Original Article

Comparison of Concurrent Chemoradiation with Daily Gefitinib versus Daily Erlotinib in Locally Advanced Oropharyngeal Cancers

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Abstract

Background: Concurrent chemoradiation had been the standard of care for locally advanced oropharyngeal cancers. The addition of newer targeted therapies such as cetuximab has resulted in improved locoregional control rates along with tolerable toxicities. The aim of this study was to evaluate the response with addition of newer generation of systemic targeted agents (gefitinib and erlotinib) in combination with chemoradiotherapy for locally advanced oropharyngeal cancer. **Materials and Methods:** A total of fifty patients of locally advanced carcinoma oropharynx were randomized by odd–even technique to two arms. Arm A (24 patients) received radiotherapy along with concurrent weekly carboplatin 150 mg and daily gefitinib 250 mg, whereas Arm B (25 patients) received erlotinib 150 mg daily along with same chemoradiation regimen as in arm A. **Results:** The mean age group in the gefitinib and erlotinib groups was 56.9 and 55.1 years. The most common subsite was base of tongue followed by tonsil. The complete response rate was nearly the same in both the arms at the end of treatment. At the end of 1 and 2 years, the disease-free survival (DFS) was more in the gefitinib group as compared to erlotinib group (41.6% vs. 29.1%) and (33.3% vs. 25%), respectively. **Conclusion:** There was no significant improvement in DFS and OS with the administration of tyrosine kinase inhibitor (TKI) along with concurrent chemoradiotherapy. This might be attributed to the fact that longer duration of TKI was not administered, variable bioavailability of TKIs, and other immune-dependent mechanism when compared to cetuximab and other monoclonal antibodies.

Keywords: *Concurrent chemoradiation, erlotinib, gefitinib, oropharyngeal cancer*

Introduction

Head-and-neck squamous cell carcinomas (HNSCC) account for around 5% of all cancers worldwide.[1] They are the 2nd most common cancer in India after lung cancer.[1] Treatment strategies of HNSCC are dependent on the subsite and stage at presentation. The majority of patients present in locally advanced stage (Stage III and IV).[2] These are best managed with a multidisciplinary approach including surgery, chemotherapy, radiotherapy as well as biological therapy.

The treatment of choice for locally advanced carcinoma oropharynx is concurrent chemoradiotherapy.[3] Newer techniques of radiotherapy such as intensity-modulated radiotherapy and volumetric arc radiotherapy have achieved better local tumor control with dose escalation, while sparing the nearby organs at risk but no significant difference has been noted in overall survival.[4]

The regimen for concurrent chemotherapy has usually been alkylating agents such as cisplatin and carboplatin (elderly patients or those with deranged kidney function tests).[5] These drugs enhance the sensitivity of tumor cells to radiotherapy while having no overlapping toxicities. This spatial cooperation was the initial rationale for the combination of chemotherapy along with radiotherapy.[6]

In recent times, targeted therapy in the form of epidermal growth factor receptor (EGFR) inhibitors (cetuximab and gefitinib) have been tried with some efficacy in the management of recurrent or metastatic head-and-neck cancer.[7] An association between EGFR expression and survival has been noted in HNSCC.[8]

Gefitinib is an EGFR small-molecule tyrosine kinase inhibitor (TKI) with radiosensitizing properties and this drug

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consistently demonstrates tumor growth delay and enhances apoptosis.[9] There have been Phase I studies which have shown feasibility of administering EGFR inhibitors concurrently with chemoradiotherapy.[10] Similarly, erlotinib is an orally active potent, selective inhibitor of the EGFR tyrosine kinase initially used in pancreatic cancer and lung cancer.

The aim of the study is to evaluate the response in terms of response rate complete response rate (CRR), disease-free survival (DFS) with the addition of TKI'S, gefitinib, and erlotinib with concurrent chemoradiotherapy with weekly carboplatin in locally advanced oropharyngeal tumors. The secondary endpoints were to evaluate their efficacy and toxicities.

