Efficacy of gefitinib in epidermal growth factor receptor-activating mutation-positive nonsmall cell lung cancer: Does exon 19 deletion differ from exon 21 mutation?

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ABSTRACT

Background: This study was designed to evaluate the differential effect of epidermal growth factor receptor (EGFR) mutation status (exon 19 vs. 21) on progression-free survival (PFS) and overall survival (OS) in treatment-naïve advanced EGFR mutation-positive nonsmall cell lung cancer (NSCLC) treated with gefitinib as first-line agent. **Methods:** This was a *post hoc* analysis of EGFR-mutated (exon 19 and 21) advanced-stage (Stage IIIB or IV), chemotherapy-naive NSCLC patients treated with gefitinib as first line in a phase 3 randomized study. Patients were treated with gefitinib 250 mg daily. Patients underwent axial imaging for response assessment on D42, D84, D126, and subsequently every 2 months till progression. Responding or stable patients were treated until progression or unacceptable toxicity. SPSS was used for statistical analysis. Kaplan–Meier method was used for survival estimation and log-rank test for comparison. Cox proportion hazard model was used for multivariate analysis. **Results:** One hundred and forty-one patients were eligible for analysis, of which 78 were males and 63 were females. A total of 127 patients (90.1%) were ECOG 0–1 while 14 patients (9.1%) were ECOG >1. Exon 21 mutation was present in 65 patients (46.1%) and exon 19 mutation in 76 patients (53.9%). One hundred and thirty-three of 141 patients were evaluable for response. Response rate of patients having exon 19 mutation was 72.9% (51 patients, *n* = 70) while it was 55.6% in patients having exon 21 mutation (35 patients, *n* = 63) (*P* = 0.046). Median PFS in exon 19-mutated patients was 9.3 months (95% confidence interval [CI] 6.832–11.768) compared to 7.8 months (95% CI 5.543–10.0) (*P* = 0.699) in exon 21-mutated patients. The median OS in exon 19-mutated patients was 19.8 months (95% CI 16.8–22.7), and it was 16.5 months (95% CI 10.9–22.1) in exon 21-mutated patients (*P* = 0.215). **Conclusion:** There were no differential outcomes in the Indian patients of advanced-stage NSCLC with exon 19 and 21 EGFR mutations treated with gefitinib.

KEY WORDS: Epidermal growth factor receptor mutation, exon 19, exon 21, gefitinib, nonsmall cell lung cancer, palliative

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INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase domain mutations are heterogeneous mutations occurring in its tyrosine kinase domain.[1] These mutations predict for the response associated with tyrosine kinase inhibitors (TKIs).[2] Certain mutations such as exon 19 deletion and exon 21 L858R are associated with high response and improvement in progression-free survival (PFS) and overall survival (OS) when treated with TKI.[3-5] Certain mutations such as exon 18 mutations and exon 20 insertions are associated with resistance to TKI treatment.[1] Exon 19 and 21 mutations were the first mutations discovered. They have a higher frequency of occurrence and are associated with improved outcomes on treatment with TKI and are called classic activating mutations. These 2 mutations were always considered together in all landmark studies performed over the last decade.[3-5]

However, recently, it was noted that exon 19 mutations have higher response rate, PFS, and OS in comparison to exon 21 mutations.[6] This evidence suggests that these 2 mutations have different outcomes and that it is inappropriate to club these two together. However, none of these datasets were from India. Hence, this analysis was performed to study the differential impact of exon 19 and 21 mutation on outcomes when these nonsmall cell lung cancer (NSCLC) patients are treated with gefitinib.

METHODS

Patient selection
The current study reports a *post hoc* analysis of a phase 3 randomized study (Clinical trial registry of India: CTRI/2015/08/006113) performed in Tata Memorial Centre, Mumbai, India. The results of this study are already published. Patients from this study were selected subjected to the following selection criteria. Adult, pathologically confirmed NSCLC with either exon 19 deletion or exon 21 L858R mutations with adequate organ function, and ECOG PS 0–2 without any uncontrolled comorbidities who were treated with gefitinib were selected for this analysis. Previously treated patients, HIV-positive, and/or HBV- or HCV-seropositive patients were excluded.

Intervention
These patients were treated with gefitinib 250 mg OD PO, which was continued till the development of progressive disease or intolerable side effects. Patients underwent axial imaging for response assessment on D42, D84, D126, and subsequently every 2 months till progression. Responding or stable patients were treated until progression or unacceptable toxicity. At progression, all patients were offered chemotherapy. Patients were followed up till death.

Statistical analysis
IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp) was used for analysis. Patients who underwent radiological assessment were included for response rate assessment. Patients who had either complete response or partial response were considered as having a response. The definition of complete and partial response used in the study was in accordance with RECIST version 1.1. The best response on gefitinib was documented. The response rates between the exon 19-deleted and exon 21-mutated patients were compared using Fisher's exact test. $P = 0.05$ or below was considered as statistically significant.

