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Original Study

Prospective observational study to assess the role of targeted agent Gefitinib as palliative treatment in residual, recurrent, and metastatic squamous cell carcinoma of head and neck

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Abstract

Background: Patients with advanced head and neck squamous cell carcinoma (HNSCC) remain at high risk of developing local recurrence and distant metastases. Some patients do respond well to treatment but still have residual disease or develop locoregional failure within 1–2 years. Treatment options are limited in such cases with dismal survival outcomes. This study was done to assess the role of Gefitinib in residual, recurrent, and metastasis HNSCC.

Objective: To assess the role of Gefitinib in residual, recurrent, and metastatic HNSCC in terms of overall response, progression–free survival, and toxicity profile of the drug in the palliative setting.

Materials and methods: This was a prospective observational study with 42 patients of advanced HNSCC who had residual, recurrent, or metastatic disease after primary treatment with concurrent chemoradiotherapy. The patients were then treated with a standard dose of 250mg which was titrated as per the toxicity profile of the drug. The drug was continued till the progression of the disease or intolerable drug toxicity.

Result: All patients showed objective clinical and radiological response after the start of treatment as per RECIST 1.1 criteria. Three patients had disease progression within 4 months of start of treatment while 11 patients showed disease progression at 6 months of treatment and rest of the patient within 1 year of start of treatment. Median Progression free survival was found to be 6.1 months [95% Confidence interval 5.563 to 6.63]. Median overall survival (OS) time was 12 months [95% Confidence interval 11.84 to 12.16].

Conclusion: This study suggests the advantage of Gefitinib in patients having residual, recurrent or metastatic HNSCC in terms of clinical response, PFS and OS; similar to the Triple drug metronomic Chemotherapy regime. Though a head on comparison in a phase III trial is required for any conclusive evidence.

Keywords: Gefitinib, residual, recurrent, metastatic, squamous cell carcinoma, head and neck

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th commonest cancer in world with an incidence of 878348 patients including carcinoma of lips and oral cavity, naso–pharynx, oro–pharynx, hypo–pharynx and larynx with mortality 364339 as per GLOBOCAN 2020 data [1] and third most cancer in India. According to GLOBOCAN 2020 data, in India, the overall incidence of cancer is 225419 annually with an overall mortality of 125244 including carcinoma of lips and oral cavity, nasopharynx, oropharynx, hypopharynx and larynx.[2] In India, 60 to 80% of patients present with advanced disease as compared to 40% in developed countries.[3] Many cases presents with locally advanced (LA), unresectable (stage Ⅲ and Ⅳ) disease where standard treatment is a platinum–based chemotherapy and radiotherapy combination strategy. Cases with advanced HNSCC are at risk of residual disease, local recurrence and distant metastasis. Treatment of residual, recurrent and metastatic cases is limited and includes chemotherapy and re–radiation, with very limited benefit. Nearly 90% of HNSCC tumors over express epidermal growth factor receptor.[4] The epidermal growth factor receptor (EGFR) is involved in angiogenesis, the ability to metastasize and inhibition of apoptosis. [5–7] It was therefore found that EGFR expression is closely related to prognosis in head and neck cancer, where higher values indicate poorer progression–free and overall survival.[8]

A M Kirby et al. [9] assessed the level of activity and toxicity of gefitinib in a patient with locally recurrent and/or metastatic head and neck cancer. Patients were started on single agent gefitinib at a dosage of 500mg/day. Clinical, symptomatic and radiological response, time to progression (TTP), survival and toxicity were recorded. The median TTP and survival were 2.6 and 4.3 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (76%) but the majority of cases were grade 1 or 2. Only four patients experienced grade 3 toxicity of any type (all cases of folliculitis). R. RANGA RAO et al. [10] assessed the survival benefit and efficacy of gefitinib in recurrent/metastatic head and neck cancer. Patients on gefitinib in combination with chemotherapy had a clinical response of 66.7% while patients who had received gefitinib as a single agent showed a response of 61.3 % (p value = 0.76). Progression free survival (PSF) in patients receiving gefitinib with Chemotherapy was 6.13 months [95% CI 0.00 to 13.59] whereas patients who received only gefitinib had PFS of 3.73 months [95% CI 3.36 to 4.10] (p value =0.39). P. N. Patel et al. [11] assessed the efficacy and toxicity of Gefitinib in palliative treatment in recurrent squamous cell carcinoma of head and neck in poor performance elderly patients. The median age of the patient was 64 years and 76 patients presented male. All these patients were then kept on oral gefitinib at a daily dose of 250 mg. The clinical response rate was 14% with a disease control rate (complete response, partial response, stable disease) of 45%. In all, 55% of patients experienced an improvement in their symptoms. The median TTP and survival were 5.3 and 10.6 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (24%) but the majority of cases were grade 1 or 2 followed by diarrhoea (16%).