Materials and Methods

A total of fifty patients were recruited of locally advanced oropharyngeal cancer over a period of 2 years. Inclusion criteria included patients who were more than 18 but <70 years of age, biopsy-proven case of locally advanced oropharyngeal cancer, and good performance status (ECOG PS 0 or 1). Patients who had evidence of distant metastasis, history of previous treatment in the form of neoadjuvant chemotherapy or radiotherapy or anti-EGFR treatments were excluded from the study. One patient in gefitinib arm was lost to follow-up so was excluded from the study and 49 patients were evaluated in the end. All patients were recruited in the study after taking written informed consent and after taking ethical clearance.

Patients underwent standard workup for head-and-neck cancers which included routine blood investigations, direct laryngoscopy, biopsy, chest X-ray, and imaging with contrast enhanced-computed tomography scan. All patients were subjected to pretreatment dental checkup and nutritional assessment. Patients were staged according to the American Joint Committee on Cancer staging criteria.[11]

The patients were randomized into two arms by odd–even method (simple randomization). Arm A received radiotherapy along with weekly concurrent carboplatin and TKI – gefitinib 250 mg OD. Arm B received radiotherapy and weekly concurrent carboplatin along with TKI – erlotinib 150 mg OD. The radiotherapy and concurrent chemotherapy with carboplatin were kept uniform in both arms so as to compare the response of TKIs.

Radiotherapy details

Patients in both arms received external beam radiotherapy to a dose of 66 Gy in 33 fractions @ 2 Gy per fraction over 6½ weeks. Patients were treated on linear accelerator using bilateral parallel opposed fields and lower anterior neck field with 6MV photon beams. Initial 46 Gy was given to the primary site and lymphatic drainage, and after 46 Gy, patients were taken on the simulator, and remaining radiotherapy was given to the primary site up to 66 Gy. If, however, there was any persistent node outside the field, it was treated using electrons.

Chemotherapy details

Carboplatin was given weekly along with radiotherapy to a dose calculated by AUC 2 administered as iv infusion over 60 min before radiotherapy. A median of six cycles was given to all patients. Chemotherapy interruption was allowed in the event of Grade 3 or 4 toxicity.

Tyrosine kinase inhibitor details

The observable side effects specific to TKIs were acneiform rash, diarrhea, skin toxicity, or photosensitivity. In the event of Grade 3 or 4 cutaneous or GI toxicity, the TKIs were interrupted until resolution to Grade 1. Control of diarrhea using antidiarrheal medications was allowed. Medicines for vomiting and skin reactions were also given according to grade of toxicity.

Weekly assessment was done for acute toxicities due to concurrent chemoradiation such as mucositis, skin reaction, vomiting, dysphagia, and dysphasia. Follow-up was done monthly for first 6 months, and patients were assessed subjectively and objectively by clinical response and radiological investigations. Patients were followed every 2 months after 6 months till 1-year and then 3 monthly visits.

Statistical analysis

For statistical analysis, the data were entered into SPSS version 22 (Corp, Armonk, NY, USA). Descriptive statistics of all parameters under study were generated. Qualitative data were summarized as frequencies and percentages. Progression was considered when there was an increase in the locoregional size of the disease or with the presence of distant metastasis after clinical remission at 3 months, while residual disease was considered if no clinical remission occurred postradiation. DFS and OS were evaluated using Kaplan–Meier analysis. Univariate analysis was done to evaluate relationship between variables under study. A $P < 0.05$ was considered statistically significant.

Results

A total of 49 patients [Table 1] were eligible for final analysis. One patient was lost to follow-up and was not included in final analysis. Finally, 24 patients in gefitinib Group (ARM A) and 25 patients in erlotinib Group (ARM B) were analyzed to a median follow-up period of 2 years (range: 17–31 months). The mean age group in the gefitinib and erlotinib groups was 56.9 and 55.1 years. Males were predominant in the study accounting for 96% and 83% in Arm A and B, respectively. The most common subsite was base of tongue followed by Tonsil. Stage III and Stage IV cancers accounted for 92% and 8%, respectively. All patients were treated with radiotherapy with

a dose of 66 Gy in 33 fractions @ 2 Gy per fraction along with concurrent carboplatin chemotherapy given weekly.

