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A Phase I Trial of Erlotinib and Concurrent Chemoradiotherapy for Stage III and IV (M0) Squamous Cell Carcinoma of the Head and Neck

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Abstract

Purpose: Erlotinib, an orally active selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, has synergistic activity with radiation and with cisplatin. The EGFR is overexpressed in the majority of head and neck cancers. The primary objective of this phase I study was to determine the maximum-tolerated dose (MTD) of erlotinib in combination with low-dose daily cisplatin and radiotherapy. We also sought evidence of biologic activity of erlotinib alone using serial 18-FDG positron emission tomography (PET) imaging.

Experimental Design: Oral erlotinib was taken daily starting with a 14-day run-in and continued until radiation therapy (RT) was completed. Low-dose daily cisplatin, 6 mg/m^2 i.v. was given concurrently with standard fractionation RT to a total dose of 66 to 70 Gy. Dose escalation followed a modified Fibonacci dose escalation design.

Results: Twenty-two patients were enrolled and 18 patients received therapy on protocol. MTD of the combination of erlotinib, cisplatin, and RT was not reached. The recommended phase II dose of erlotinib is 150 mg per day in combination with cisplatin and RT, the highest dose of erlotinib evaluated in this study. 18F-FDG PET showed evidence for metabolic response to single-agent erlotinib. Per PERCIST criteria, the overall metabolic response rate at day 14 was 38.8% (95% CI: 17.3–64.3). On completion of concurrent chemoradiotherapy, overall response rate derived from tumor measurements based on imaging studies was 83% for all dose levels combined.

Conclusions: Erlotinib in combination with low-dose daily cisplatin and RT is well tolerated and shows evidence of clinical efficacy. The combination should be evaluated further. *Clin Cancer Res; 18(6); 1735–42.* ©*2012 AACR.*

Introduction

Forty thousand incident cases of squamous cell carcinoma of the head and neck are diagnosed in the United States each year. Despite standard-of-care platinum-based concurrent chemoradiotherapy (CCR) or surgery plus adjuvant radiotherapy (with or without chemotherapy), the overall survival of patients with local regionally advanced (stages III–IV, M0) oral squamous cell carcinoma [head and neck cancer (HNC)] remains poor. In particular, patients with human papillomavirus (HPV) negative cancers have a 2-year overall survival of less than 60% (1).

Intergroup Trial 9111 has established high-dose cisplatin concurrently administered with radiation therapy (RT) as the standard of care for organ preservation for advanced laryngeal cancer (2). This combination has also been applied as a nonsurgical, curative approach to locally advanced cancers arising from other anatomic sites (3–5). A meta-analysis found that cisplatin-based CCR led to the greatest improvement in overall survival (4). However the optimal dose and schedule of cisplatin has not been determined by comparison in clinical trials. Two clinical trials have shown that low-dose daily radiosensitizing cisplatin (6 mg/m^2 per radiation fraction), administered concurrent with either standard fractionation or hyperfractionation RT improved local regional control and overall survival and reduced rates of distant metastases when compared with radiation alone. This dose and schedule of cisplatin was associated with reduced hematologic and nonhematologic toxicities, and therefore may allow for the safe addition of targeted therapies (6–7).

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Translational Relevance

This study evaluates the addition of an epidermal growth factor receptor (EGFR) inhibitor to the traditional concurrent chemoradiotherapy (CCR) backbone of head and neck cancer (HNC) therapy. Given the overexpression of the EGFR in a majority of HNC, this regimen potentially builds on the efficacy of CCR alone. In addition, imaging of response to CCR per Response Evaluation Criteria in Solid Tumors criteria proves challenging in both pretreatment and posttreatment HNC, and molecularly targeted agents may not elicit traditional measurable responses but rather stable disease and progression-free survival. This study shows the tolerability of erlotinib with traditional CCR. Moreover, the 14-day run-in period of erlotinib showed evidence of single-agent activity and the potential for ^{18}F-FDG positron emission tomography to evaluate evidence of clinical response and its role as a potential biomarker for response or clinical benefit.

