

## Original Article-I

# Survival Benefit and Efficacy of Gefitinib in Recurrent/Metastatic Head and Neck Cancer

R. RANGA RAO, KONNPAL ANIL, LALIT BANSAL, AMIT DHIMAN, SAMEER KHATRI, SHNEH RAWAT AND AJAY DEWAN

### ABSTRACT

**Background:** Patients with advanced head and neck cancer (HNSCC) are at high risk to develop local recurrence and distant metastasis. Treatment options are limited for such cases. This study assesses the efficacy of gefitinib as an alternative treatment option for symptomatic patients with recurrent/metastatic HNSCC.

**Patients and Methods:** We reviewed 40 pretreated patients of recurrent/metastatic HNSCC who received gefitinib (500mg/day), as a single agent or in combination with chemotherapy (CT).

**Results:** 25 of 40 patients (62.5%) had symptomatic improvement. Ten patients were radiologically assessed and 7 (70%) had partial response (PR) and stable disease while 3 (30%) had progression as per RECIST criteria. Overall response (symptomatic and/or radiological response) was seen in 23 of 40 (57.5%) patients. The median progression free survival (PFS) was 3.7 months for all patients. PFS for patients who responded symptomatically was 6.13 months and that of non-responders was 2.13 months [P=0.0000]. Skin rash was common toxicity (42.5%) followed by diarrhoea (15%). Patients who developed skin rash had better overall (7.33 vs 4.73 months) and progression-free survival (PFS) (5.37 vs 2.53 months) Patients with poor performance status (PS) (ECOG 3 & 4) also benefited in terms of clinical (80%) and overall response (80%).

**Conclusion:** Our study suggest the benefit of gefitinib in patients with recurrent/metastatic HNSCC and in patients with poor performance status Further trials to evaluate the role of gefitinib in HNSCC are warranted.

### INTRODUCTION

Head and neck (HN) cancers are amongst the commonest cancers in India accounting for 21% of all malignancies with an annual incidence of around 1.8 lakh cases (Male: female; 5: 1), contributing to 7% of the annual worldwide incidence of 8 lakhs<sup>1</sup>. Patients with advanced head and neck Squamous Cell Carcinoma (HNSCC) have risk of local recurrence and distant metastasis. Treatment options for recurrent disease are limited consisting of chemotherapy and re-irradiation in some, with extremely limited benefits. Approximately 90% of (HNSCC) tumours overexpress epidermal growth factor receptor. Anti-EGFR agents like tyrosine kinase inhibitors (TKI) (gefitinib and erlotinib) and monoclonal antibodies (cetuximab, matuzumab, panitumumab) are being investigated in HNSCC with some exciting results. While role of monoclonal antibodies like cetuximab is established, data regarding use of TKI is limited. Gefitinib in doses of 500mg/day<sup>3,4,5</sup> is an orally active agent having low toxicity profile and good potential for treatment in HNSCC. Studies have also shown that there is no significant change in EGFR over-expression with gefitinib treatment<sup>3</sup>.

This study reports our experience in 40 patients in whom gefitinib was used as a single agent or in combination with chemotherapeutic drugs in pretreated patients with recurrent or metastatic HNSCC.

## PATIENTS AND METHODS

Forty patients with recurrent/metastatic HNSCC, were treated with gefitinib (Gefitinat), as a single agent or in combination with chemotherapy (CT) (Taxanes/Gemcitabine/Platins) from March 2006-July 2007. All patients were heavily pretreated with multimodal strategies. Patients with poor performance status (PS) (ECOG 3 & 4) were also included. Administration of gefitinib were considered in patients with normal renal, cardiopulmonary and liver function test and written informed consent was obtained before starting the treatment.

## TREATMENT PROTOCOL

Gefitinib was initially administered orally in a dose of 250 mg once daily either as a single agent or in combination with CT. Patients with low PS received gefitinib as a single agent while in selected cases with good PS it was given in combination with CT. After 7 days the dose of gefitinib was escalated to 500mg per day. All patients were treated until disease progression, unacceptable toxicity or death. Patients were assessed fortnightly and toxicity was graded according to the World Health Organization (WHO).<sup>6</sup> On occurrence of skin toxicity, dose of gefitinib was reduced to 250mg (grade 2) or stopped (grade 3). After improvement gefitinib was recommenced in daily dose of 250mg and later escalated to 500mg/day. Diarrhea was managed with anti-diarrhoeal therapy with no dose modification. EGFR assay was not performed in this study.