In toxicity analysis [Table 2], acute toxicity was more severe in erlotinib group, in which two patients died due to treatment complications. One patient died 10 days after completion of radiotherapy due to severe Grade IV skin reaction which got infected. The incidence of acneiform rash was similar in both the arms. [Figure 1b]. The other patient died during treatment, had developed Grade IV diarrhea during the 2nd week of radiotherapy. No patient died in the gefitinib arm, and all patients were able to complete the treatment.

The incidence of Grade III skin desquamation [Figure 1c] was also more in the erlotinib group (37.5% vs. 21%), while the incidence of Grade III mucositis [Figure 1a] was similar in both the groups (91.6% vs. 87.5%). Dysphagia, dysphasia, candidiasis, febrile neutropenia, diarrhea, and nephrotoxicity were more common in the erlotinib group as shown in Table 2. Xerostomia which is the most predominant and irreversible complication of radiotherapy was seen in all patients as the patients were treated using conventional radiotherapy with the portals encompassing bilateral parotid glands. Out of all, two patients had developed Grade III xerostomia in both the arms that required administration of artificial sialagogues, while rest of them had Grade I/II xerostomia.

The CRR was nearly the same in both the arms at the end of treatment. Thereafter, the patients were followed up regularly. At the end of 3 months, number of patients with CRR in Arm A and Arm B were 17 patients (70.8%) and 12 patients (48%), respectively (P = 0.07). At the end of 1 year, ten patients (41.6%) in Arm A and seven patients (28%) in Arm B had complete response (P = 0.18).

In terms of residual disease, there was a higher incidence of residual disease in the erlotinib group (33.1%) as compared to 4.1% in the gefitinib group during the first follow-up of up to 3 months. On the contrary, gefitinib Arm had more recurrent lesions at 6 months as compared to erlotinib arm (25% vs. 9%, respectively).

At the end of 1 and 2 years, the DFS was more in the gefitinib group as compared to erlotinib group (41.6% vs. 29.1%) and (33.3% vs. 25%), respectively [Figure 2].

The overall survival was more in the erlotinib Arm as compared to the gefitinib Arm at the end of 2 years (58.3% vs. 54.1%, respectively) (P = 0.38) which was statistically insignificant [Figure 3].

Table 1: The baseline characteristics of patients in our study

Characteristic	Value
Mean age (years)	56
Age range (years)	42-76
Male:female	8.8:1
Smoking (%)	40 patients (81.6)
Tobacco (%)	20 patients (40.8)
Comorbidities (%)	9 patients (18.3)
Stage III (%)	92
Stage IV (%)	8
Median radiotherapy dose	66 Gy/33# @2 Gy/fraction
Median cycles of carboplatin in Group A (cycles)	6
Median cycles of carboplatin in Group B (cycles)	6

Table 2: The toxicity profile of patients in both arms of the study (the values show the number of patients)

Side effects	Arm 1 - gefitinib (n=24)		Arm 2 - erlotinib (n=25)	
	Grade III	Grade IV	Grade III	Grade IV
Dysphagia	1	0	2	2
Dysphasia	4	0	6	1
Candidiasis	5		9	
Febrile neutropenia	4		7	
Acneiform rash	2		2	
Nephrotoxicity	0		2	
Pulmonary toxicity	0		0	
Diarrhea	3		2	
Side effects	**Grade II**	**Grade III**	**Grade II**	**Grade III**
Xerostomia	14	2	18	2

