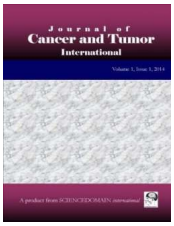

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Evaluation of Efficacy of Gefinitib in Comparison with Chemotherapy in Patients with Non-Small Cell Lung Carcinoma from India

Shyam Aggarwal[1], Sachin Minhas[1*], Mayank Jauhri[1], Yogender Shokeen[1], Madhusudan Ganvir[1], Manish Pungliya[2], C. T. Sateesh[3], H. P. Shashidhara[3] and Shekar Patil[3]

[1]Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, India.
[2]AyuGen Biosciences Pvt. Ltd., Shivajinagar, Pune, India.
[3]HCG Oncology, Bengaluru, India.

Authors' contributions

Authors SA and SP helped in the concept, design, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. Author SM helped in concept, design, literature search, clinical studies, experimental studies, data acquisition and data analysis. Authors MJ, YS, MG, MP, CTS and HPS did the literature search, data acquisition, data analysis and statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Tyrosine kinase inhibitors (TKIs) are a new class of drugs that are proven to be more efficacious than chemotherapy in certain cancers including lung cancer. However, the efficacy of TKIs may vary in different global populations as different ethnic populations have different genetic and/or environmental background. In this study, we have evaluated the efficacy of gefinitib in comparison with chemotherapy in patients with non-small cell lung carcinoma (NSCLC) from India. **Methods:** 50 Non-smokers or ex-light-smokers patients with histologically proven diagnosis of NSCLC were included in this study. 28 patients were positive for EGFR mutations and 18 patients negative for EGFR mutations. We compared the response rates and overall survival of EGFR

**Corresponding author: Email: sachin24minhas@hotmail.com;*

mutation positive patients and EGFR mutation negative patients with respect to the gefitinib treatment. The statistical significance was calculated using Chi-square test.

Results: The overall response rate in patients with EGFR mutation-positive tumors treated with gefitinib was found to be 67% as compared to only 12.5% in case of EGFR mutation negative patients treated with gefitinib. The overall survival rate was found to be better in patients who were EGFR positive (15.58±6.39 months) as compared to patients who were EGFR negative (6.63±5.78 months), when treated upfront with gefitinib (p=0.005).

Conclusion: In conclusion, the results of the present study demonstrate that Indian NSCLC patients who were EGFR positive respond favorably to gefitinib and it may be considered as a more suitable option, in comparison to chemotherapy, for the treatment of NSCLC Indian patients who are EGFR mutation positive.

Keywords: Gefitinib; EGFR mutation; lung cancer; NSCLC; oncology.

1. INTRODUCTION

Lung cancer contributes to a significant cause of morbidity and mortality in cancer patients [1]. It is estimated that 70,000 Indian patients are diagnosed with lung cancer every year and 64,000 die of the disease [2]. Indian patients are more likely to present with the disease at a younger age than Western patients [3]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. It grows and spreads comparatively over a longer period of time as compared with small cell lung cancer. NSCLC accounts for approximately 85% of lung cancer cases. Chemotherapy is only marginally effective in patients with NSCLC [4].