The epidermal growth factor receptor (EGFR) and its ligands, EGF and TGF-α, play important roles in cell proliferation, motility, adhesion, invasion, survival, and angiogenesis (8). Abnormalities of EGFR signal transduction are common in squamous cell carcinomas of the head and neck. Overexpression of EGFR has been shown in the majority (80%–100%) and may be related to advanced T stage and presence of nodal disease. EGFR overexpression has also been shown to be a predictor of survival (9–10).

Treatment of tumor cells *in vitro* with anti-EGFR antibody induces arrest of cells in G_1 with an increase in the cyclin-dependent kinase inhibitor p27kip1 and a decrease in retinoblastoma protein (Rb) phosphorylation (11). Moreover, synergy exists between EGFR inhibition, radiation, and chemotherapy. Although not completely understood, these observations may be related to inhibition of multiple growth-promoting signals such as the antiapoptotic effect of EGFR and EGF-related growth. In addition, inhibition of cross-talk between the EGFR signaling and other growth-promoting pathways may heighten sensitivity to the cytotoxic effects of traditional chemotherapeutic agents (12–15).

Erlotinib is an orally active potent, selective inhibitor of the EGFR tyrosine kinase. In a phase II trial, single-agent erlotinib showed a low response rate (approximately 4%) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). In combination with cisplatin, a response rate of 21% was observed in a phase I/II trial in a similar patient population, and rates of grade 3 and 4 toxicity were minimal. Although the safety and tolerability of combination therapy with erlotinib, cisplatin, and radiation has already been investigated in other malignancies, this regimen may not be as well tolerated for head and neck primary tumors (16–18).

This trial was designed to evaluate whether the addition of erlotinib to CCR would produce acceptable toxicities and preliminary evidence of efficacy in patients with locally advanced oral cavity or oropharyngeal cancer. Moreover, the trial aimed to determine the maximum-tolerated dose (MTD) of the combination of daily oral erlotinib in combination with cisplatin and RT. The pharmacokinetic sampling scheme employed in this trial was designed to measure the erlotinib steady-state concentrations achieved and to ensure that adequate concentrations are sustained during chronic oral administration of erlotinib alone and in combination with standard fractionation external beam RT with or without low-dose daily cisplatin chemotherapy. Finally, the trial evaluated whether a 2-week window period of erlotinib alone could elicit evidence of a metabolic response on serial ^{18}F-FDG positron emission tomography (PET) imaging.

Patients and Methods

Patients

Eligibility requirements included a new diagnosis of histologically confirmed AJCC Stage III (T_3N_{0-1}) or IV ($T_{1-4}N_{2-3}M_0$, $T_4N_0M_0$) squamous cell carcinoma of the oral cavity or oropharynx. Other criteria included the following: no prior therapy for the SCCHN; no diagnosis of other malignancy within the prior 3 years; age 18 years or more; ECOG PS 0–2; adequate organ and marrow function as denoted by ANC 1,500/mm^3 or more, platelets 100,000/mm^3 or more, total bilirubin within institutional upper limit of normal (ULN), transaminases less than 2.5 × ULN, creatinine within ULN or creatinine clearance 60 mL/min/1.73 m^2 or more.

Clinical staging was done at presentation with a combination of operative direct laryngoscopy, esophagoscopy, and bronchoscopy. Moreover, appropriate baseline imaging was obtained (CT scan or MRI chosen per investigator discretion). Baseline evaluations were to be conducted within 1 week before start of protocol therapy. Scans and x-rays for eligibility were done 4 weeks or earlier before the start of therapy.

The protocol was approved by Institutional Review Boards of The Johns Hopkins Hospital in Baltimore, MD and the Louisiana State University Health Sciences Center in New Orleans (LSUHSC). Patients were required to provide written informed consent.

