Original Article

Frequency of T790M mutations after progression on epidermal growth factor receptor tyrosine kinase inhibitor in metastatic non-small cell lung cancer in Indian patients: real-time data from tertiary cancer hospital

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ABSTRACT

Aim: The aim of this study is to determine the incidence of T790M mutations after progression on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) and median duration on TKI before progression on TKI. **Methods:** Records of Rajiv Gandhi Cancer Institute and Research Centre, of patients who were diagnosed with metastatic adenocarcinoma of the lung and progressed on oral EGFR TKIs and underwent T790M mutation analysis in the last 6 months were retrospectively reviewed. The incidence of T790M positivity, sites of progression, and median duration of TKI treatment before progression was calculated. **Results:** Among 31 patients, 10 patients have undergone rebiopsy, and 24 patients had undergone liquid biopsy by Droplet Digital polymerase chain reaction (ddPCR), and three patients had undergone both tests. Among all, the rate of T790M positivity was 54.8%. Among these 17 patients positive for T790M, seven patients were positive by biopsy, and 11 patients were positive by ddPCR. Among three patients who underwent both, one was positive by both. The most common site of progression among all patients is pleura, and 10% of patients progressed in brain post-TKI. Median progression-free survival on TKI before progression is 289.7 days, highest being 1290 days, and lowest 45 days. **Conclusions:** Exact incidence of T790M mutations after progression on TKI s in Asian population is not exactly known and requires large data, as incidence may be different than reported in the Western population. Rebiopsy and ddPCR help to determine the most common type of resistance after progression on TKI, for which effective targeted therapy is available.

KEY WORDS: Epidermal growth factor receptor mutation, nonsmall cell lung cancer, osimertinib, T790M mutation

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INTRODUCTION

Nonsmall cell lung cancer (NSCLC) is most commonly diagnosed type of lung cancer. Lung cancer accounts for the most common cause of cancer-related death across the globe[1,2] More than three-fourths of patients are diagnosed in an advanced stage and portends a poor prognosis once diagnosed in an advanced stage, which was changing gradually with advancements in science.[3] The discovery

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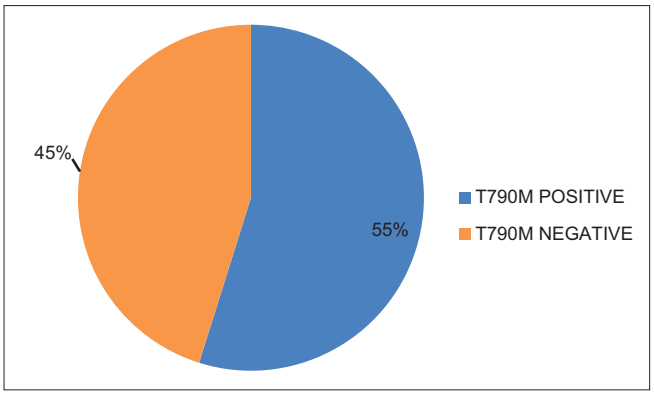

Figure 1: Frequency of T790M mutation ($n = 31$)

Table 1: Methods used for Testing for T790M mutation

	Total number of patients undergone testing	T790M positive patients
Number of patients underwent testing	31	17
Tissue biopsy	10	7
Liquid biopsy	24	11
Both tissue and liquid biopsies	3	1

of epidermal growth factor receptor (EGFR), the role of mutation of kinase domain in the pathogenesis of NSCLC, particularly adenocarcinoma has brought a revolution in the way of approaching the treatment of lung cancer. The discovery of drugs targeting this mutation in patients who were positive for EGFR mutation has been a remarkable milestone in the medical oncology.[4-8]

The tyrosine kinase inhibitors (TKIs) are small molecules which act against the ATP-binding sites of the intracellular kinase domain of EGFR receptor and prevent the sequential activation of downstream signaling pathways that lead to cell proliferation and survival. However, almost all tumors which initially responded to EGFR-TKIs stop responding to these drugs after a mean duration of 9–12 months. The reason for this nonresponsiveness is due to the development of resistance by various mechanisms, most common of which is the development of T790M mutation.[9-12] In this mutation in the ATP-binding domain of exon 12 of EGFR kinase domain, at 790 position amino acid, threonine is replaced by methionine, causing steric hindrance to bind TKI.[13] This mutation is reported in more than half of the patients progressing on EGFR TKIs. However, most of this data are from western population. Other mechanisms of resistance are MET amplification, Her-2 mutation, PIK3CA mutation, BRAF mutation, and small cell transformation.[11,12,14-16]

The data on the incidence of T790M in Asian patients are very scarce. Like the difference in the frequencies of EGFR mutations in the Asian and Western population, there may be difference in the incidence of T790M mutation in the Asian and Western population. We have done this study to study the incidence of T790M mutations in Indian population after progression on EGFR TKI's.