For better efficacy and safety, newer anticancer therapies have been developed which bind to the molecular targets in cancer cell growth pathways and halt the tumor development. One such molecular target is called as the epidermal growth factor receptor (EGFR) [5]. EGFR is a tyrosine kinase based growth factor receptor. The ligands for this receptor promote solid tumor growth and have been identified as a common component of multiple cancer types [6]. EGFR is highly expressed in 88–99% of NSCLC and its expression most likely contributes to the responses occurring in adenocarcinoma and squamous cell carcinoma of lung when treated with drugs like erlotinib, afatinib and cetuximab [7-9]. Mutations in the EGFR gene mainly occur within the exons 18–21, which encodes a portion of the EGFR tyrosine kinase domain. Since, most chemotherapeutic regimens appear to have restricted efficacy and are less cost-effective with poor survival results for NSCLC [4,10-12], EGFR-tyrosine kinase has become a promising drug target for the treatment of patients with NSCLC. Gefitinib, an orally active drug entity targets EGFR tyrosine kinase to demonstrate its anti-tumor activity in NSCLC patients. Further, the effect of gefitinib has been evaluated in several phase I clinical trials wherein, it was found to be efficacious [13,14]. Various studies have been conducted till date to evaluate the effect of gefitinib and chemotherapy in EGFR-positive and EGFR-negative patients. One interesting observation about this drug is the significant variability in the response rate. Results of phase II clinical studies have shown that gefitinib has been effective in only 10–19% of patients with advanced NSCLC as second- and third-line treatment, however; the effect demonstrated was rapid and profound with mild side effects (in lower doses) [15,16]. The efficacy of gefitinib was been shown to be similar for both the low and high dose groups in these studies. A phase II randomized trial conducted to evaluate the effect of gefitinib in chemotherapy naïve patients with advanced non-squamous NSCLC showed an improvement in the progression-free survival (PFS) in patients with EGFR mutations [17]. Douillard et al. evaluated the efficacy and safety/tolerability of gefitinib in Caucasian EGFR mutation-positive NSCLC patients and showed good tolerability [18]. The objective of the present investigator initiated, observational, retrospective study was to evaluate the effect of gefitinib and chemotherapy in EGFR mutation-positive and EGFR mutation-negative patients with NSCLC in an Indian population.

2. METHODS

2.1 Patients

This investigator-initiated, observational, retro-spective study was conducted in two investigational sites across two different regions of India (Sir Ganga Ram Hospital, New Delhi and

HCG Oncology, Bangaluru). The study was conducted between years 2011-2015.

This study was approved by the Institutional Ethics Committees of both the institutes. The study was conducted as per the ethical principles for medical research (Declaration of Helsinki). All patients gave a written informed consent for use of their cancer tissue and clinical records for research purposes.

Non-smokers or ex-light-smokers aged 18 yr and above with histologically proven diagnosis of NSCLC were included in the study. Additionally, patients receiving either chemotherapy or gefitinib and those with a histologically proven diagnosis of NSCLC were identified from the records in the respective hospitals for inclusion.

A total of 50 patients with known EGFR mutation status were enrolled in this study. Out of these 50 patients, clinically relevant data was available for 46 patients. Of the 46 patients, 28 patients (60.9%) were positive for EGFR mutations; 18 patients (39.1%) were negative for EGFR mutations. The mean age of EGFR positive mutation patients was 61±9.9 yr, whereas it was 62.61±14.4 yr for EGFR negative mutation patients (Table 1).

2.2 Data Collection

The timing and order of various chemotherapy regimens were as per the physician's discretion. Clinical data of patients, demographic information, date of diagnosis, all chemotherapy received, and responsiveness to the therapy were recorded. Non-smokers were defined as those who had smoked fewer than 100 cigarettes in their lifetime. Ex-smokers were defined as those who had smoked more than 100 cigarettes in their lifetime but had stopped smoking for at least 1 year before recruitment. Light-ex-smokers were defined as those who had stopped smoking more than 15 years ago and had smoked fewer than 10 packs per year.

2.3 Statistical Analysis

The statistical significance was calculated using Chi-square test. The main variables in our analyses were response rates and overall survival of EGFR mutation positive patients and EGFR mutation negative patients with respect to the therapy given. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1 Response Rates of EGFR Mutation Positive and EGFR Mutation Negative Patients

Complete response was observed in a greater proportion of EGFR positive patients (n=4, 14.3%) as compared with the EGFR negative patients (n=1, 5.6%) however; the difference between the two groups did not achieve significance (p=0.634). No response was observed in 16.7% of the EGFR negative patients (n=3) and 7.1% of the EGFR positive patients (n=2). Although, patients showing progressive disease were greater in the EGFR negative patients (n=6, 33.3%) as compared with the EGFR positive patients (n=3, 10.7%); patients who showed stable disease were higher in the EGFR negative group (n=6, 33.3%) as compared with the EGFR positive group (n=6, 21.4%). A significantly (p=0.007) higher proportion of patients in the EGFR positive group (n=12, 42.9%) showed partial response as compared with the EGFR negative group (n=1, 5.6%).