## RESPONSE ASSESSMENT

All patients were assessed on the basis of symptomatic and clinical improvement. Radiological response was assessed when clinical assessment was inadequate and was graded according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).<sup>7</sup> Clinical response was defined as improvement in clinical symptoms such as pain, swallowing and/or stiffness (patients own

assessment) and clinical signs as decrease in size of tumour. Clinical progression (non-responders) was defined as worsening of symptoms, appearance of new lesions or increase in size of tumour. The first clinical assessment was generally performed at 1 week after initiation of treatment and thereafter every fortnight.

## STATISTICAL ANALYSIS

Statistical analysis of the survival was done using Kaplan–Meier product-limit method (SPSS version 10). Overall survival (OS) time was defined as the duration from the initiation of gefitinib treatment to follow up or the death of the patient. Progression-free survival (PFS) was evaluated from initiation of gefitinib treatment till documented clinical/radiological progression or date of last follow up in responders. Differences between Kaplan–Meier curves were evaluated by log-rank test. To test the significance of symptomatic and clinical response, Chi-Square test was done.

## RESULTS

### Patient's Demographics:

Forty patients (men-38 (95%) and women-2 (05%); median age 57 years, range, 34 to 88 years) received treatment with gefitinib. The baseline demographic data of the patients are summarized in *Table 1*. Gefitinib as a single agent was given in 31 (77.5%) patients and 9 (22.5%) patients had received it in combination with CT. Gefitinib treatment was discontinued in 29 patients as they had disease progression, of which 7 are alive and 22 have expired. In 11 patients who did not progress on gefitinib, 6 are still on treatment and 5 have expired. Dose modification was done in 10 patients who developed grade 2 and grade 3 rash. Follow up ranged from 0.9 months to 16.5 months (median = 4.76 months).

### RESPONSE TO THERAPY

All treated patients were included in the analysis of survival and toxicity. Of 40 patients, 25 (62.5%) showed clinical response. Ten patients were radiologically assessed of which

**Table 1: Patients' Demographics**

Sno	Characteristics	No of Patients (%)
1.	Age group (years):	
	31 – 50	13 (32.5)
	51 - 70	22 (55)
	71 - 90	05 (12.5)
	Median (years)	57
2.	Gender:	
	Male	38 (95)
	Female	02 (05)
3	Habit:	
	Smoker	17 (42.5)
	Non-Smoker	23 (57.5)

**Table 2: Prognostic Factors**

S No.	Factors	No of Patients (%)	Clinical Response* (%)	Progression free Survival** (Months)	Median over all Survival*** (Months)	P Value
1	Co-morbidity (IHD, HTN, DM, and/or COPD)					
	Yes	18 (45)	07 (38.9)	2.53	6.9	0.005*
	No.18	22 (55)	18 (81.8)	5.37	4.77	0.15**
2.	Performance Status: ECOG					
	Poor (3,4)	05 (12.5)	04 (80)	3.73	7.33	0.38*
	Good (1,2)	35 (87.5)	21 (60)	3.73	5.3	0.88***
3.	Rash					
	Yes	17 (42.5)	15 (88.2)	5.37	7.33	0.004*
	No	23 (57.5)	10 (43.5)	2.53	4.73	0.35**
4.	Previous Treatment					
	CT+RT+SURG	09 (22.5)	05 (55.6)	3.5	4.77	0.47*
	CT+RT	22 (55)	16 (72.7)	5.37	7.33	
	SUGR+RT	05 (12.5)	02 (40)	2.1	5.40	
CT OR RT	04 (10)	02 (50)	0.77			
5.	Gefitinib					
	Alone	31 (77.5)	19 (61.3)	3.73	4.96	0.76*
	With CT	09 (22.5)	06 (66.7)	6.13	8.36	0.09***

