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Phase II Study of Erlotinib and Docetaxel with Concurrent Intensity Modulated Radiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Background—To establish the efficacy and toxicities of concurrent erlotinib and docetaxel with IMRT for locally advanced head and neck squamous cell carcinoma (HNSCC).

Methods—Patients received daily erlotinib for two weeks, followed by daily IMRT with concurrent weekly docetaxel and daily erlotinib, followed by daily erlotinib for up to two years. The primary objective was disease-free survival (DFS). Secondary objectives included overall survival (OS), patterns of failure, and toxicities. Forty-three patients were recruited.

Results—With a median follow-up of 48.7 months, the 3 year DFS, OS, locoregional failure free survival and distant metastasis free survival was 69.5%, 81%, 82.4%, and 83.7%, respectively. The most common grade III/IV local toxicities were dysphagia, dermatitis and mucositis. Patients with P16+ tumor had significantly better outcomes.

Conclusions—The regimen is tolerable and effective. It is worthy of further investigation in selected patients and may be useful in patients who cannot tolerate cisplatin.

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Keywords

head and neck cancer; radiation; erlotinib; docetaxel; chemoradiation

Introduction

Head and neck cancer is the eighth most common cancer in the United States (1). For locally advanced HNSCC, concurrent chemoradiotherapy (chemo-RT) has been established as the standard treatment with multiple randomized trials and meta-analyses (2-6). However, despite incremental improvements in locoregional control and survival, a significant number of patients have persistent or recurrent disease. The combination of new agents with radiation therapy is of great interest to further improve treatment outcomes.

Most HNSCC have over-expression of epidermal growth factor receptor (EGFR), which plays an important role in several cellular processes associated with malignancy. Targeting EGFR has gained importance in recent years. Cetuximab, a chimeric antibody against EGFR, has been shown to improve survival when given concurrently with radiation in HNSCC (7, 8). However, cetuximab is expensive, requires weekly intravenous administration, and carries a risk of allergic reaction. Erlotinib is an oral tyrosine kinase inhibitor of EGFR. A preclinical model has shown that erlotinib has a significant radiosensitizing effect (9). Clinically, it has been approved for use in non-small cell lung cancer and advanced pancreatic cancer. It has also been shown to be effective in HNSCC. In a pilot study of neoadjuvant treatment in HNSCC, erlotinib was given to 35 patients for a median of 20 days before surgery and 29% patients had tumor shrinkage (10). In a phase II trial of erlotinib and cisplatin in recurrent/metastatic HNSCC, a 21% response rate was noted with 1 complete response and 8 partial responses; 49% of the patients had stable disease (11). Therefore, erlotinib merits further evaluation in the treatment of HNSCC.

Cisplatin is the most common chemotherapeutic agent given concurrently with radiation in HNSCC. However, many patients cannot tolerate cisplatin due to its toxicity. Furthermore, recent data have emerged that the addition of EGFR inhibitors to concurrent cisplatin chemoradiation did not improve treatment outcomes, possibly due to the similar effects on DNA repair by these agents (12-15). Therefore, chemotherapeutic agents other than cisplatin should be evaluated in combination with EGFR inhibitors and radiotherapy.

Docetaxel is a potent radiosensitizer and also has a favorable toxicity profile when compared to cisplatin (16). Human tumor xenograft studies have indicated that cetuximab is more effective in combination with docetaxel and radiation than with cisplatin and radiation (17). Our group has extensive experience in studying the efficacy and toxicity of targeted therapies added to a docetaxel-based chemo-RT regimen both in phase I and phase II setting (18-20). We have completed a phase I trial combining erlotinib, docetaxel, and concurrent radiation in HNSCC and found the regimen to be feasible and tolerated (18). We are now reporting a phase II trial of this treatment regimen.

Materials and Methods

This is a nonrandomized open label phase II study approved by the Institutional Review Boards (IRB) of Case Comprehensive Cancer Center. All patients provided IRB-approved written informed consent prior to study enrollment.

Patient Eligibility and Baseline Assessment

Eligible patients had histologically confirmed previously untreated stage III to IVA/B HNSCC. Patients were evaluated by a multidisciplinary team that included otolaryngologists, medical oncologists, and radiation oncologists. Each case was presented at a multidisciplinary tumor board for treatment recommendation and eligibility for this clinical trial. Pretreatment evaluation included history, physical examination, triple endoscopy, and radiographic imaging of the neck and chest. All patients underwent dental evaluation prior to treatment. All patients were required to have an ECOG performance status of 0-2, and adequate bone marrow, renal, and hepatic functions. Percutaneous gastrostomy (PEG) tubes were placed in the majority of patients prior to treatment.