3.2 Response Rates with Gefitinib and Chemotherapy

Of the 28 EGFR positive patients, four showed complete response (chemotherapy: n=1, 6.3%; gefitinib: n=3, 25%). The difference in the proportion of patients achieving complete response was not significant (p=0.285) between the chemotherapy and gefitinib groups. Partial response was observed in 12 EGFR positive patients (chemotherapy: n=7, 43.8%; gefitinib: n=5, 41.7%). The difference in the proportion of patients achieving partial response was also not significant (p=1.000). Out of total 18 EGFR negative patients, one patient showed complete response to chemotherapy (n=1, 10%) and one patient showed partial response to gefitinib (n=1, 12.5%). There was no significant difference in the outcome of patients treated with gefitinib and chemotherapy (gefitinib, p=0.444; chemotherapy, p=1.000) (Table 2).

3.3 Overall Survival Rates

The overall survival was compared between the EGFR positive and EGFR negative groups and the results revealed that the EGFR positive patients (15.36±6.73 months) showed a significantly (p=0.0101) higher rate of overall

survival as compared with the EGFR negative patients (10.22±6.67 months). To further assess the effect of each treatment group *viz.* gefitinib and chemotherapy, the effect of these drugs among the EGFR positive and EGFR negative patients was evaluated. The EGFR positive patients responded better to gefitinib as compared with chemotherapy although the results were not statistically significant (p=0.709). The overall survival with gefitinib was 15.58±6.39 months in comparison to 15.19±7.18 months with chemotherapy among the EGFR positive patients. A statistically significant result was found when EGFR negative patients showed an overall survival of 6.63±5.78 months with gefitinib and 13.1±6.11 months with chemotherapy as first line therapy (p=0.014) (Table 2).

3.4 Objective Response Rate and Disease Control Rate of EGFR Positive and EGFR Negative Patients with Gefitinib

Objective response rate (ORR) of EGFR positive and EGFR negative patients with gefitinib was compared to evaluate the effect of gefitinib in patients. Eight EGFR positive patients (67%) responded completely or partially to gefitinib when compared to EGFR negative patients in which only one patient (12.5%) responded. A statistically significant result (p=0.028) was also obtained from this comparison. Disease control rate (DCR) was also evaluated in EGFR positive and EGFR negative patients with gefitinib. DCR was 50% in EGFR negative patients when compared to EGFR positive patients in which DCR was 92%. The difference was not statistically significant between these two groups (p=0.109). The overall survival was compared between EGFR positive and EGFR negative groups with gefitinib. The results revealed that the EGFR positive patients (15.58±6.39 months) showed a statistically significant (p=0.005), higher overall survival as compared to EGFR negative patients (6.63±5.78 months) (Table 3).

4. DISCUSSION

EGFR is an important actionable target in NSCLC. In a previous study, the EFGR mutation incidence was found to be 56% in the Indian population [19]. This remarkably high rate of positive mutation in NSCLC can provide important directions in the development of newer targeted therapies like tyrosine kinase inhibitors. The present study showed that patients with EGFR positive mutation tend to show a better response to gefitinib therapy in comparison to patients with EGFR negative mutation. The overall survival rate was found to be better in patients who were EGFR positive (15.58±6.39 months) as compared to patients who were EGFR negative (6.63±5.78 months), when treated upfront with gefitinib (p=0.005). On the other hand, EGFR negative patients showed an overall survival of 6.63 months with gefitinib as compared to 13.1 months with chemotherapy as first line therapy (p=0.014). The results indicate that NSCLC patients must not be given gefitinib as first line therapy unless we have documented EGFR mutation positive report.

The EGFR TKI (gefitinib) has been shown to prolong progression-free survival (PFS) compared with first-line chemotherapy in patients with advanced NSCLC with activating mutations of the EGFR gene, and has been associated with improved tolerability and quality of life compared with chemotherapy [20-23]. Complete response was observed in 14.3% of EGFR mutation positive patients who received gefitinib. A Malaysian study evaluating the efficacy of gefitinib as a first line therapeutic agent for the treatment of EGFR mutation positive NSCLC patients reported that 54.5% of the study population achieved complete response to the drug [24].