CT : Chemotherapy, RT : Radio therapy, SURG : Surgery

7 (70%) showed disease control (PR and SD) and 3 (30%) had progression as per RECIST criteria. Median OS and PFS of all patients was 5.3 months [95% CI 4.4 to 6.2] and 3.7 months [95% CI 1.45 to 6.02], respectively. In patients who responded symptomatically and who did not respond, the OS was of 7.33 and 3.43 months ( $P=0.0006$ ) and PFS was 6.13 months [95% CI 4.75 to 7.52] and 2.13 months [95% CI 1.62 to 2.65], respectively ( $P=.0000$ ) (Fig 1).

We analysed impact of some important factors on outcome (Table 2). Patients (22/40) with no associated co-morbidity (diabetes, IHD, HTN and/or COPD) had better clinical benefit (81.8%; 18) as compared to patients with co-morbidities (38.9% vs 7) ( $P=0.005$ ). PFS in

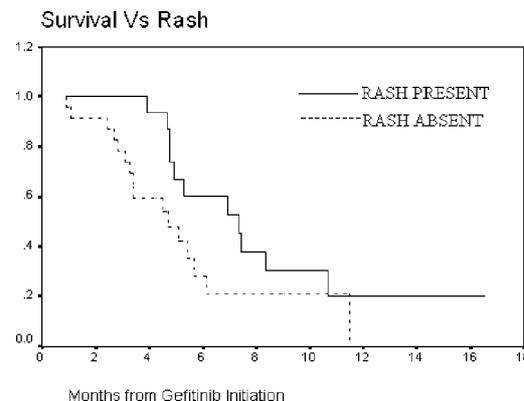


Fig.2. Median Overall Survival in patients with rash was 7.33 months and in patients without rash was 4.73 months (Log-rank test;  $P=0.05$ ).

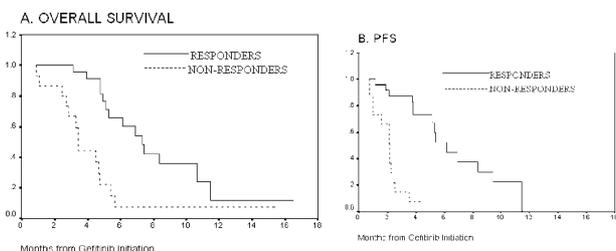


Fig. 1. (A) Overall Survival: Median Survival in responders: 7.33 months and in non responders: 3.43 months (log-rank test;  $P =0.0006$ ). (B) Progression-free survival (PFS): Median PFS in responders: 6.13 months and in non responders: 2.13 months (log-rank test;  $P =0.0000$ ).

patients with no co-morbidity was 5.37 months [95% CI 4 to 6.74] in comparison to who had co-morbidity (2.53 months) [95% CI 0.05 to 5.01] ( $P=0.155$ ). Analysis revealed that patients with poor PS (ECOG 3&4) as well as good PS (ECOG 1&2) have benefited equally with similar PFS (3.73 months). On treatment with gefitinib rash was observed in seventeen patients of whom 15 (88.2%) had clinical improvement ( $P=0.004$ ) (Fig 2). Patients with rash had longer PFS (5.37months) [95% CI 3.06 to 7.67] then who did not have rash (2.53 months) [95% CI 0.69 to 4.38] ( $P=0.35$ )).

Patients on gefitinib in combination with CT (9) had a clinical response of 66.7% (06) while patients who had received gefitinib as a single agent (31) showed a response of 61.3% (19) ( $P=0.76$ ). PFS in patients receiving gefitinib

with CT was 6.13 months [95% CI 0.00 to 13.59] where as patients who received only gefitinib had PFS of 3.73 months [95% CI 3.36 to 4.10] ( $P=0.39$ ). Patients with well to moderately differentiated grade of SCC have responded better (67.9%) than patients with poorly-undifferentiated grade, 6 (50%). However the PFS for well-moderately differentiated was less (3.73 months) [95% CI 3.38 to 4.09] in comparison to poorly-undifferentiated grade (5.30 months) [95% CI 0.28 to 10.32] ( $P=0.07$ ). Status of smoking, age, gender or recurrence did not seem to affect the clinical response or the PFS.

