Anderson Institutional Review Board and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Trial Registration: http://www.clinicaltrials.gov (NCT00054691)

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Results—The overall response rate was 16% (95% confidence interval [CI] 0.06–0.32; 6 partial responses in 37 evaluable patients). An additional 13 patients had stable disease at eight weeks (35%). The median duration of response and progression-free survival were 24.8 months (range 0.9–47.2 months), and 3.8 months (95% CI 2.2–5.7 months), respectively. The side effect profile was consistent with the previous experience with gefitinib in other tumor types.

Limitations—Single institution, single arm study. The pre-specified target response rate was not met.

Conclusions—Gefitinib demonstrated modest activity in incurable CSCC, with a favorable adverse event profile.

INTRODUCTION

Treatment options for advanced or recurrent cutaneous squamous cell carcinoma (CSCC) are limited, and patients in whom surgery, radiation and/or chemotherapy have failed have a poor prognosis.

The epidermal growth factor receptor (EGFR) plays a major role in ultraviolet light-induced skin tumorigenesis.[1] Ultra-violet light irradiation activates EGFR in cultured keratinocytes and skin, leading to keratinocyte proliferation, suppression of apoptosis, and epidermal hyperplasia.[2] In animal models of skin carcinogenesis, EGFR and its ligand TGF-alpha have been shown to be critical mediators of keratinocyte proliferation and skin tumor growth,[3] in part through stimulation of downstream effectors Akt and STAT3.[4, 5]

EGFR is overexpressed in 35%–100% of CSCC,[6–8] and is associated with increased risk of disease progression.[8] In animal genetic models[9] and xenograft models,[10] the EGFR tyrosine kinase inhibitors AG1478 or AEE788 induced keratinocyte apoptosis,[9, 10] delayed onset of epidermal hyperplasia,[9] and reduced tumor growth.[10]

There have been limited studies of EGFR inhibitors in CSCC.[11–13] Herein we report the results of a phase II clinical trial with the EGFR tyrosine kinase inhibitor gefitinib in patients with incurable recurrent and/or metastatic CSCC.

PATIENTS AND METHODS

This single-arm, phase II study was conducted at The University of Texas M. D. Anderson Cancer Center.

Eligible patients had locoregionally recurrent and/or metastatic CSCC not amenable to curative therapy including surgery or radiation, ECOG performance status 0–2, no more than one prior chemotherapy regimen, and no prior EGFR inhibitors.

Patients received gefitinib 250 mg orally daily, until disease progression or unacceptable toxicity. Assesment of response was performed every 2 cycles (each cycle=28 days).

The primary endpoint was to determine the objective response rate (ORR), assessed according to the World Health Organization criteria.[14] Secondary objectives included

determining the duration of response, overall survival, and adverse events (assessed using the National Cancer Institute Common Toxicity Criteria, Version 2.0).

A two-stage phase II design was used with a power of 90% and a type I error rate of 5%. The target ORR of interest for gefitinib was assumed to be 20%, and the lower activity level was taken to be 5%. The treatment would be accepted as effective if the ORR was ≥ 5/39, and rejected otherwise.

RESULTS

Forty patients were enrolled (Table 1). The median time on treatment was 3.4 months (range 0.9–33.5 months). Gefitinib toxicity profile was favorable (median of 2 adverse events/ patient, most grade 1–2), as summarized in Supplemental Table 1.

Thirty-seven out of 40 patients were evaluable for response. Confirmed partial responses were observed in 6 patients, yielding an ORR of 16% (95% CI 0.06 – 0.32) (Table 2). An additional 13 patients had stable disease at eight weeks (35%, 95% CI 0.20 – 0.53). The median duration of response was 31.4 months (95% CI 3.91 - NA months). ORR were higher in patients with locally advanced (defined as unresectable disease in patients without distant metastases) or locoregionally recurrent disease (6/29 evaluable patients), compared to metastatic disease (0/8 evaluable patients).