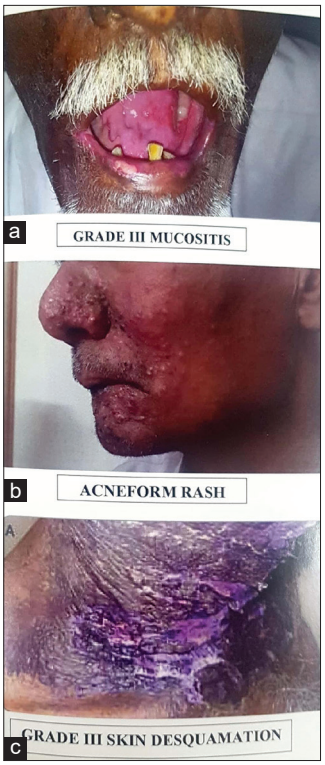

Figure 1: Shows Grade III Mucositis (a), Acneiform Rash (b), Grade III Skin Desquamation (c)

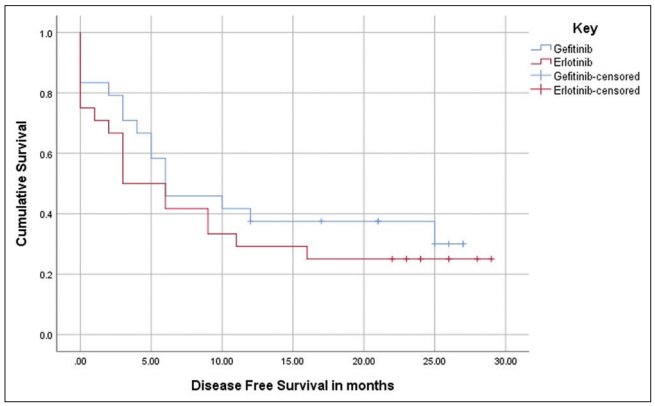

Figure 2: Comparison of disease-free survival between two groups – gefitinib (blue) and erlotinib (red)

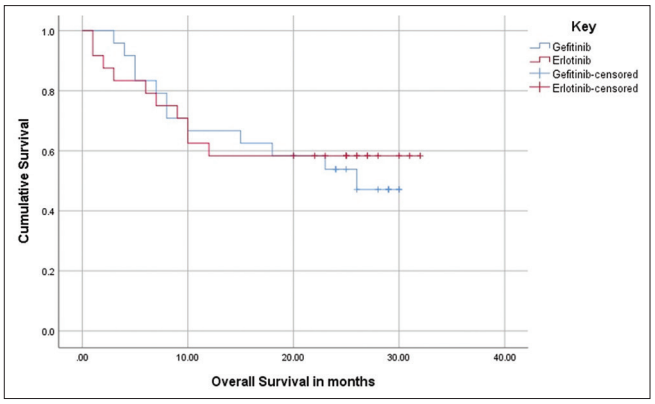

Figure 3: Comparison of Overall Survival between two groups – gefitinib (blue) and erlotinib (red)

Discussion

The standard management of locally advanced oropharyngeal cancers remains concurrent chemoradiotherapy. In a study done by David *et al*.,[12] addition of chemotherapy to radiation resulted in 3-year overall survival of 37%. In view to improve results, extensive research has been conducted in HNSCC, where EGFR remains the only nonchemotherapeutic molecular target that has been successfully translated into a biologic therapy with a clinical benefit. EGFR overexpression remains a major interest in head-and-neck cancer treatment as >90% of carcinomas overexpress it.[13] The potential value of EGFR as a therapeutic target is also supported by the observation that poor prognostic outcomes have been correlated with increased EGFR protein expression.[14]

Currently, anti-EGFR strategies include monoclonal antibodies (MABs) that block the extracellular ligand-binding domain and small-molecule inhibitors that reversibly inhibit the activation of cytoplasmic tyrosine kinase. The success of cetuximab with an overall survival of 45% at the end of 5 years as shown by Bonner *et al*.[15] has not been observed with the small-molecule TKIs despite them having a common target of EGFR.