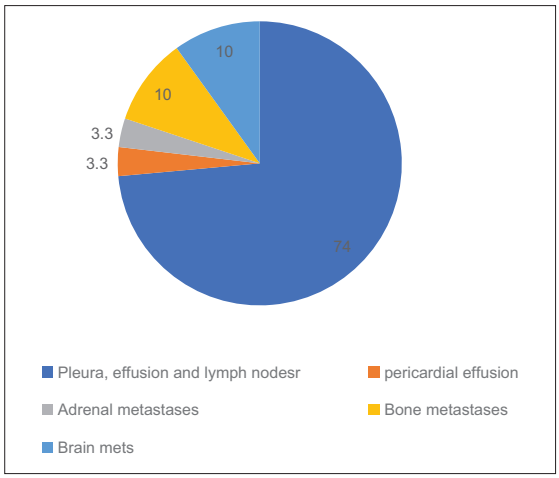

Figure 2: Percentage of involvement of sites on progression on tyrosine kinase inhibitors

METHODS

A retrospective chart review was conducted of patients with metastatic Nonsmall cell lung carcinoma (NSCLC) who were histologically proven adenocarcinoma of the lung and were detected with EGFR mutation positive by amplification-refractory mutation system-polymerase reaction test done at Rajiv Gandhi Cancer Institute and Research Centre. Patients who underwent diagnostic test to detect T790M mutation either by tissue biopsy or Droplet Digital polymerase chain reaction (ddPCR) at progression in the last 6 months from June to November 2017 were selected. Patients were required to have bidimensionally measurable disease with age >18 years. All patients received TKIs and underwent diagnostic tests at progression at our institute. Complete blood counts and clinical assessment were carried every month. Acquired resistance was defined according to the Jackman's criteria.[17] Responsiveness to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumours 1.1.[18] Progression-free survival (PFS) was defined as the duration between the start of TKI to the time of progression or death from any cause. All categorical variables were analyzed by Chi-square test or Fisher's test as appropriate. Statistical analysis was performed using SAS 8.02 (SAS Institute Inc, Cary, North Carolina, USA). Patients with dual malignancies were excluded from the study. Written consent after the detailed explanation was taken from all patients who underwent biopsy or ddPCR at progression. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration and the applicable guidelines for good clinical practice.

RESULTS

Patient characteristics

A total of 31 patients with NSCLC harboring EGFR sensitizing mutations who underwent either tissue biopsy or liquid biopsy by ddPCR after acquired resistance

Table 2: Characteristics of patients who tested positive for T790M

Age of patients years	Sex	Baseline EGFR mutation	Rebiopsy done yes/no	ddPCR done	Percentage of T790M positivity	PFS on TKI
86	Female	del 19	Yes	No		1290
68	Female	L858R	No	Yes	7.4	480
52	Male	del 19	Yes	No		380
54	Female	del 19	Yes	No		330
54	Male	del 19	Yes	No		854
50	Female	L858R	No	Yes	0.23	210
57	Female	del 19	No	Yes	0.13	190
80	Female	L858R	Yes	No		240
47	Male	del 19	No	Yes	0.27	350
47	Female	del 19	Yes: Mutations	Yes	0.16	206
56	Female	L858R	Neg	Yes	0	120
56	Male	L858R	Yes	Yes	4.5	298
48	Female	del 19	No	Yes	1.1	45
47	Male	L858R	No	Yes	14	166
67	Female	del 19	No	Yes	8.2	338
47	Female	L858R	No	Yes	3.8	168
62	Female	del 19	No	Yes	0.28	446

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitors, PFS: Progression-free survival

with demonstrable clinical progression radiologically according to RECIST criteria at Rajiv Gandhi Cancer Institute and Research Centre were included in this study. The median age of study population in this study was 53.8 years. The youngest patient was 36 years, and highest age of the patient was 86 years. A total of 16 patients (51.6%) were female, and 15 patients (48.3%) were male. About 24 patients (77.4%) were never smokers, and seven patients (22.5%) were former or current smokers.

Mutational status

Only two common EGFR sensitizing mutations were detected among these 31 patients. Two patients who had baseline T790M and sensitizing EGFR mutations during the retrospective review were excluded from the study. Nearly 18 patients (58%) had baseline del 19 EGFR mutation, and 13 patients (42%) had L858R mutations in exon 21 were seen.