Median overall survival was 12.9 months (95% CI 8.5 – 25.0). Median progression-free survival was 3.8 months (95% CI 2.2–5.7) (Supplemental Figure 1).

DISCUSSION

In this phase II study for incurable CSCC, gefitinib was associated with an ORR of 16% and a disease control rate of 51%. Treatment was well tolerated. The ORR of 16% did not meet the rate targeted in the study design of 20%.

Investigation of systemic treatment for advanced or recurrent CSCC has been limited with few prospective trials. Maubec et al reported results of the first prospective evaluation of cetuximab, a monoclonal antibody to EGFR, in 36 chemotherapy-naive patients with unresectable CSCC[13], and showed an ORR of 28% and disease control rate of 69% at six weeks. Notably, only 3/36 patients had metastatic disease, and 15/36 patients had no prior therapy.

Although we observed lower response and disease control rates with gefitinib than in the trial by Maubec et al., direct comparison is problematic due to significant differences in the patient populations. Our population included a higher percentage of patients with recurrence following surgery and/or radiation (88% and 83%) and 22% of patients had distant metastasis. Prior chemotherapy had been given to 45%. Given these characteristics, the activity of gefitinib observed is of interest. We have also studied gefitinib in patients with aggressive or recurrent CSCC who were candidates for either resection or definitive radiation.[15] In the neoadjuvant setting, the ORR to gefitinib was 45% (10/22), with 3/4

complete responses confirmed pathologically. Taken together, these results suggest that gefitinib has at least modest activity.

Patients with aggressive CSCC in routine clinical practice often present at advanced age, and frequently have additional comorbidities that lead to immunosuppression, rendering them suboptimal candidates for cytotoxic therapy. The activity of EGFR single agents in this setting is therefore relevant, especially if disease control rates in the range of 50% can be achieved with a favorable adverse event profile.

Efforts to characterize the molecular landscape of CSCC have recently been completed, which could assist in developing novel drugs and/or identifying biomarkers of response to therapy. These studies highlight a high mutational load as a key characteristic of CSCC.[16–18] Unfortunately, many of these mutations occur in tumor suppressor genes, for which therapeutic interventions are challenging. Notably, EGFR activating mutations were infrequently seen in these reports and others,[19–21] and are therefore unlikely to explain the ORR associated with gefitinib in our study. In our previous trial of neoadjuvant gefitinib in CSCC, we did not identify any associations between EGFR mutations, gene copy number gains, or protein expression/phosphorylation and outcomes.[15]

In conclusion, this phase II trial demonstrated modest activity of gefitinib in metastatic or locoregionally recurrent CSCC. These results support a potential therapeutic role of EGFR tyrosine kinase inhibitors in this disease, for which there are no approved drugs. Further studies are needed, however, to identify patients that are more likely to respond to these agents, and how to best integrate them into the treatment strategy in both curative-intent and palliative settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient Characteristics

	Number of Patients (%) N = 40
Median age, years (range)	67 (37–95)
Gender	
Male	30 (75%)
Female	10 (25%)
Performance Status	
0	4 (10%)
1	32 (80%)
2	4 (10%)
Prior therapy for skin cancer	
Surgery	35 (88%)
Radiotherapy	33 (83%)
Chemotherapy	18 (45%)
Exent of disease	
Locally advanced	4 (10%)
Recurrent	27 (67.5%)
Metastatic	9 (22.5%)
Location of Primary	
Head and neck	32 (80%)
Extremity	6 (15%)
Trunk	2 (5%)

Table 2

Efficacy Summary

		Extent of disease		
Number of Patients	**All Patients N=40**	**Metastatic N=9**	**Recurrent N=27**	**Locally advanced N=4**
Partial response (PR)	6	0	5	1
Stable disease (SD)	13	3	10	0
Progressive disease (PD)	18	5	11	2
Not Evaluable	3	1	1	1