PFS was defined as time in months from randomization to objective progressive disease, change in treatment, or death from any cause. OS was defined as time in months from randomization to death from any cause. Kaplan–Meier time to event analysis was carried out for the estimation of PFS and OS. Log-rank test was used for comparison of PFS and OS between exon 19-deleted and exon 21-mutated patients. Factors known in literature to impact PFS and OS were selected for univariate analysis and compared using log-rank test. The variables which were associated with P value ~0.2 or below were selected for multivariate analysis along with type of mutation. The Cox regression analysis was used to estimate the hazard ratio (HR) with its 95% confidence interval. $P = 0.05$ or below was considered as statistically significant.

RESULTS

Baseline details
A total of 141 patients received gefitinib [Supplementary Figure 1]. Sixty-five patients (46.1%) had exon 21 mutation while 76 patients (53.9%) had exon 19 mutation. The median age was 55 years (26–80 years). There were 63 males (44.7%) and 78 females (55.3%). Thirty-one patients (22.0%) had a history of previous smoking. The stage was Stage IIIB in 2 patients and Stage IV disease in the remaining patients. The ECOG PS was 0–1 in 127 patients (90.1%) and 2 in 14 patients (9.9%). The distribution of baseline characteristics in accordance with the type of mutation is shown in Table 1.

Response rate
Of 141 patients, 8 patients were ineligible for response assessment. The overall response rate among evaluable patients was 46.1% [Table 2]. There was 1 case of complete response. Response rates in evaluable patients were 72.9% in exon 19 patients (51 patients, $n = 70$) and 55.5% in exon 21 patients (35 patients, $n = 63$) ($P = 0.046$, Fisher's exact two-sided P value).

Adverse events
Data about adverse events were available for 132 patients. There was no difference in the incidence and type of adverse events seen between the exon 19- and exon 21-mutated cohorts. The details of adverse events are shown in Supplementary Appendix Table S1. A temporary stoppage of gefitinib was required in 11 patients (18.6%, $n = 59$) with exon 21 mutation and in 15 patients (20.5%, $n = 73$) with exon 19 deletion.

Progression-free survival

At the time of data cutoff, 85.1% of the patients had progressed. The overall median PFS was 8.467 months (95% CI 6.116–10.818). The median PFS in exon 19 and 21 cohorts was 9.3 months (95% CI 6.832–11.768) and 7.8 months (95% CI 5.543–10.057), respectively [Table S2]. There was no differential impact of EGFR mutation on PFS ($P = 0.655$, HR = 1.087, 95% CI 0.754–1.567) [Figure 1]. Table 3 provides details of Cox regression analysis results.

Overall survival

At the time of data cutoff, 58.9% of the patients had died. The overall median survival was 18.033 months (95% CI 15.737–20.330 months). The median OS in exon 19 patients was (19.767 months, 95% CI 16.836–22.697 months) not significantly better than that seen in exon 21-mutated patients (16.533 months, 95% CI 10.943–22.124 months, $P = 0.215$) [Figure 2] and [Table S3]. Table 4 provides details of Cox regression analysis results.

DISCUSSION

The management of NSCLC has changed dramatically over the last one and half decades. The discovery of EGFR mutation with the development of TKIs and their subsequent generations has led to a substantial improvement in PFS and OS in these cancers. Different type of EGFR mutations have differential impact on response to TKIs.[6] TKIs are currently prescribed in activating EGFR mutations. Exon 19 deletion and exon 21 mutation are considered as the classic activating mutations. The incidence of EGFR-mutated lung cancer is not similar across the globe, varying from 10% to 20% in Western countries to 30%–40% in Chinese regions.[7] However, the response rate, PFS, and OS differ substantially between the Indian patients and patients from other parts of the world.[3,5,8,9] Hence, this analysis was performed to study whether exon 19 deletion had superior outcomes in the Indian patients. As these mutations are mutually exclusive, it is worthwhile to know their clinical significance in the Indian context.