Study design and dose escalation

The principal objective of the study was to determine the MTD of erlotinib in combination with low-dose daily cisplatin and radiotherapy. Oral erlotinib was taken daily starting as a 14-day run-in and continued until RT was completed. Erlotonib was allowed to be crushed and placed in a PEG tube. Low-dose daily cisplatin, 6 mg/m^2 i.v., was started together with radiotherapy on day 15 and given for 5 doses each week (Monday–Friday) for a total of 35 doses (thus cumulative cisplatin dose was 210 mgs/m^2). The cisplatin was diluted with sodium chloride (0.45%) to a total volume of 100 mL. Cisplatin was administered over 20 minutes, 3 hours before RT. Pre- or postcisplatin hydration

Table 1. Dose escalation

Dose-escalation schedule				
Dose level	**Dose**			
	Erlotinib[a]	**Standard fraction external beam radiation therapy**	**Cisplatin (given on days of radiation administration)**	**Cohort size**
Level 1	50 mg	70 Gy, 2 Gy per fraction	6 mg/m^2/d	3
Level 2	100 mg	"	6 mg/m^2/d	3
Level 3	150 mg	"	6 mg/m^2/d	3

[a]Doses are stated as exact dose in mg per day.

was not required. Odansetron 8 mg i.v. was administered before cisplatin. Carboplatin 25 mg/m^2 i.v. per day was substituted for cisplatin in the event of persistent elevation of creatinine to more than 1.5 mg/dL despite prehydration or for grade 2 or more electrolyte wasting.

Standard fractionation RT was delivered daily for 5 days per week starting on day 15 to a total dose of 66 to 70 Gy in 2 Gy daily fractions over 7 weeks. Either 3D conformal treatment planning or IMRT were used. Clinically positive neck nodes received a dose of 68 to 70-Gy in 35 fractions, and the clinically uninvolved neck received a total dose of 50 Gy (including N_0 disease).

Dose escalation followed a modified Fibonacci dose escalation design (Tables 1 and 2). The dose of erlotinib was escalated from a starting dose of 50 mg/d. This dose represented one-third the recommended daily dose of single-agent erlotinib in phase II trials. Patients were treated in successive cohorts of 3 patients. Intrapatient dose escalation was not allowed. All patients in each cohort completed chemoradiation before expansion to the next cohort.

A dose-limiting toxicity (DLT) was defined as the following: grade 3 or 4 neutropenia associated with fever or neutropenia lasting longer than 5 days; grade 3 or 4 thrombocytopenia; any grade 3 or 4 nonhematologic toxicity per NCI/CTC criteria with the exception of grade 4 mucositis that resolves to grade 2 or less with a treatment break not to exceed 10 days. Grade 3 diarrhea was dose limiting only if persistent after the initiation of pharmacologic antidiarrheal therapy. Toxicity was graded using National Cancer Institute (NCI) Common Toxicity Criteria version 2.0.

The MTD was defined as the dose of erlotinib in combination with cisplatin and RT in which less than 2 of 6 patients experiences a DLT. After the recommended phase II dose (MTD) was defined, 6 additional patients were enrolled at that dose level.

Table 2. Study schema

Schema	
Day −28 to −1	Baseline {^{18}F}-FDG PET and CT scan
Day 1–14 induction "window"	Single-agent, daily oral erlotinib
Day 14	Repeat {^{18}F}-FDG PET and CT scan
Day 15–63	RT × 7 wk with concurrent daily low dose cisplatin (6 mg/m^2) and daily oral erlotinib
Day 64 (wk 10)	Radiation and cisplatin and erlotinib completed Pharmacokinetic studies completed.
Day 120 (wk 18)	Repeat imaging including {^{18}F}-FDG PET and CT scan

Dose modifications

Dose adjustments were made for grade 3 or 4 toxicity. The offending agents could be held for up to 14 days until toxicity resolved to grade 1 or less. RT was allowed to continue if erlotinib, the platinum or both were held. If erlotinib was held, RT and platinum could continue at the discretion of the investigator. If platinum held, erlotinib and RT could continue at the discretion of the investigator. If RT held, erlotinib could continue but platinum was held. If the agent causing the toxicity was unknown, then all 3 were held until toxicity resolved to grade 1 or less. The erlotinib was then dose reduced per guidelines. Patients were removed from study if toxicity did not resolve within 14 days or if greater than 2 dose adjustments were required.