Ezra E.W. Cohen et al. [12] assessed phase II trial of Gefitinib 250 mg daily in patients with recurrent and/or metastatic HNSCC. At the time of this analysis, with a median follow–up of 18 months, all patients have either experienced progressive disease or died. The median progression–free survival and overall survival for the entire cohort were 1.8 months (95% CI, 1.7–3.1) and 5.5 months (95% CI, 4.0–7.0), respectively. The 6–month and 1–year survival rates were 47% (95% CI, 35–58%) and 19% (95% CI, 11–29%), respectively. Grade of skin toxicity positively corresponded with both progression–free survival (p value = 0.001) and overall survival (p value = 0.008). The 13 subjects who developed grade 2 or greater skin toxicity encountered median progression–free survival and overall survival of 4.4 and 7.6 months, respectively.

Gefitinib is orally active, selective EGFR tyrosine kinase inhibitor, which blocks the signals transduction pathway and inhibits cell proliferation in dose–dependent manner.

This study is designed to assess palliative role of Gefitinib as single agent drug in pre–treated patients with residual, recurrent and metastatic HNSCC.

Patients & Methods

Study Details and Design: – This study was a prospective observational study conducted in Department of Radiation oncology, Gandhi Medical college and associated Hamidia hospital, Bhopal, Madhya Pradesh, India, which included a total of 42 patients with advanced HNSCC who had received complete treatment involving chemotherapy and radiotherapy and presenting to our department with a residual, recurrent or metastatic disease between January 2017 to July 2018.

Written informed consent was obtained from all patients and Institutional Ethics Committee of Gandhi Medical College approved the study protocol (letter no: GMC/IEC/ dated 20/02/2017). Gefitinib was provided to the patients free–of–cost in the state government scheme policy. These patients were then started on Gefitinib as palliative oral therapy at a standard dose of 250 mg/day and was titrated as per the patients' toxicity profile. Gefitinib administration was considered in patients with normal hemogram test, renal function test, cardiopulmonary and hepatic function tests with Karnofsky performance sore ≥70.

Initially, Gefitinib was given orally at a dose of 250 mg once a day. All the patients were treated until the disease progression occurred or toxicity to unacceptable level or death. Grading of toxicity in patients was done after at least two weeks after treatment initiation and then every two months. according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 criteria.[13] After high grade skin toxicity, stopping Gefitinib was done and on improvement there was again start of Gefitinib at daily dose of 250mg. In case of diarrhoea, anti–diarrhoeal therapy was given and there was no modification of dose.

Response Assessment

The patients were evaluated on the basis of symptoms and clinical recovery. The radiological response was only evaluated when clinical assessment was inadequate and the grading was done according to RECIST 1.1(response evaluation criteria in solid tumors) criteria as complete response, CR, partial response, PR, stable disease, SD or progressive disease, PD. [14] Clinical response measured the improvement of clinical symptoms e.g., pain, swelling, stiffness and clinical signs such as reduced size of tumor. Clinical progression was indicated by worsening of symptoms, occurrence of new lesions or increased size of tumor. The clinical assessment was generally done at least two weeks after treatment initiation and then every two months.

Statistical Analysis

Parameters such as age, gender, disease status, histopathology grade, Karnofsky performance score, were recorded. The compilation of data was done in Excel and IBM SPSS Statistics for Windows, Version 21.0 (Released 2012; IBM Corp; Armonk, New York, United States) was used for its analysis. The quantitative and qualitative data were analysed using the student's t–test and the chi–square test, respectively where p value< 0.05 was considered statistically significant. Kaplan–Meier product–limit method was used for statistical analysis by IBM SPSS. Overall survival (OS) time was measuring the time from initiation of the Gefitinib treatment to last follow up or death of patient. The progression–free survival (PFS) was calculated from the date of start of Gefitinib treatment to documented clinical/radiological progression of disease.

Results

Patients Demographics:

Among 42 patients 39 were male and three females. Twenty–eight patients had residual disease, 9 patients had recurrent disease and rest 5 patients had metastatic disease.

