Original Article

A randomized trial comparing radiotherapy alone versus radiotherapy with Geftinib in locally advance oral cavity cancer

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ABSTRACT

Background: Concurrent chemo radiation is the current standard of care in locally advanced head and neck cancer, but in our set–up, all patients cannot be admitted for chemotherapy or cannot tolerate chemo radiation, or do not want surgery and/or surgery is not possible. The present study was planned to compare the efficacy of concomitantly administered Gefitinib with radiation therapy and radiation alone in locally advanced oral cavity cancer that are not fit or able to tolerate concurrent chemotherapy. **Material and Methods:** This was a single center, nonstratified, single blind, nonplacebo-controlled, parallel group intervention study with imbalanced randomization performed at our institute. Adult patients aged 40-65 years, male or female, irrespective of epidermal growth factor receptor (EGFR) status, Karnofsky scale score more than 70, biopsy-proven SCC, locally advance oral cavity cancer, normal hematology parameters, renal function and liver function tests for normal before recruitment were enrolled in the study. Exclusion criteria were patients who were previously treated with either chemotherapy or radiotherapy (RT). Arm1 include only RT, whereas arm 2 includes Gefitinib with RT. **Results:** Sixty patients were included in the study, 30 in each arm. In Gefitinib plus RT arm, complete response was seen in 18 patients (60%), in only RT arm, complete response was seen in 10 patients (33.33%). There was no significant difference in acute toxicities and late toxicities. **Conclusion:** This study shows significant response to treatment and improvement in the Gefitinib plus RT as compared with RT alone. However, the findings of this study need to be confirmed by a study with a larger group of patients and a longer period of follow-up.

Key words: Chemo radiation, epidermal growth factor receptor, Gefitinib, oral cavity, radiotherapy

INTRODUCTION

In early stages of head and neck cancers both surgery and radiation therapy are equally curative but, in advance cases, the likelihood of local control with either modality markedly diminishes. This fact is evident by Radiation Therapy Oncology Group (RTOG) trail 1516 on head and neck cancer patients, in which when radiotherapy (RT) alone was used for the treatment, it revealed tumor clearance as high as 97% for T1N0 M0 stage but only 33% for T4N3M0 stage.[1] Only a minority of patients with loco regionally advanced disease can undergo adequate surgical resections and the outcomes are poor with respect to survival and organ preservation. Majority of the loco regionally advanced tumors are unresectable, especially if preservation is the goal. The rationale for use of concurrent chemo radiation is that it significantly adds to the curability of head and neck cancer and preservation of organ function, and reduction toxic effects. There are reports of higher expression of epidermal growth factor receptors (EGFRs) in head and neck cancer, which is correlated with poor prognosis.[2] In SCCHN, EGFR, and its ligands, transforming growth factor alpha (TGF-α), are over expressed in 80-90% of cases; the corresponding magnitudes of increase are 1.7-fold and 1.9-fold, respectively, EGFR over expression is an early event in carcinogenesis; it is already present in "healthy" mucosa. This over expression will increase steadily in parallel to observed histological abnormalities, from hyperplasia to invasive carcinoma, through dysplasia and *in situ* carcinoma.