Response evaluation and follow-up

Although response was not the primary endpoint of this trial, patients who completed chemoradiotherapy were evaluable for response. Patients with progressive disease were evaluable if they received at least 30 days of combined modality therapy. Response and progression were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST; ref. 19). Disease response was assessed by clinical examination and repeat of baseline imaging on days 15 and 120 (approximately 12 weeks postcompletion of RT).

For investigative purposes only, baseline ^{18}F-FDG PET was carried out within 28 days pretherapy and on day 14 of

study treatment, before initiation of CCR. All PET readings were done by the same designated study radiologist to prevent interpretation variability. Assessment of metabolic response to 14 days of single-agent erlotinib and to the entire treatment algorithm was done via serial ^{18}F-FDG PET at baseline, days 14 and 120, done and interpreted per PERRECIST criteria (20). Patients were fasting for at least 4 to 6 hours and had serum glucose less than 200 mg/dL. Baseline and repeat PET were obtained within 50 to 70 minutes of tracer injection. Follow-up scan was done within 15 minutes of baseline injection time. The region of interest was the measurable target lesion in the primary tumor with maximal 3.0-cm diameter volume SUV [Lesion 1-SUVmax (3 cm)] on the baseline scan. Lesion 1-SUVmax (3 cm) was adjusted to lean body mass [Lesion 1-SUV-LBMmax (3 cm)] and normalized to the average liver SUV-LBMmax (3 cm). A metabolic response was defined as a 30% or greater change in adjusted Lesion 1-SUV-LBMmax (3 cm) when values from days 14 and 120 were compared with the baseline values. A modified radical neck dissection was planned for patients with initial presentation that showed N2a or greater neck involvement at presentation. A biopsy at the primary site was carried out if recurrence was suspected.

Pharmacokinetic sampling and analysis

Whole blood samples were collected on days 1 and 2 and then weekly for 10 weeks before drug administration. Plasma was separated by centrifugation and frozen at −70°C until analysis. Plasma concentrations of erlotinib 1 (range 0–10,000 ng/mL) and OSI-420 (1–1,000 ng/mL), the major active metabolite, were measured using a validated reversed-phase high-performance liquid chromatography assay with tandem mass spectrometry detection (21). Quality control samples were assayed with each analytic run and were within 15% of the nominal concentration.

Erlotinib pretreatment trough concentration (C_{min}) was evaluable if the sample was collected 18 to 30 hours after drug dose and the patient was compliant (e.g., 80% of drug administration during sampling interval). C_{min} at steady state ($C_{ss,min}$) was determined as the average of the pretreatment erlotinib and OSI-420 concentrations on days 8 and 15 (when administered alone) and on days 22, 29, 36, 43, 207, 57, and 64 (when administered in combination with radiation with or without cisplatin). The $C_{ss,min}$ ratio of metabolite to erlotinib was calculated.

Statistical analysis

Toxicity, responses, and pharmacokinetics were summarized using descriptive statistics. A Wilcoxon matched pairs signed-rank test was used to compare $C_{ss,min}$ when administered alone versus in combination with radiation with or without cisplatin. A Kruskal–Wallis ANOVA by ranks was used to compare the differences in dose-normalized $C_{ss,min}$ as a function of dose level and to correlate pharmacokinetic and pharmacodynamic endpoints. Statistical tests were done using JMP Statistical Discovery software, version 4.0.4 (SAS Institute).

Table 3. Treated patient characteristics

Patients	$N = 18$
Gender	
Female	3
Male	15
Age range	42–66 y
Median	55
Mean	58
Disease site	
Oral cavity	2
Oropharynx	16
Stage	
III	0
IV	18
ECOG performance status	
0	13
1	5

Results

Patients

Twenty-two patients were enrolled and 18 patients received therapy on protocol. Four patients were excluded because of screening failure ($n = 2$), disease progression before treatment initiation ($n = 1$), and withdrawal of consent ($n = 1$). The baseline characteristics of the 18 patients who received therapy are shown in Table 3. Median age was 56 (range: 42–66), and the majority were Caucasian males.