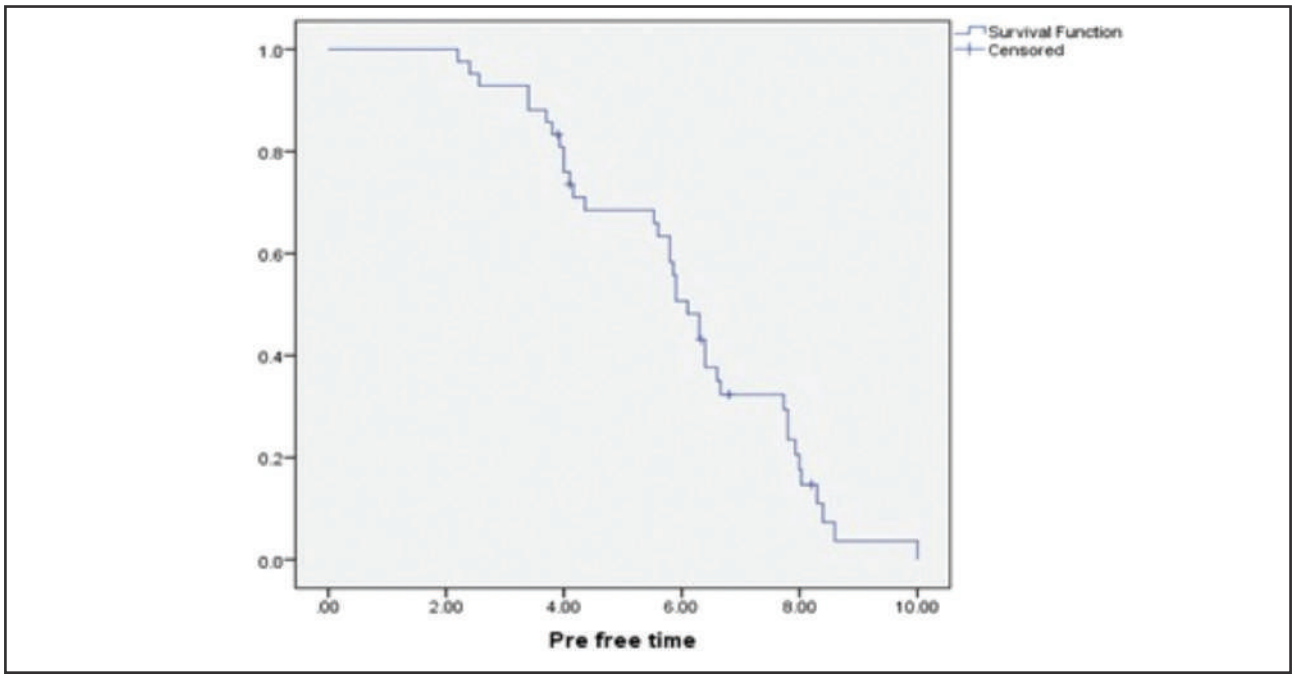
Mean age of patients in the study was 45.6 years. Ten patients were of age below 40 years, twenty–two patients belong to age group of 41–60 years and rest of patients were of age above 60 years. Thirty–one patients presented with a KPS score of 80 and 9 patients were with KPS score of 90 before starting treatment while rest 2 patients had KPS of 70. As per stage wise distribution 31 patient belonging to stage IV and rest of 11 patient belongs to stage III. Majority of the patients in the study were tongue cancer, supraglottic followed by buccal mucosa. The patient demographic details are shown in (table 1).

Analysis was done on intention to treat basis. Of 42 patients, all patients showed clinical response after start of treatment at first follow up. Three patients had progression within 4 months of starting of treatment while 11 patients progressed after 6 months of treatment and all patient had progression of disease at the end of 1 year of follow–up. Median progression free survival was found to be 6.1 months [95% Confidence interval 5.563 to 6.63]. Median overall survival (OS) time was 12 months [95% Confidence interval 11.84 to 12.16]. These are shown in (graph 1) and (graph 2).