Patients with squamous cell carcinoma of salivary glands, paranasal sinuses and nasopharynx were excluded from the study. Other exclusion criteria were > grade 2 pre-existing peripheral neuropathy, history of allergic reactions to the chemotherapeutic agents, uncontrolled intercurrent diseases, and positive HIV status.

Protocol Treatment

The treatment schema is summarized in Figure 1.

Chemotherapy

The treatment was administered on an outpatient basis. Erlotinib 150 mg/day was administered orally or via PEG tube for two weeks prior to radiation, during radiation, and up to two years following completion of radiation. Adjuvant erlotinib was terminated if the patient refused, had significant toxicity, or had disease progression. Docetaxel was administered intravenously at the beginning of radiation and weekly during the course of radiation. A dose of 20 mg/m² was given over a 60-minute infusion. Premedication included dexamethasone 4 mg orally daily for 3 days starting 24 hours prior to docetaxel, and Benadryl 50 mg and ranitidine 50 mg intravenously 30 minutes prior to docetaxel. Antiemetic agents were also administered 30 minutes prior to docetaxel.

Radiation Therapy

Radiation therapy was delivered concurrently with chemotherapy using standard once-daily fractionation five days a week. All patients were treated with intensity-modulated radiation therapy (IMRT). In general, three target volumes were defined. Clinical target volume (CTV) 1 was the primary tumor and involved nodes with a margin that was treated to 70 Gy. CTV2 was the high risk areas that may harbor microscopic disease, including soft tissue around CTV1 and the high-risk lymphatic regions. CTV2 was treated to 63 Gy. CTV3 was the intermediate risk areas and was treated to 56 Gy. All these volumes were treated simultaneously using the dose painting technique in 35 daily fractions.

Study Evaluation and Assessment of Response

The adverse events were evaluated weekly using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3. Computer tomography (CT) of the neck and chest and optional fluorodeoxyglucose positron emission tomography scans were obtained 8 to 12 weeks following completion of concurrent chemoradiation therapy. Salvage surgery was performed for patients with persistent or recurrent disease. The patients were seen monthly if they remained on adjuvant erlotinib for up to two years, and every 3 months thereafter.

Study Objectives and Statistical Considerations

The primary objective of the study was to determine the 3 year disease-free survival (DFS) of patients with locally advanced HNSCC treated with the combination of docetaxel, erlotinib and concurrent radiotherapy. Secondary endpoints included locoregional control rate, duration of response, patterns of failure, and overall survival. Based on phase II/III clinical trials of chemoradiation in the treatment of locally advanced HNSCC at the time the study was designed, it was estimated that the probability of disease free survival at 3 years after treatment was about 50%. To detect an improvement in the 3-year DFS rate from 50% to 70% with a significance level of 0.05 and 80% power, the study required 43 patients.

Disease-free survival (DFS), overall survival (OS), distant metastasis free survival (DMFS), local failure free survival (LFFS), regional failure free survival (RFFS) and locoregional failure free survival (LRFFS) was estimated by Kaplan-Meier method and the difference of survival between groups was examined by log-rank test. All tests are two-sided and p-values 0.05 were considered statistically significant. All survivals were calculated from the start of treatment to the date of the event and censored at the date of last follow-up for those alive and without event.

Results

Patient Characteristics

From August 2005 through December 2011, 43 patients were enrolled on the study. Patient characteristics are summarized in table 1. The median age was 57 years (range 35 – 75). The primary sites included 29 oropharynx, 11 larynx, and 3 oral cavity (2 oral tongue and 1 retromolar trigone). The majority of patients had stage IVA/B disease (81%). The primary T classification was split between T1/T2 (47%) and T3/T4 (53%). The majority of patients had N2-3 nodal disease (72%).

The HPV status was determined retrospectively using p16 as a surrogate marker on 36 patients that had tissue available for further testing. Of these patients, 23 were HPV positive, all with oropharyngeal cancer. Of the 13 patients with p16 negative tumor, 4 had oropharyngeal cancer. All 3 oral cavity cancer patients were p16 negative and 6 of 11 patients with laryngeal cancer that were tested had p16 negative tumor.

Treatment Delivery and Toxicities

Of the 43 patients enrolled in the study, 41 completed the full course of radiation therapy, with a median of 52 days (range: 45 – 64 days). One patient refused to continue at 62 Gy due to side effects. One patient died suddenly at 36 Gy of unknown cause.

Thirty seven of 43 patients received 6 or more infusions of docetaxel concurrently with radiation. One patient received 5 infusions, four patients 4 infusions, and one patient 3 infusions. Seven patients required a dose reduction to 15 mg/m², mainly because of elevated liver enzymes.