Three patients were withdrawn from protocol therapy. One patient experienced grade 3 pneumonitis ($n = 1$). This patient also had a possible pulmonary infection. The relationship to erlotinib was deemed possible and patient was removed from study before completing CCR. Two other patients were withdrawn from protocol without experiencing DLT. One patient was diagnosed with Fanconi's anemia ($n = 1$) and another had a diagnosis of metastatic disease by PET on day 14. These 3 patients were subsequently replaced on study.

Safety experience: dose escalation

One of 3 patients at dose level 1 (50 mg erlotinib) experienced grade 3 neutropenia and fever and therefore the first cohort was expanded to 6. No DLT was noted in the 3 additional patients. A total of 5 patients were enrolled on dose level 2, erlotinib 100 mg/d. Two were removed from protocol therapy, 1 due to grade 3 pneumonitis with an attribution of possibly related to erlotinib. One was removed because of a diagnosis of Fanconi's anemia. Three patients completed this dose level without DLT. Three patients at the third dose level of erlotinib 150 mg/d had grade 3 anorexia and 1 patient showed grade 3 radiation dermatitis. However, these toxicities were not attributed to the investigational drug. This cohort was then expanded to 9 patients. In the expanded cohort, 1 patient experienced

Table 4. Grade 3/4 toxicities

	Grade 3/4 toxicity N = patients	Dose level (erlotinib dose mg)
Nausea	2	50
Anorexia	2	50
	2	100
	7	150
Xerostomia	1	50
	1	100
	1	150
Pneumonitis	1	100
Diarrhea	1	100
Lymphopenia	4	50
	4	100
	7	150
Mucositis	2	50
	2	100
	5	150
Radiation dermatitis	2	150
Rash	3	150

grade 3 neutropenia and 1 experienced grade 3 anorexia. However, these toxicities were not considered dose limiting. Grade 3/4 toxicities attributed to the addition of erlotinib to CCR include lymphopenia, diarrhea, rash, and pneumonitis.

One patient in dose level 1 required an 8-day treatment break for grade 4 mucositis. Otherwise, no treatment breaks greater than 3 days occurred. The details of the RT from the LSU site are not known because of destruction of patient records in Hurricane Katrina. See Table 4 for grade 3/4 toxicities.

Response evaluation

A total of 18 patients were evaluable for response assessment at the completion of combined modality treatment. The average time to clinical response determination was 119 days (range: 64–194 days). Best overall response is summarized in Table 5.

Table 5. Best overall response

Dose level	Best overall response (N = number of patients)
1	CR 3
	SD 2
	PD 1
2	CR 1
	PR 2
3	CR 4
	PR 5

Thus, overall response rate derived from tumor measurements based on imaging studies was 83% for all dose levels combined. Response evaluation took place at an average of 83 days post-CCR (range: 64–194 days).

Pharmacokinetic evaluation

Plasma pharmacokinetic studies were conducted on specimens from 16 patients. One patient was removed from evaluation because of noncompliance. Trough values were obtained 65% of the time. There was no difference in erlotinib $C_{ss,min}$ ($P = 0.30$), OSI-420 $C_{ss,min}$ ($P = 0.20$), or the $C_{ss,min}$ ratio of OSI-410:erlotinib ($P = 0.30$) when erlotinib was administered alone or in combination with radiation and cisplatin (see Table 6). In addition, there was no difference in dose-normalized $C_{ss,min}$ as a function of dose level for erlotinib ($P = 0.14$) or OSI-410 ($P = 0.23$) or in the ratio of OSI-410:erlotinib ($P = 0.07$) with increasing ratios with increasing erlotinib dose.

Pharmacokinetic–pharmacodynamic correlations

No correlation was observed between clinical responses (Tables 1 and 2) and pharmacokinetic parameters [erlotinib $C_{ss,min}$ ($P = 0.55$), OSI-410 $C_{ss,min}$ ($P = 0.71$), or the $C_{ss,min}$ ratio of OSI-410:erlotinib ($P = 0.71$)].