Over the last few years, evidence has suggested that the clinical outcomes of exon 19-mutated patients were better than exon 21-mutated patients.[6,10-12] In the joint analysis of LUX-Lung 3 and 6 study reported by Yang *et al.*, a comparison was made between EGFR-mutated patients treated with afatinib (irreversible TKI) with either pemetrexed and cisplatin or gemcitabine-cisplatin doublet chemotherapy. Overall, afatinib did not improve OS in this analysis. However, patients who had exon 19 deletion had a significant improvement in OS when compared against either pemetrexed and cisplatin (HR 0.54, 95% CI 0.36–0.79, $P = 0.0015$) or gemcitabine-cisplatin doublet chemotherapy (HR 0.64, 95% CI 0.44–0.94, $P = 0.023$). This analysis does suggested that probably in the eastern Asians and Caucasians, these mutations were

Table 1: Baseline details in the 2 cohorts

Variable	Exon 19 (*n*=76), *n* (%)	Exon 21 (*n*=65), *n* (%)
Median age	53.5 (38-76)	57 (26-80)
Gender		
Male	39 (51.3)	24 (36.9)
Female	37 (48.7)	41 (63.1)
ECOG PS		
0-1	71 (93.4)	56 (86.2)
2	5 (6.6)	9 (13.8)
Habits		
Ex-smoker	20 (26.3)	11 (16.9)
Stage		
III	2 (2.6)	-
IV	74 (97.4)	65 (100.0)
Brain metastasis	14 (18.4)	7 (10.8)
Liver metastasis	16 (21.1)	18 (27.7)

ECOG PS: Eastern Cooperative Oncology Group performance status

Table 2: Response between the 2 cohorts

Variable	Exon 19 (*n*=76)	Exon 21 (*n*=65)
CR	0	1
PR	51	34
SD	14	22
PD	5	6
Not evaluable	6	2

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 3: Results of multivariate analysis for progression-free survival

Variable	Hazard ratio	*P* value on Cox regression analysis
Gender	1.6 (1.106-2.313)	0.012
Liver metastasis	1.496 (0.962-2.327)	0.074
Brain metastasis	1.419 (0.863-2.334)	0.168
EGFR mutation type	1.087 (0.754-1.567)	0.655

EGFR: Epidermal growth factor receptor

Table 4: Results of multivariate analysis for overall survival

Variable	Hazard ratio	*P* value on Cox regression analysis
Elderly	1.339 (0.629-2.848)	0.449
Gender	1.461 (1.054-2.944)	0.031
ECOG PS	0.587 (0.306-1.126)	0.109
Smoking status	1.035 (0.593-1.805)	0.904
Brain metastasis	1.461 (0.807-2.646)	0.210
EGFR mutation type	1.293 (0.830-2.014)	0.255

ECOG PS: Eastern Cooperative Oncology Group performance status, EGFR: Epidermal growth factor receptor

different.[12] These higher outcomes are probably due to the strong affinity and binding of the drug to exon 19-deleted EGFR receptor or due to the biological differential behavior of these 2 mutations.[6] Similar conclusion was drawn by a meta-analysis reported by Kuan *et al*.[10] In this study, it appeared that patients with exon 19 deletion when they receive irreversible TKI like afatinib, it is associated with a statistically significant OS benefit in these patients (irreversible TKIs, HR: 0.59, 95% CI: 0.47–0.73). However, these findings were not seen in patients receiving reversible TKI like gefitinib or erlotinib (HR: 0.84, 95% CI: 0.69–1.02).
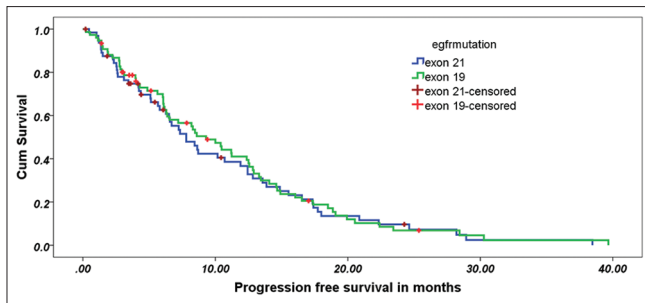
Figure 1: The estimated progression-free survival between the 2 arms

Figure 2: The estimated overall survival between the 2 arms

In our study, we found similar PFS and OS in exon 19- and exon 21-mutated patients. Although exon 19 patients had a superior response rate, the other efficacy outcomes were similar. This may be due to the fact that disease stabilization rate was higher in exon 21 patients compared to exon 19-deleted patients. A suggestion to this hypothesis is seen in the differential stable rate (33.8% versus 18.4%) between the two exon cohorts. The data suggest that in addition to the treatment, probably in exon 19 patients, we do have an ethnic difference which dictates response. We failed to find any study reported from India or Indian subcontinent on differential response of gefitinib in EGFR exon 19- versus exon 21-mutated patients. The survival outcomes reported in the study are similar to those reported from other centers in India by Doval *et al*.[13]

The study has its own limitations and strengths. It is one of the largest series studying the outcomes of exon 19 versus exon 21 mutations. The data were collected prospectively, and hence, missing data were minimal. This is the first study from India reporting on differential outcomes seen with exon 19 and exon 21 mutations. The limitations of the study were that it was a single-center study and that the analysis done was *post hoc*.