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.110768

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The EGFR is the cell-surface receptor for members of the epidermal growth factor (EGF) family of extracellular protein ligands. It is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: ErbB-1, Her 1, Her 2, Her 3, and Her 4.[3] EGFR is a glycoprotein of 170 kDa, encoded by a gene located on chromosome 7p12. Its known ligands are EGF, TGF-α, amphiregulin, heparin-binding EGF, betacellulin, epiregulin, and NRG2-α.[4] EGFR dimerization stimulates its intrinsic intracellular protein–tyrosine kinase activity. As a result, autophosphorylation of several tyrosine residues in the C terminal domain of EGFR occurs. This autophosphorylation elicits downstream activation and signaling by several other proteins that associate with the phosphorylated tyrosines through their own phosphotyrosine-binding SH2 domains. These downstream signaling proteins initiate several signal transduction cascades, principally the MAPK, Akt, and JNK pathways, leading to deoxyribonucleic acid (DNA) synthesis and cell proliferation, decreasing apoptosis potential and increasing angiogenesis.[5,6] Inhibition of the EGFR can affect the extracellular or intracellular domains. Two complementary therapeutic strategies have been developed. Inhibition of the extracellular domain of the receptor with MoAbs prevents activation of the receptor by endogeneous ligands through competitive inhibition; it also results in internalization and degradation of the antibody–receptor complex, downregulating EGFR expression. Targeting the intracellular domain of the receptor with low molecular weight tyrosine kinase inhibitors (TKIs) competes with adenosine triphosphate (ATP) for its binding site on the intracellular domain of EGFR.[7] Two complementary therapeutic strategies have been developed. The first one targets the extracellular domain of the receptor with monoclonal antibodies. Cetuximab binding of the antibody to the EGFR prevents activation of the receptor by endogenous ligands through competitive inhibition; it also results in internalization and degradation of the antibody–receptor complex, downregulating EGFR expression. The second strategy targets the intracellular domain of the receptor with low molecular weight TKIs (Gefitinib, Erlotinib) competing with ATP for its binding site on the intracellular domain of EGFR.[8,9]

Gefitinib is an orally active selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK) an enzyme that regulates intracellular signaling pathways implicated in the proliferation and survival of cancer cells Gefitinib is slowly absorbed with peak level occurring 3.7 hours after dosing; steady state is achieved in 7-10 days.[10]

MATERIALS AND METHODS

This was a single center, nonstratified, single blind, nonplacebo-controlled, parallel group intervention study with imbalanced randomization that was performed at our institute. Patients and treatment characteristic are listed in Table 1. The case materials for this study were selected from the patients registered at our institute who received treatment between December 2008 and August 2010. Eligible participants were previously untreated patients of carcinoma oral cavity of any AJCC stage with measurable and evaluable disease, Karnofsky performance score ≥ 70. Normal hematology parameters renal function and liver function tests were performed before recruitment. A total of 60 patients were randomized by simple randomization to two treatment arms. The participants and the outcome adjudicators were blinded about allocation to treatment arms. EGFR status was not determined because it was not available in city and majority of patients could not afford it due to the cost factor. Of the 60 patients, 30 patients were enrolled in arm 1; this group included patients who had been treated with only external beam RT The remaining 30 patients were enrolled in arm 2; this group included patients who had been treated with tab Gefitinib 250 mg PO daily for 7 days before starting RT and continued up to 90 days. RT was planned by using two dimensional techniques, proper immobilization by thermoplastic immobilization cast, portal marked under fluoroscopy. The field arrangement was individualized. Radiation dose to all the patients was 70 Gy to be given in 7 weeks. The portals included the primary disease as well as the neck nodes till 4600 cGy after which the spine cord had been protected by moving the posterior margin anteriorly. The last 2400 cGy had been given as boost to the involved site only. The patients had received five fractions per week

Table 1: Patient's characteristics

Charactestic	RT only	Gefitinib/RT
Age(median)	53 years	55 years
Sex		
Male	23	25
Female	7	5
Site		
Alveolus	3	3
Buccal mucosa	15	13
Tongue	11	7
RMT	1	5
Hard palate	0	2
T stage		
T1	1	0
T2	7	10
T3	6	8
T4	16	12
N stage		
N0	18	18
N1	7	8
N2	5	4
Tobacco		
Never	3	4
Former	12	13
Current	15	13
Hb		
≥10gm	17	20
<10 gm >8.5gm	13	10