A summary of the baseline, day 14 and day 120 findings for the primary tumor on ^{18}F-FDG PET are shown in Table 7, stratified by erlotinib dose level. Scans for 2 patients at dose level 2 on day 120 were not done per patient request. There

Table 6. Plasma exposure to erlotinib during the course of chemoradiation

	Erlotinib $C_{ss,min}$ (ng/mL)	OSI-420 $C_{ss,min}$ (ng/mL)	OSI-420: Erlotinib $C_{ss,min}$ ratio
50 mg alone	563.2 ± 238.9 (4)	39.5 ± 20.9 (4)	0.07 ± 0.01 (4)
50 mg combination	808.7 ± 536.4 (4)	61.8 ± 45.5 (4)	0.08 ± 0.01 (4)
100 mg alone	489.9, 542.8 (2)	30.6, 59.4 (2)	0.08, 0.12 (2)
100 mg combination	299.2 (1)	25.0 (1)	0.09 (1)
150 mg alone	741.9 ± 469.6 (7)	67.8 ± 53.7 (7)	0.09 ± 0.03 (7)
150 mg combination	949.3 ± 756.2 (9)	101.3 ± 90.9 (9)	0.10 ± 0.03 (9)

NOTE: Values are expressed as mean ± SD (n) or as individual concentrations if $n < 2$. $C_{ss,min}$ = average steady-state trough plasma concentration.

Table 7. Percent change in adjusted SUV-LBM (3 cm), by treatment group

	SUV-LBM (3 cm) adjusted value				
Dose level	**Baseline**	**Day 14**	**% Change[a]**	**Day 120**	**% Change[a]**
1					
	7.25	6.0	−17.2	1.83	**−82.1**
	3.92	2.6	**−33.7**	1.27	**−67.6**
	7.2	7.46	3.6	2.04	**−71.7**
	7.13	7.55	5.9	2.08	**−70.8**
2					
	8.46	3.85	**−54.5**	—	—
	11.92	6.25	**−47.6**	—	—
	8.17	7.65	−6.4	1.0	**−87.8**
	10.25	9.25	−9.8	4.29	**−58.1**
3					
	6.53	5.2	−20.4	2.72	**−58.3**
	3.38	2.33	**−31.1**	2.39	−29.3
	4.67	4.8	2.8	4.3	−7.9
	12.35	9.47	−23.3	1.0	**−91.9**
	10.43	9.53	−8.6	1.0	**−90.4**
	3.94	3.82	−12	1.0	**−74.6**
	7.64	5.25	**−31.3**	1.0	**−86.9**
	9.0	1.0	**−88.9**	1.0	**−88.9**
	8.44	5.0	**−40.8**	1.0	**−88.2**
	5.82	5.15	−11.5	1.0	**−82.8**

[a]Compared with baseline.

was evidence for metabolic response to single-agent erlotinib. Per PERCIST criteria, the overall metabolic response rate at day 14 was 38.8% (95% CI: 17.3–64.3). Median percent reduction in SUVmax of the primary tumor at day 14 appeared greater at the second and third dose levels, but differences were nonsignificant (median 6.8 vs. 28.7 vs. 21.8, Kruskal–Wallis $P = 0.41$, dose levels 1, 2, and 3, respectively). All but 2 evaluable patients had a metabolic response to treatment at the day 120 evaluation, with the majority (7 of 10) of the patients at the highest dose level having no SUV uptake over background at this time point.

Discussion

On the basis of this phase I investigation, the combination of standard fractionation RT, low-dose daily cisplatin and daily erlotinib is well tolerated. MTD was not reached. The recommended phase II dose of erlotinib is 150 mg per day in combination with cisplatin and RT, the highest dose of erlotinib evaluated in this study. Importantly, although 1 patient showed grade 3 rash, overall skin toxicity (including radiation dermatitis) and mucositis were consistent with historical controls that used concurrent RT and platinum. In addition, only 2 patients had treatment breaks and one of these breaks was due to nonstudy–related issues, again showing the tolerability of the regimen. Only 1 patient had a break due to mucositis. Pill diaries and pharmacokinetic assessment showed good compliance with the daily dosing of the erlotinib. Our pharmacokinetic data showed that cisplatin and RT did not affect steady-state levels of erlotinib and is consistent with previously published data (18).