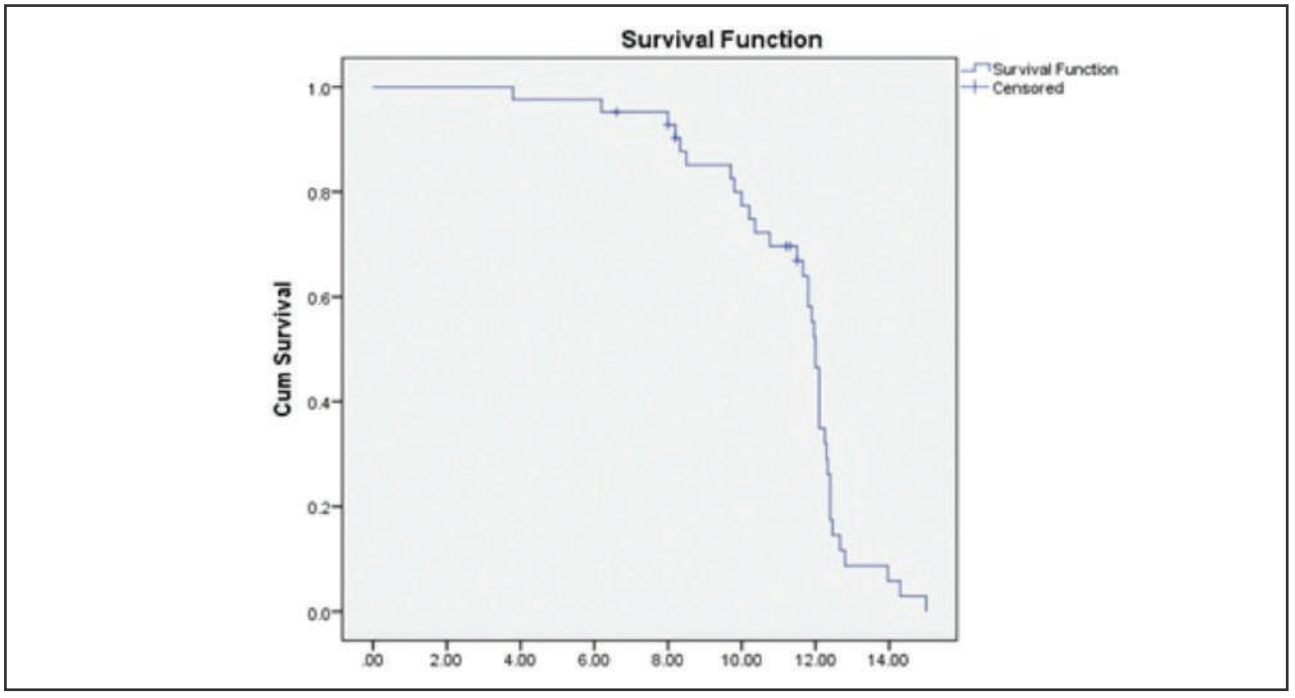
All patients receiving palliative treatment with Gefitinib were also assessed for toxicity at each follow–up. All drug related toxicity was evaluated as per CTCAE (Common Terminology Criteria for Adverse Events) v5.0 criteria.[13] Major drug toxicities were observed in majority, ie, 33

S. No.	Characteristics		No. of Patients (%)	P Value
1.	Age Group (Years)	<40	10 (23.8%)	0.032*
		41–60	22 (52.3%)	
		>61	10 (23.8%)	
2.	Gender	Male	39 (92.8%)	0.0001*
		Female	3 (7.14%)	
3.	Disease	Residual	28 (66.66%)	0.0001*
		Recurrent	9 (21.42%)	
		Metastasis	5 (11.90%)	
4.	Histopathology	WDSCC	19 (45.23%)	0.168
		MDSCC	14 (33.33%)	
		PDSCC	9 (21.42%)	
5.	Kernofsky Performance Score	70	2 (4.76%)	0.0001*
		80	31 (73.8%)	
		90	9 (21.42%)	

Table 1. Patients Demographics (WDSCC; Well–Differentiated Squamous Cell Carcinoma, MDSCC; Moderately Differentiated Squamous Cell Carcinoma, PDSCC; Poorly Differentiated Squamous Cell Carcinoma)



Graph 1. Kaplan–Meier curve for progression free survival in months



Graph 2. Kaplan–Meier curve for overall survival time in months

patients, included acneiform eruption, anorexia, fatigue and diarrhoea. Nine patients did not show any type of drug related toxicity.

Most common toxicity observed was skin toxicity in the form of Acneiform folliculitis. It was observed in 23 patients and affected face and trunk. 21 experienced grade 1–2 reaction with only 2 patients showing grade 3 skin reaction. Two patients temporarily stopped gefitinib due to grade 3 skin reaction and was managed conservatively after resolving adverse reaction again started treatment. Figure 1 shown below shows an example of patient having acneiform eruptions. Grade 1/2 diarrhea affected 5 of the patients followed by anorexia and fatigue in 2 patients each. Toxicity profile is shown in (table 2).