Previous therapies and type of tyrosine kinase inhibitors

About nine patients (29%) had received previous chemotherapy including all settings of adjuvant, concurrent, and metastatic setting. Nearly 26 patients (83.8%) received gefitinib as EGFR TKI, and the rest of the patients received erlotinib. No patient had received second-generation TKI who were included in this study.

Investigations at progression of disease

The patients who were having demonstrable radiological progression with RECIST criteria were counseled about the need for an investigation to know the mechanism of resistance. Among these patients, 10 patients have undergone rebiopsy. A total of 24 patients had undergone liquid biopsy by ddPCR. A total of three patients had undergone both ddPCR and rebiopsy [Table 1].

Frequency of T790M mutation

Among 31 patients who underwent abovementioned investigations, 17 patients (54.8%) were found to have T790M mutation positive [Figure 1]. Among these patients who were positive for T790M, seven patients were positive by biopsy, and 11 patients were positive by ddPCR. Among three patients who underwent both, one patient was positive by both. The most common site of progression among all patients is pleura, pleural effusion, and lymph nodes and was seen in 81% of patients. One patient had pericardial effusion, one patient had new adrenal metastases, three patients had bone metastases (10%), and three patients (10%) have developed new brain metastasis [Figure 2]. Median duration of the treatment on TKI before progression is 289.7 days, highest duration being 1290 days, and lowest 45 days [Table 2].

DISCUSSION

Almost all patients who had dramatic initial response to EGFR TKIs s ultimately will have progression of disease. Nearly half of these patients harbor a new second-point mutation in EGFR gene, in which methionine replaces threonine at amino acid position 790 (T790M) resulting in increased affinity for ATP to kinase rather than to kinase inhibitor.[19] The other explanation of why T790M causes acquired resistance is explained by the bulky methionine at 790 position causing steric hindrance to TKI but not ATP.[19] Data from Western population have reported the incidence of T790M mutation in NSCLC patients who had progressed on TKI's ranging from 49% to 69%. Rebiopsy was done in all these patients for the detection of T790M mutation.[11,12,20] Two Japanese studies reported the incidence of T790M mutations in similar clinical setting to a rate of 34.4%–38%[21,22] which was far less than the incidence of this mutation reported in Western population. The exact incidence of this mutation in Indian population is not known. This study is an attempt to find the frequency of most common resistance mutation in Indian setting.

The reason for higher incidence of these resistant mutations in the Western population is not known. However, there was abundant preclinical data which showed that continuous exposure to EGFR-TKI-induced

T790M mutation in NSCLC cell lines.[23] Most of the patients included in these studies of Western population data, who progressed on EGFR TKI's further continued the therapy with same drugs. This was as high as 89%–91% in some studies.[12,20] Even in these studies, it was observed that patients who were continued on TKIs beyond progression had more incidence of T790M mutations than those who were not. None of the patients included in the present study received first- or second-generation TKI beyond progression. While trying to estimate the differences in the frequencies of T790M mutations, the potential for EGFR TKIs to promote the same mutation should not be overseen. Molecular studies hypothesize that selection pressure by EGFR TKIs may promote KRAS mutation, however, must be confirmed by further clinical studies.[24]

The option of continuation of same generation TKI is no more viable, as seen in IMPRESS trial, such patients have not shown prolongation of PFS and overall survival with continuation of gefitinib after progression.[25] Moreover, with the introduction of third-generation EGFR TKI that works effectively even in the presence of T790M mutation, with a PFS benefit of 11.7 versus 5.6 months in chemotherapy arm (hazard ratio 0.32; 95% confidence interval = 0.15, 0.69; P = 0.004) made it much more important to detect this mutation at progression either by biopsy or liquid biopsy. This drug also showed excellent intracranial response which was not seen with earlier EGFR-TKIs.[26] Although tissue biopsy is more useful to know the exact mechanism of resistance including transformation to small cell carcinoma, rebiopsy which is invasive is not feasible in all patients and clinical setups. The value of liquid biopsy to detect T790M mutation was established in osimertinib approval Phase III AURA3 trial.

There are several limitations to our study, most important being small sample size and retrospective study. The small sample size may be due to the recent approval of targeted therapy to T790M mutated lung cancer in India. In addition, recent data show that higher ratio of T790M to baseline EGFR mutations predict the outcome with third-generation TKI for targeting T790M. Further, large size prospective studies are needed to estimate the frequency of T790M mutations and mechanisms.

CONCLUSIONS

The frequency of T790M mutations may differ by ethnicity, genetic factors, smoking status such as EGFR sensitizing mutations. The frequency may be different in Indian population as reflected in our study which was higher than in Western population and far higher than in Japanese population. Rebiopsy and ddPCR help to determine the most common type of resistance after progression on TKI, for which effective targeted therapy is available.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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