with the remaining to be received on Saturday and Sunday. Weekly evaluation of complete blood count, liver function test, and renal function test was done in the two arms. Response and side effects evaluation was done weekly during treatment, at the end of RT and then monthly following completion of treatment. Response was evaluated after 2 months of completion of RT as per 1982 World Health Organization (WHO) criteria as complete response (CR), partial response (PR), no response (NR), and disease progression (DP). Both acute and late radiation reactions were assessed as per RTOG criteria. Acute systemic toxicity was assessed as per WHO criteria. The primary end-point was overall response. The secondary endpoints were grade of mucositis; skin reaction, hematological toxicity, incidence and grade of diarrhea, and vomiting were used to assess the significance in primary and secondary endpoints. For statistical analysis data was arranged using SPSS software version 18. Descriptive studies were done for all parameter, Kaplan–Meier analysis was used for survival analysis. *P* value <0.05 was considered as statically significant.

RESULTS

A total of 60 patients were available for final analysis; 45 male and 15 female patients and median age of the patients was 55 years. Thirty patients were included in each group. The most common sites are buccal mucosa and oral tongue. Stage III 26.7% and stage IV 73.3%. The median duration of symptoms was 6 month. Ulceration in oral cavity is the most common presenting symptoms. A significant difference in overall response between the two study groups was found, with a complete response of 33.33% in RT alone vs. 60% in concurrent oral Gefitinib [Table 2]. The partial response was 63.34% vs. 33.33% in RT alone vs. RT + Gefitinib, respectively. A significant difference in complete response at primary site was found (33.33% vs. 60% in RT only vs. concurrent Gefitinib, respectively). Acute mucositis ≥ grade 3 was seen in 70% of the cases in the concurrent Gefitinib arm compared with 63% in the RT only arm [Tables 3 and 4]. The acute toxicities in both the arms are not significantly different The average duration to complete the treatment is almost same (55 vs. 56 days) in both the arms indicating no significant toxicity-related treatment delay The common side effects expected due to Gefitinib like diarrhea, nausea, and vomiting were not significantly increased in the concurrent Gefitinib arm compared with the RT only arm. There is no significant difference in hematological, hepatic, and renal toxicity. The late reactions (at 90 days) are not significantly different in the two arms. At 10 months, patients who received Gefitinib with RT had better DFS compared with those who did not receive chemotherapy, although not statistically significant. On 20 months of follow–up, no difference was observed in both the arms [Figure 1].

Table 2: Treatment response

Response	RT Only	%	Gefitinib with RT	%
Complete response	10	33.33	18	60
Partial response	19	63.34	10	33.33
No response	1	3.33	2	6.7

Table 3: Toxicity mucositis

Mucositis	RT Only		Gefitinib with RT	
	No.	%	No.	%
Grade 0	0	0	0	0
Grade I	0	0	0	0
Grade II	11	36%	9	30%
Grade III	18	60%	18	60%
Grade IV	1	3%	3	10%

Table 4: Toxicity skin reaction

Skin reaction	RT Only		Gefitinib With RT	
	No.	%	No.	%
Grade 0	0	0	0	0
Grade I	0	0	0	0
Grade II	19	64%	18	60%
Grade III	10	33%	11	36.67%
Grade IV	1	3%	1	3.33%

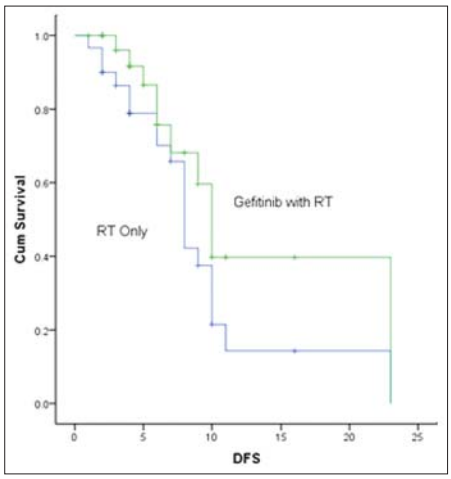

Figure 1: Disease free survival among radiotherapy alone and Gefitinib with radiotherapy. The Kaplan–Meier method was used to estimate survival