During chemoradiation, 31 patients received full dosage of erlotinib with no dose reduction. Ten patients had one dose reduction to 100 mg daily due to skin rashes (5), elevation of liver enzymes (3), mucositis (1) and hypertension (1). Two patients had two dose reductions to 50 mg due to skin rashes (1) and gastritis with nausea (1). After chemoradiation 28 patients received adjuvant erlotinib for a median of 5 months. Five of them received more than 20 months of adjuvant erlotinib. The major reason for patients not completing adjuvant erlotinib was patient refusal (58%), followed by disease progression (24%), intercurrent diseases and surgical procedures. Only 2 patients discontinued adjuvant erlotinib due to skin toxicity.

Selected acute toxicities of the treatments are shown in Table 2. The most common hematologic grade III or higher toxicity was lymphopenia (95%). The most common non-hematologic grade III or higher toxicities were dysphagia (49%), dermatitis (37%) and mucositis (35%). There was 9% grade III acneform skin rash. Grade III late toxicities included mandibular osteoradionecrosis (2 patients, one due to dental extraction), dysphagia (4 patients), and laryngeal cartilage necrosis (1 patient who continued to smoke after treatment). A prophylactic PEG tube was placed routinely. Most patients had their tube removed 1 to 3 months after radiation treatment. Two patients remained PEG tube dependent for more than one year after radiation.

Survival and Patterns of Failure

The median follow-up was 48.7 months (range: 1.4-82.1). The 3-year DFS, OS, LFFS, RFFS, LRFFS, and DMFS was 69.5%, 81%, 90%, 87.1%, 82.4%, and 83.7%, respectively (Figure 2). Twenty eight patients received adjuvant erlotinib after chemoradiation. There was no significant difference in any outcome in these patients compared to those who did not receive adjuvant therapy (data not shown).

Patients with a p16+ tumor had significantly better DFS, OS, RFFS, and LRRFS than those with a p16– tumor (Table 3). The difference in LFFS was borderline significant, 95.7% for p16+ patients vs. 72.9% for p16– patients ($p = 0.06$). There was no significant difference in 3-year DMFS between those who were p16+ versus those p16–, with a trend favouring p16+ patients (86.4% vs. 71.4%, $p = 0.608$).

Of 29 patients with oropharyngeal cancer, one had local failure, 2 had regional failure, and 4 had distant failure as the only site of failure. At last follow-up, 7 patients had died, 4 from distant disease, 1 from locoregional disease and 2 from other causes. Of 11 patients with laryngeal cancer, 1 had local failure, 1 had both local and regional recurrence and 1 patient

had distant failure only. At last follow up, 8 patients were alive and 7 of them kept their larynx. Of the 3 patients with oral cavity cancer, one died at 32 Gy of unknown reason, one had persistent unsalvageable disease after treatment, and the third patient developed regional recurrence and later died of lung metastases.

Discussion

We are reporting here a nonrandomized open label phase II clinical trial using a novel combination of concurrent erlotinib, docetaxel and radiation in the management of locally advanced HNSCC. There are three other phase II studies that have been published recently combining erlotinib and other chemotherapeutic agent(s) with radiation in HNSCC. They are summarized in Table 4 (21-23). Haisworth et al (21) combined bevacizumab, erlotinib, paclitaxel and radiation. In their nonrandomized phase II trial, patients were treated with two cycles of neoadjuvant chemotherapy with bevacizumab, carboplatin, paclitaxel and 5-fluoruracil before concurrent chemo-RT. Yoo et al (22) combined bevacizumab, erlotinib, cisplatin and radiation. Radiation was delivered twice daily at 1.25 Gy per fraction with a 6 hours interfraction interval and a planned one-week break during week 4. Martines et al (23) reported a randomized phase II trial comparing cisplatin and radiotherapy with or without erlotinib. All these studies showed that the addition of erlotinib to chemoradiation in HNSCC was feasible and tolerable. The treatment outcomes were comparable to those treated with standard chemoradiation regimens in recent clinical trials, such as Radiation Therapy Oncology Group (RTOG) 0129 and RTOG 0522 (Table 4). RTOG 0129 (24) is a phase III randomized trial comparing concurrent cisplatin with an accelerated concomitant boost (AFX-C) versus standard fractionation radiation (SFX) in locally advanced HNSCC. From July 2002 to May 2005, 743 cases were entered. There were no differences observed between the two arms in 5 year overall survival (59% vs. 56%; $p=0.18$), 5 year disease-free survival (45% vs. 44%; $p=0.42$), 5 year locoregional failure (31% vs. 28%; $p=0.76$), or 5 year distant metastasis (18% vs. 22%; $p=0.06$). RTOG 0522 (12) is a randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for locally advanced HNSCC. In the analysis of 891 patients entered in the trial at a median follow-up of 3.8 years, the 3 year disease-progression-free survival was 61.2% vs. 58.9% ($p = 0.76$), and the 3 year overall survival was 72.9% vs. 75.8% ($p = 0.32$) in the patients treated without or with cetuximab, respectively.