Table 1. Patient demographics and baseline characteristics of patients

Demographic parameter	EGFR positive (N=28)	EGFR negative (N=18)
Gender n (%)		
Male	11 (39.3%)	10 (55.6%)
Female	17 (60.7%)	8 (44.4%)
Age (Mean ± SD), years	61.00 ± 9.90	62.61 ± 14.40
Treatment group n (%)		
Chemotherapy	16 (57.14%)	10 (55.6%)
Gefitinib	12 (42.86%)	8 (44.4%)

Table 2. Subject responses and overall survival (months) in EGFR positive and negative patients

Response	EGFR (Mutation) negative			EGFR (Mutation) positive		
	Chemo n (%)	Gefitinib n (%)	*p* value	Chemo n (%)	Gefitinib n (%)	*p* value
CR	1 (10%)	0 (0%)	1.000	1 (6.3%)	3 (25%)	0.285
NR	2 (20%)	1 (12.5%)	1.000	2 (12.5%)	0 (0%)	0.492
PD	3 (30%)	3 (37.5%)	1.000	3 (18.8%)	0 (0%)	0.238
PR	0 (0%)	1 (12.5%)	0.444	7 (43.8%)	5 (41.7%)	1.000
SD	3 (30%)	3 (37.5%)	1.000	3 (18.8%)	3 (25%)	1.000
UK	1 (10%)	0 (0%)	1.000	0 (0%)	1 (8.3%)	0.429
OS (Mean±SD)	13.10±6.11	6.63 ± 5.78	0.014	15.19±7.18	15.58 ± 6.39	0.709
Total no. of patients	10	8		16	12	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NR, no response; UK, unknown; OS, overall survival; SD, standard deviation

Table 3. Objective response rate and disease control rate in EGFR positive and negative patients treated with Gefitinib

Parameter	EGFR mutation negative	EGFR mutation positive	p value
	Gefitinib	Gefitinib	
Objective response rate (ORR)=CR+PR	1 (12.5%)	8 (67%)	0.028*
Disease control rate (DCR)=CR+PR+SD	4 (50%)	11 (92%)	0.109
Overall survival (Mean±SD)	6.63 ± 5.78	15.58 ± 6.39	0.005*
Total no. of patients	8	12	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; SD, standard deviation

The ORR in EGFR positive patients also showed a statistically significant value (p=0.028) as compared with EGFR negative patients. ORRs in patients with EGFR mutation-positive tumors treated with gefitinib have been reported between 62% and 85% [20-23]. The ORR in patients with EGFR mutation-positive tumors treated with gefitinib in the present study (67%) is consistent with the results from previous studies. Another study demonstrated an ORR of 50% in NSCLC EGFR mutation positive patients [25]. The study further reported that the duration of response with gefitinib was 6 months. The study conducted in Malaysian patients reported an ORR of 60.6% in EGFR mutation positive NSCLC patients who were treated with gefitinib [24]. Lastly, it must be noted that we observed an ORR of 12.5% and a DCR of 50% in case of EGFR mutation negative patients treated with gefitinib. A recent phase III Study on TKIs in patients with previously treated advanced lung adenocarcinoma also reported similar results with the use of TKIs in wild-type EGFR patients [26]. There is a possibility that these EGFR mutation negative patients could be overexpressing EGFR. There is evidence that EGFR overexpression shows response towards treatment by gefitinib and other tyrosine kinase inhibitors [27]. In the BR.21 trial, patients showing overexpression of EGFR who were treated with erlotinib had a significantly longer survival duration than placebo-treated patients [28-29]. Similar findings were also reported in the FLEX trial in which the investigators used cetuximab, a monoclonal antibody that binds to EGFR [30].

5. CONCLUSION

In conclusion, the results of the present study have demonstrated that Indian NSCLC patients who were EGFR positive responded favorably to gefitinib in terms of overall survival, ORR, and complete response. Gefitinib may be considered as a suitable option for the treatment of NSCLC Indian patients who are EGFR mutation positive in comparison to chemotherapy. However; long term studies which can establish the tolerability and safety of gefitinib in a larger cohort of patients is extremely essential.

A smaller sample size of the present study may be considered as a limitation of the study. Additionally, the present study did not evaluate the adverse effects of gefitinib in the study population.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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