In comparison with literature for the use of targeted therapy in locally advanced head-and-neck cancers, Tan *et al*. used gefitinib with concurrent chemoradiotherapy and showed 3-year DFS of 42% and OS of 48% with the median time for disease progression being 1.3 years.[16] Another study by Cohen *et al*.[17] depicted better results with a 4-year OS and DFS being 72% and 89%. In our study, the results were at par when compared to any other trial of concurrent chemoradiation in head-and-neck cancer with the OS being in the range of 50%–60% and DFS being 41% and 29% in the gefitinib and rrlotinib arm, respectively. However, the addition of targeted therapies did not resulted in improved DFS or overall survival as mentioned in quoted literature. These lower results in our study might be due to the fact that, in our study, the administration of gefitinib and erlotinib was done only in the concurrent setting, while in the abovementioned studies, it was used for a prolonged period. Tan *et al*. had used gefitinib 3 weeks before the commencement of chemoradiotherapy and continued maintenance therapy for up to 4 months after completion of treatment. In the other study done by Cohen *et al*., it was administered as maintenance therapy till a period of 2 years.

Martin *et al*.[18] used concurrent Erlotinib with concurrent chemoradiotherapy and found a CRR of 52% out of 204 patients. This is in concordance with our study, in which the erlotinib arm had a CRR of 48% at first follow-up. The role of erlotinib has already been established in head-and-neck cancer in the recurrent setting as shown by Siu *et al*.[19]

Another difference in the response of cetuximab and small TKIs might be due to reversible binding of these small molecules to their target as a Phase II study done by Seiwert *et al*.,[20] compared nonreversible binding TKI (Afatinib) with cetuximab and achieved similar results.

In addition, immune-effector mechanisms such as cetuximab-mediated antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and complement-dependent cell-mediated cytotoxicity may play an influential role in the observed clinical activity of MABs over TKI. The difference in pharmacokinetic profiles may further explain the different efficacy between MABs and TKIs in SCCHN including longer half-lives of MABs (mean half-life of cetuximab, 112 h; mean half-life of erlotinib, 36 h; gefitinib being 6–49 h), variable bioavailability of EGFR TKI,[21] higher interpatient variability for TKI degradation resulting from cytochrome P450 polymorphisms, and lower TKI specificity for EGFR in comparison with MAB.[22] Another reason which can be postulated is the lack of activating mutations in head-and-neck cancers as compared to response of TKI in nonsmall-cell lung cancer, but it needs further study.[23,24]

Thus, it appears that both gefitinib and erlotinib have their own results and impact on OS and DFS highly depending

on the duration of administration of the drug. Since the concurrent administration of targeted therapy along with chemotherapy and radiotherapy in head-and-neck cancer is a new concept, there has been no head-to-head comparison of gefitinib and erlotinib done. The high incidence of recurrences might be attributed to the lack of maintenance therapy of TKI as well as other reasons postulated above.

The treatment arms did differ in acute toxicity profile. Grade III mucositis was nearly similar in both arms; however, it was higher when compared to other studies. The incidence of Grade III skin reactions, dysphagia, and dysphasia was higher in the erlotinib arm as compared to the gefitinib arm.

There was no significant improvement in DFS and OS with the administration of TKI along with concurrent chemoradiotherapy. This might be attributed to the fact that longer duration of TKI was not administered as mentioned in literature which might have led to a better outcome as well as other reasons cited above. Furthermore, continued smoking which many of patients did not quit while on treatment is a well-known reason for poorer results. One of the major limitations of our study is that it was a small cohort study and the use of conventional technique of radiotherapy.

To our knowledge, this is the first attempt in literature to compare head-to-head two different TKIs along with concurrent chemoradiation for locally advanced oropharyngeal carcinomas. Further studies will be needed in future regarding the dosing and schedule of TKIs. Few pertinent questions that remained unanswered are the role of maintenance therapy or TKIs and whether or not there is a role of these TKIs in the neoadjuvant setting before starting primary chemoradiotherapy.

Conclusion

The role of oral TKIs in locally advanced oropharyngeal cancers has some positive results but the benefit cannot be elicited when administered only with concurrent chemoradiation without maintenance therapy.

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Conflicts of interest

There are no conflicts of interest.

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