DISCUSSION

The story of EGFR TKI in advanced nonsmall cell lung cancer (NSCLC) with Gefitinib or Erlotinib is well-known and is a good example of how to identify the right patient-population for treatment. Gefitinib and Erlotinib have been found to be active in SCHNC albeit at a modest level.[11-14] Cohen's study has shown the lack of correlation of EGFR protein expression and EGFR FISH with response and survival outcome. This is consistent

with the findings of the phase III study by Stewart *et al.*,[14] which is the largest study to date, which showed that EGFR FISH was not predictive of response or survival outcome to Gefitinib. The presence of EGFR mutations is an established predictive biomarker in NSCLC and of the many types of known mutations; however, several retrospective studies showed that EGFR mutations are distinctly less common in SCHNC. Lee, *et al.*,[15] from South Korea found three EGFR mutations (7.3%) in 41 SCHNC tumor samples. A second Korean study showed EGFR mutations in 16% of 110 patients with squamous cell carcinoma of the tongue or tonsil.[16] Studies from Japan and the West showed low mutation rate ranging from 0% to 8%. Cohen, *et al.*,[17] found no EGFR mutations in the eight EGFR TKI responders. The study by Na, *et al.*,[16] does suggest that they may be more frequent in tongue and tensile cancers. Second, the distribution of these mutations appears different from NSCLC in that mutations involving exon 20 were detected more frequently. The current study showed that administration of Gefitinib 250 mg daily and definitive RT were well tolerated. The profile of acute toxicity during concurrent Gefitinib and chemo RT was consistent with the toxicity profile reported in the larger chemo RT trials, with grade 3 mucositis in the range of 43-77%. Gefitinib does not seem to increase chemo RT-related mucositis and skin reaction. It is unclear at this point where EGFR-TKIs will fit into the targeted therapy armamentarium with chemo RT. The potential advantages of EGFR-TKIs include ease of administration and no issues with infusion reactions. Monotherapy trials seem to show similar response rates and survival rates between EGFR antibodies and EGFR-TKIs in metastatic, chemotherapy-refractory HNC. It is unlikely that a clinical trial will directly compare the two approaches with RT. The success of inhibition, which may improve the therapeutic ratio for anti-EGFR, targeted therapies. Our goal was to evaluate whether maintenance Gefitinib was indeed feasible and safe. The true efficacy of Gefitinib maintenance therapy in LAHNC can only be determined in phase II and III trials. Cetuximab with RT led to the ongoing RTOG 0522 phase III trial comparing chemo RT with chemo RT and Cetuximab. Cetuximab effectiveness was greater when administered as both concurrent and maintenance therapy. In conclusion, Gefitinib at daily dose of either 250 mg was well tolerated with RT. Oral administration of Gefitinib for patients aged up to 90 years at 250 mg daily was also tolerated well. Adverse effects did not seem to accumulate over protracted administration. The clinically appropriate dose of Gefitinib (250 mg) in combination with chemo RT and the efficacy of Gefitinib as concurrent and maintenance therapy in LAHNC can only be determined in efficacy trials. The preliminary results of a phase II study from the University of Chicago demonstrate that adding Gefitinib 250 mg daily to concurrent chemo RT after induction therapy and as adjuvant therapy for 2 years is tolerable and feasible. Favorable survival (73% at 3 years) and complete response data (91%) suggest that this is a promising regimen for patients with LAHNC.

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Cite this article as: Singh PK, Dixit AK, Prashad SN, Saxena T, Shahoo DP, Sharma D. A randomized trial comparing radiotherapy alone versus radiotherapy with Geftinib in locally advance oral cavity cancer. Clin Cancer Investig J 2013;2:29-33.

Source of Support: Nil, **Conflict of Interest:** No.