Of note, Martins et al (23) in a randomized phase II study showed that erlotinib did not improve the complete response rate and DFS in patients with locally advanced HNSCC when added to cisplatin-radiotherapy. However, cisplatin might not be the most optimal cytotoxic radiosensitizing agent when EGFR inhibitor is added to concurrent chemo-RT. In addition to the RTOG 0522 trial mentioned above, Eriksen et al (14) recently reported a Danish randomized study (DAHANCA 19) showing that the addition of zalutumumab, a monoclonal antibody to EGFR receptor, to cisplatin-radiotherapy and nimorazole did not increase the local-regional control, disease-specific, or overall survival at 3 years. Mesia et al also reported that the addition of panitumumab, a fully human monoclonal antibody targeting EGFR, to standard fractionation radiotherapy and cisplatin did not confer any benefit in patients with locally advanced HNSCC (15). Therefore, chemotherapeutic agents

other than cisplatin should be evaluated when an EGFR inhibitor is added to chemoradiation regimen.

RTOG 0234 was a phase II randomized clinical trial evaluating postoperative radiation plus concurrent docetaxel and cetuximab versus postoperative radiation plus cisplatin and cetuximab for high-risk HNSCC after surgery. The results showed an impressive improvement in 2 year overall survival and disease-free survival of the docetaxel arm compared to the cisplatin arm (79% versus 69%, and 66% versus 57% respectively) (13). When compared to the historical controls of patients treated with cisplatin and radiation from RTOG 9501, there was an absolute improvement in 2 year DFS of 11.1% and 2.5%, respectively. Although the benefit of the docetaxel arm appeared to be related to the better control of distant disease, these results led to a phase III randomized RTOG trial, RTOG 1216, which compares postoperative radiation with concurrent cisplatin versus docetaxel versus docetaxel and cetuximab for high-risk HNSCC patients (25).

Our study is the first evaluating the combination of erlotinib and docetaxel administered concurrently with radiation therapy. Erlotinib is a small molecule tyrosine kinase inhibitor of EGFR administered orally. This is more convenient to patients, and it does not have the same allergic reaction potential as cetuximab.

Our results showed that such a regimen is feasible. The major local side effects noted in our trial were dysphagia, mucositis and dermatitis. These are consistent with other reports as well as those reported in clinical trials using standard concurrent chemo-RT in HNSCC (2-4, 12, 13, and 24). This suggests that erlotinib did not increase the acute local toxicities of chemoradiation. The grade III dysphagia in our trial might be over-rated due to our routine PEG tube placement. Our patients likely use their tube feeding earlier in the treatment course, which is graded as grade 3 toxicity in CTCAE. Most patients had their PEG tube removed 1 to 3 months after treatment except for two patients who kept the tube for more than one year.

The decision to include adjuvant erlotinib was based upon preclinical data by Milas et al. (26) showing that the addition of a few doses of cetuximab following radiation plus concurrent cetuximab improved the curative effect of the treatment. In the EXTREME trial (27) in which patients were randomized to chemotherapy alone or chemotherapy plus cetuximab, chemotherapy was given for up to 6 cycles, but cetuximab was continued beyond chemotherapy until disease progression or unacceptable toxicity. In this trial, the addition of adjuvant erlotinib did not provide any benefit in treatment outcomes. Many patients refused to continue the medication due to the inconvenience of monthly follow-up and lab tests to monitor the side effects. Therefore, in future clinical trials if adjuvant targeted therapy is considered, it may be better to limit the treatment duration to 1 to 3 months after chemoradiation to improve compliance.

This trial also provides valuable data regarding the optimal weekly dosage of docetaxel given concurrently with radiation. In our study, docetaxel administered at a weekly dose of 20 mg/m² during concurrent radiation treatment was well tolerated. Our group has also completed a phase II study combining radiation, docetaxel, and bevacizumab and has

demonstrated that docetaxel at 20 mg/m²/week was well tolerated in combination with bevacizumab and radiation (20). It is of interest to note that a lower docetaxel dose (15 mg/m²/week) was selected in the phase III RTOG 1216 clinical trial (25).