CONCLUSION

There were no differential outcomes in Indian patients of advanced-stage NSCLC with exon 19 and 21 EGFR mutations treated with gefitinib.

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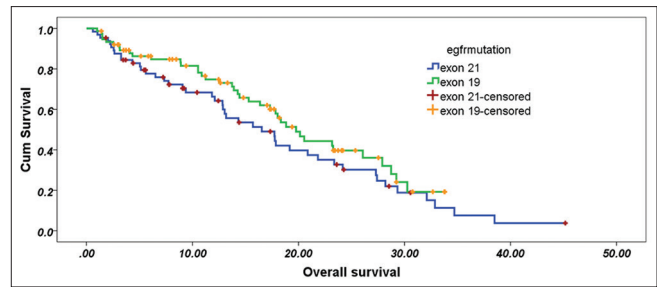### Conflicts of interest
There are no conflicts of interest.

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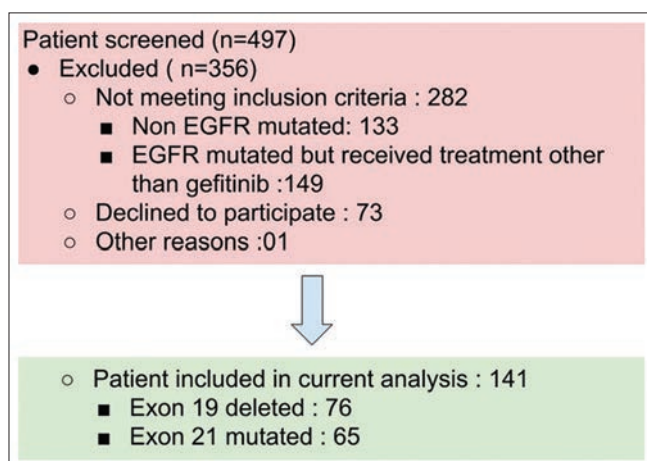
SUPPLEMENTARY APPENDIX

Figure S1: Diagram explaining selection of patients for the current analysis

Table S1: Adverse events details

Grade 24 adverse events reported on CTCAE scale 4.02	Exon 19 deletion cohort (n=73), n (%)	Exon 21-mutated cohort (n=59), n (%)
Skin rash	25 (34.2)	17 (28.8)
Loose motions	22 (30.1)	9 (15.3)
SGOT rise	7 (9.6)	6 (10.2)
SGPT rise	10 (13.7)	6 (10.2)
Pruritus	10 (13.7)	6 (10.2)
Anorexia	4 (5.5)	6 (10.2)

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, CTCAE: Common terminology criteria for adverse event

Table S2: Univariate analysis for progression-free survival

Variable	Median PFS	95% CI	P
Age			
Nonelderly	8.467	6.016-10.917	0.964
Elderly	6.567	2.201-10.932	
Gender			
Male	6.100	4.305-7.895	0.019
Female	10.700	6.911-14.489	
Smoking status			
Yes	6.167	3.422-8.911	0.337
No	8.633	5.857-11.410	
Tobacco chewing status			
Yes	8.433	4.734-12.133	0.682
No	8.633	5.596-11.671	
Liver metastasis status			
Present	7.200	4.601-9.799	0.111
Absent	10.000	6.744-13.256	
Brain metastasis status			
Present	6.700	4.456-8.944	0.203
Absent	8.633	6.193-11.074	
EGFR mutation type			
Exon 21 mutation	7.800	5.543-10.057	0.699
Exon 19 deletion	9.300	6.832-11.768	

EGFR: Epidermal growth factor receptor, PFS: Progression-free survival, CI: Confidence interval

Table S3: Univariate analysis for overall survival

Variable	Median OS	95% CI	P
Age			
Nonelderly	17.867	14.863-20.870	0.127
Elderly	27.900	15.105-40.695	
Gender			
Male	14.267	9.771-18.762	0.012
Female	23.167	14.706-31.627	
Smoking status			
Yes	13.900	7.653-20.147	0.072
No	20.133	16.091-24.176	
Tobacco chewing status			
Yes	17.767	12.590-22.943	0.877
No	18.333	15.039-21.627	
ECOG PS			
0-1	19.167	16.543-21.790	0.174
2	13.733	11.665-15.802	
Liver metastasis status			
Present	15.300	9.575-21.025	0.472
Absent	20.133	16.458-23.809	
Brain metastasis status			
Present	13.733	10.694-16.773	0.023
Absent	21.833	17.759-25.908	
EGFR mutation type			
Exon 21 mutation	16.533	10.943-22.124	0.215
Exon 19 deletion	19.767	16.836-22.697	

EGFR: Epidermal growth factor receptor, ECOG PS: Eastern cooperative oncology group performance status, OS: Overall survival, CI: Confidence interval