Discussion And Conclusion

Palliative treatment is the last resort for residual and recurrent/metastatic HNSCC. Although many

chemotherapy drug (5–floro–uracil, cisplatin, cetuximab) [19], oral metronomic therapy regimes; both double and triple drug regimes[20]; and lately; low dose immunotherapy have shown some promise in these patients[21], especially in our LMIC country. But they have their own toxicity, cost as well as issues of availability throughout the country. Epidermal growth factor receptor (EGFR) is overexpressed in several epithelial malignancies, including HNSCC, which exhibits EGFR overexpression in up to 90% of tumors.[15] Anti–EGFR therapy is an option in HNSCC as neo–adjuvant, concurrent, and palliative setting. In a phase Ⅱ trial, Gefitinib has shown a median OS and PFS of 6 and 3 months in residual and recurrent/metastatic HNSCC.[12] While Cetuximab had shown median OS and PFS of 5.9 and 2.3 months as the second line treatment in residual and recurrent/metastatic HNSCC.[16] Study was carried out by Kirby et al. showed its use in disease control rate of 36%, clinical response of 8% and median OS and PFS of 4.3 and 2.6 months respectively.[9] Similar benefits were seen in this study with better palliation and enhanced PFS.

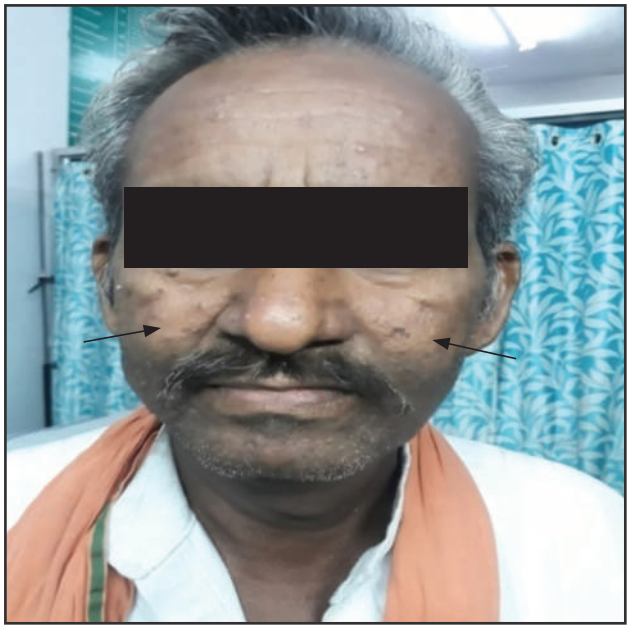


Figure 1. Patient showing Acneiform eruption during treatment

Longer PFS was observed in those patients having previous treatment with concurrent chemo–radiotherapy as compared to patients having other combinations in their treatment. The patients who had to have a surgery were having PFS of 3.5 months while those who had no surgery had 6.13 months PFS (P value= 0.18).[10] Further research is requested to study the effect of surgery on biology of EGFR and response with EGFR blockers drug.

Gefitinib use in residual, recurrent and metastatic HNSCC has been associated with good response, meaningful PFS and can also be used in cases having poor performance status. Skin rash with Gefitinib had a strong relationship with response and an association with overall survival has also been observed.

In the past couple of years, many studies have focused on various prognostic factors that predict response to Gefitinib in cases of other tumors like lung cancer. It appears that cases with mutations in exons 18–21 of the EGFR gene respond to treatment.[17] These mutations have been identified in patients having mainly in adenocarcinoma pathology some patients with squamous cell lung cancer. In case of HNC, one Korean study has identified similar result of deletions in 19 exons in 3 patients out of 41.[18]

Based on treatment evidence the use of gefitinib in HNC is being re–established. In future there are possibilities that gefitinib may play a role in combination with existing and upcoming therapy for HNC. To conclude, in addition to other agents targeting the EGFR pathway, Gefitinib requires to be involved along with a plethora of new drugs targeting cellular targets. In specific way, agents that target different growth factor receptors, the angiogenic switch & apoptotic pathway hold incredible guarantee in management of head & neck cancer. This study suggests the advantage of Gefitinib in patients having residual, recurrent or metastatic HNSCC in terms of clinical response, PFS and OS; similar to the Triple drug metronomic Chemotherapy regime. Though a head on comparison in a phase III trial is required for any conclusive evidence.

Toxicity	Grade (number of patients affected)					
	No. of patients	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
No toxicity	9 (21%)	–	–	–	–	–
Skin eruption	23 (54%)	9	12	2	0	0
Anorexia	3 (7%)	2	0	0	0	0
Diarrhoea	5 (11%)	3	2	0	0	0
Fatigue	2 (4.7%)	2	0	0	0	0

Table 2. Toxicity grades

Acknowledgment

None

Ethical Statement

Written informed consent was obtained from all patients and Institutional Ethics Committee of Gandhi Medical College, Bhopal approved the study protocol (letter no: GMC/IEC/dated 20/02/2017) The study was performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

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