Previous investigations of EGFR inhibitors in combination with RT or chemoRT have been reported. Cetuximab concurrent with RT showed clinical benefit but some limitations. Bonner and colleagues showed the superior clinical outcomes of RT plus EGFR inhibition (cetuximab) versus RT alone in locally advanced HNC (22). The combination of radiation and cetuximab has been associated with grade 3 and 4 skin reactions. Moreover, cetuximab has been associated with potentially life-threatening infusion reactions, with a higher rate in some parts of the United States. The superiority of this regimen over cisplatin-based CCR has not yet been shown. It remains unclear whether toxicity of the combination of cisplatin and EGFR inhibition is acceptable. In fact, a phase II trial of concurrent cetuximab 400 mg/m^2 week 1 and then 250 mg/m^2 weekly, cisplatin 100 mg/m^2 weeks 1 and 4 and concomitant boost RT (1.8 Gy/d for total 70 Gy) for locally advanced HNC closed early because of significant adverse events (23). Although further investigation of the safety profile of that combination is needed, the study did show a 3-year overall survival rate of 76% and a 3-year progression-free survival of 56% (23).

Our regimen also shows similar response rates to other phase I investigations of TKI-based therapy in HNC. Chen and colleagues treated 23 patients with locally advanced

HNC with a gefitinib plus radiation or gefitinib plus radiation and weekly cisplatin. The most common acute grade 3–4 toxicity for gefitinib plus radiotherapy alone was mucositis, but the prevalence was consistent with RT alone. Clinical complete response rate was 91% (24). In a small phase I trial of gefitinib with paclitaxel and RT, investigators noted prolonged stomatitis (beyond expected for RT alone) and a response rate of 70%. In our study, EGFR inhibition did not increase the rate of grade 3–4 mucositis over CCR alone and compares favorably with others studies of EGFR inhibition plus CCR (25). Our overall response rate of 83% is consistent with prior reports of EGFR inhibition plus CCR as noted above. Whereas Worden and colleagues did not evaluate TKI-based therapy, this CCR-based study did concentrate on oropharyngeal tumors, which provided the mainstay of our study population. Worden showed CCR of 92% but this trial was designed to evaluate response rate and the majority were HPV positive (26). A phase II trial of the regimen would need to be done to determine whether responses to this regimen compare favorably with those as noted above.

Thus, investigation of alternate methods of EGFR inhibition proves to be potentially important. Ultimately, further questions will need to be addressed: (i) can the addition of EGFR inhibition to the backbone of chemotherapy and RT improve clinical outcomes, (ii) do certain HNC populations benefit more than others (e.g., HPV positive vs. negative tumors). Although these questions are outside the scope of this investigation, they provide a rational basis for why a well tolerated, easily administered EGFR inhibitor should be evaluated for curative therapy of locally advanced HNC. The low-dose daily cisplatin regimen proved attractive for this investigation as Jeremic and colleagues showed its tolerability as well as the oral dosing of erlotinib. Moreover, the drug can be crushed and placed in a gastrostomy tube if necessary. Given the need to identify efficacious, well-tolerated novel regimens, we conducted this phase I trial of RT in combination with erlotinib and daily low-dose cisplatin.

The potential for ^{18}F-FDG PET to evaluate evidence of clinical response was preliminarily explored in this study. Interestingly, several patients showed significant decrease in FDG avidity from baseline on the day 14 PET. Although this did not correlate with any pharmacodynamic data, future studies should further evaluate biomarkers for response to erlotinib. In summary, this phase I evaluation showed that the combination is well tolerated. Evidence of biologic effect of single-agent erlotinib was observed as early as 14 days after initiation of the drug. Future investigation will evaluate efficacy of this combination of agents. It remains unclear whether the addition of erlotinib to CCR improves on the efficacy of CCR (cisplatin based) alone. However, prospective evaluations are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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