We attempted to determine if type of previous treatment affected the benefit of gefitinib. Patients who were pretreated with combination of CT and radiotherapy (RT) had maximal benefit and response (16; 72.7%). (PFS 5.37 months) [95% CI 4.05-6.68]. Also twenty four patients who did not have local surgery in the past have responded better (66.7%) with PFS of 6.13 months as compared to sixteen patients who had surgery in the past (56.3%) (PFS = 3.5 months).

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Rash (Fig 3) of all grades was observed in 42.5% patients (17 out of 40) with grade 1 in 7 patients, grade-II in 8 and grade-III in 2 patients. The rash

developed within 2 to 149 days of initiation of therapy (median-41 days). Diarrhea was seen in 15% of the patients with half of them having grade 3-4. Other common side effects, observed were-weakness (10%), mucositis (grade 2) (7.5%), anorexia (7.5%), tinnitus and hearing loss (5%), pruritus (5%), pyoderma/paronychia (5%) and vomiting (2.5%).

## DISCUSSION

Palliative treatment options available for recurrent/metastatic HNSCC are limited. The impact on disease stabilization during



Fig 3: Gefitinib induced rash

treatment with molecular targeted drugs has aroused a great deal of interest. Gefitinib in phase II trials in recurrent/metastatic HNSCC have revealed promising results with an median OS and PFS of 6 and 3 months, respectively<sup>4</sup>. Another study had demonstrated its benefits as disease control rate (CR, PR, and SD) of 36%, an observed clinical response of 8% and median OS and PFS of 4.3 and 2.6 months respectively<sup>5</sup>. Our study demonstrates similar benefits with good palliation and improved OS and PFS. Cetuximab as second line treatment in recurrent/metastatic HNSCC had shown a median OS and PFS of 5.9 and 2.3 months respectively.<sup>8</sup> With this study, benefit of gefitinib seemed similar to cetuximab in treatment of recurrent/ metastatic HNSCC.

There is no definitive data regarding the use of gefitinib treatment on survival in patients with poor PS. Our study shows that gefitinib is well tolerated by patients with poor PS and have similar survival benefit. No life threatening adverse effects were observed during treatment and none of the patient had to discontinue gefitinib permanently. This adds to safety potential of gefitinib in patients with poor PS.

Targeted therapy along with chemotherapy is now emerging as a new treatment protocol for many cancers. In our study patients who had chemotherapy along with gefitinib responded better (PFS of 6.13 months), though it was statistically insignificant ( $P=0.39$ ). Since this study group was small, it is not possible to draw conclusions about concomitant use of gefitinib and CT.

Patients who were pretreated with CT and RT had longer PFS than patients who had received other treatment combinations. Interestingly we observed that patients who underwent local surgery in the past (16) had PFS of only 3.5 months as compared to patients who did not undergo surgery<sup>24</sup> (6.13 months) ( $P=0.18$ ). This observation requires further confirmation and may indicate the effect of surgery on biology of EGFR and thereby the response.

Rash was the commonest adverse effect observed, with majority (41.2%) of the patients developing rash in the first month of the treatment. Incidence of rash in literature with 500mg dosing is 48%<sup>3</sup> and studies have shown that patients who were on anti-EGFR and had developed rash have responded better<sup>4</sup>. Our study has shown similar results. Patients developing rash have responded better ( $P=0.03$ ) with a definite survival benefit ( $P=0.05$ ) (*Fig 2*) and a longer PFS ( $P=0.35$ ). Time to appearance of rash although did not contributed to PFS.

Gefitinib in lung cancer has shown to benefit non-smokers better than smokers<sup>9</sup>. In our study the status of smoking did not seem to influence the response or the PFS in HNSCC. The cause of this observation is unclear,

whether it is due to biology of disease or due to the high dose (500 mg) of gefitinib used in HNSCC.

In conclusion, our data suggests that use of gefitinib in patients of recurrent/metastatic HNSCC is associated with good response, better survival and longer PFS, and can be used in patients with poor PS. Also skin rash with gefitinib is strongly related with better response and overall survival.

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