Recently, there has been a significant increase in the incidence of human papilloma virus (HPV) related oropharyngeal cancer (28). This represents a separate entity of head and neck cancer with a very good response to treatment, and a significantly better prognosis as compared to HPV negative cancer (29). Our limited data in oropharyngeal cancer have confirmed these findings. Currently, clinical trials looking at treatment de-intensification are underway for HPV-related oropharyngeal cancer (30). However, all 3 oral cavity cancer patients recruited in this trial died of disease progression. These patients probably should have had surgery first followed by adjuvant (chemo)radiation based on the pathology features rather than being treated with definitive chemoradiation. For laryngeal cancer, this regimen may be promising. We recruited 11 laryngeal cancer patients in the trial, all with locally advanced disease (8 with stage T3 and 3 with T4A disease). There were only 2 local failures that required salvage laryngectomy. At last follow-up, 8 patients were alive and 7 of them kept their larynx. This regimen may be worthy of further investigation in laryngeal cancer. It may also be useful as an alternative in patients who cannot tolerate cisplatin-based chemoradiation.

Conclusion

We are reporting the results of our phase II trial looking at the combination of erlotinib and docetaxel given concurrently with IMRT in locally advanced HNSCC. The treatment regimen is feasible with an expected side effect profile that is similar to standard chemoradiation. Patients with p16+ oropharyngeal cancer had a very good response to the treatment with 96% locoregional control. This treatment regimen showed promising treatment outcomes in a small number of laryngeal cancer patients, and may be worthy of further evaluation for laryngeal preservation. This combination may also be useful as an alternative for patients who cannot tolerate cisplatin-based chemoradiation.

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SCHEMA

Figure 1.
The treatment schema

A **B**

Figure 2.

Kaplan-Meier estimates of survivals with 95% confidence interval. A. disease-free survival; B. overall survival; C. locoregional failure free survival; D. distant metastasis free survival.

Table 1

Patient Characteristics

Characteristic	Number of Patients
Gender	
Male	33
Female	10
Age median 57 Range 35-75	
Primary Tumor Site	
Oropharynx	29
Larynx	11
Oral cavity	3
T Stage	
T1	6
T2	14
T3	13
T4	10
N Stage	
N0	8
N1	4
N2	28
N3	3
AJCC Stage	
III	8
IVA and IVB	35
HPV Status	
Positive	23
Negative	13
Unknown	7

Table 2

Acute Grade III/IV Treatment-Related Toxicity

Toxicity	Grade III	Grade IV	Total (%)
Hematologic			
Lymphopenia	24	17	41 (95%)
Neutropenia	2		2 (5%)
Anemia	3		3 (7%)
Nonhematologic			
Oral mucositis	14	1	15 (35%)
Radiation Dermatitis	15	1	16 (37%)
Acneform Skin Rash	4		4 (9%)
Dysphagia	20	1	21 (49%)
Anorexia	13		12 (30%)
Nausea/Vomiting	7		7 (16%)
Dehydration	2		2 (5%)

Table 3

The 3-Year Survivals among Patients with P16 Positive and P16 Negative Tumor

	DFS	OS	LFFS	RFFS	LRFFS	DMFS
P16 + (23)	82.6%	87%	95.7%	100%	95.7%	86.4%
P16 – (13)	43.3%	68.4%	72.9%	64.3%	56.3%	71.4%
p value	0.006	0.049	0.06	0.004	0.006	0.608

Abbreviation: DFS, Disease-free survival; OS, overall survival; LFFS, local failure free survival; RFFS, regional failure free survival; LRFFS, locoregional failure free survival; DMFS, distant metastasis free survival

Table 4

Comparison of clinical trials combining erlotinib and radiation in locally advanced head and neck cancer and comparison to RTOG 0522.

Study	Patient	Other Chemo Agents	Erlotinib Dose	3 Year LRFFS	3 Year DFS	3 Year DMFS	3 Year OS
Hainsworth (21)	60	Paclitaxel Bevacizumab	150 mg/day	N/A	71%		82%
Yoo (22)	29	Cisplatin Bevacizumab	100 mg/day	85%	82%		86%
Martins (23)		Cisplatin	150 mg/day	80%	67%		72%
Current study	43	docetaxel	150 mg/day	82.4%	69.5%	83.7%	81%
RTOG 0522 (12)	891	Cisplatin without vs with cetuximab		80.1% v.s. 74.1%	61.2% v.s. 58.9%	87% v.s. 90.3%	72.9% v.s. 75.8%

Abbreviation: LRFFS, locoregional failure free survival; DFS, Disease-free survival; DMFS, distant metastasis free survival; OS, overall survival.