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Original Research Paper

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# A PROSPECTIVE OBSERVATIONAL STUDY ON ROLE OF GEFITINIB, AS FIRST LINE MONOTHERAPY IN EGFR GENE MUTATION POSITIVE NSCLC PATIENTS

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**KEYWORDS :** Epidermal Growth Factor Receptor (EGFR), Tyrosine Kinase Inhibitors (TKIs), Overall response rate (ORR), Progression Free Survival (PFS).

## AIMS AND OBJECTIVES

### AIM OF THE STUDY:

**"To study Role of TKIs as first line monotherapy in EGFR gene mutation Positive NSCLC patients."**

### PRIMARY OBJECTIVES:

- To study the effectiveness of TKIs as first line monotherapy in EGFR gene mutation positive NSCLC patients at tertiary care centre.
- To study the spectrum of different types of activating mutations in kinase domain in EGFR gene mutation positive NSCLC patients.

### SECONDARY OBJECTIVES:

- To assess the Clinicopathological correlation of EGFR gene mutation positive NSCLC patients.
- To assess the Quality of life (QOL) of the patients during the treatment with TKIs.

## 4. MATERIAL AND METHODS

**4.1 Study site:** Apollo speciality cancer hospital and tertiary care Centre, Teynampet, Chennai-600035 (Tamil Nadu, India).

**4.2 Study population:** All EGFR gene mutation positive NSCLC patients.

**4.3 Study duration:** June 2016 to February 2018.

**4.4 Study design:** Prospective Observational study

### 4.5 Sample size:

The sample size calculation was derived based on the following formula;

$$n = \frac{Z^2pq}{d^2}$$

Where;

Z = standard normal variate value = 1.96,

p = EGFR gene mutation positivity rate in NSCLC patients = 30%

(ref -Hirano R,et al.[63]),

q = 1p = 70%

d = clinical allowable error = 10%

So therefore required sample size = **80 cases**.

### INCLUSION CRITERIA:

1. Newly diagnosed EGFR mutation positive NSCLC patients started on first line TKIs as monotherapy.
2. Newly diagnosed NSCLC patients started on conventional Chemotherapy before EGFR mutation positive report came and later started on first line TKIs as monotherapy.

### Exclusion Criteria:

1. Patients having progressive disease on conventional chemotherapy.
2. Patients who have already completed first line conventional chemotherapy for NSCLC
3. Patients with performance status >2.

## 5. METHODOLOGY

All newly diagnosed EGFR mutation positive NSCLC patients started on first line TKis as monotherapy, newly diagnosed NSCLC patients started on conventional chemotherapy before EGFR mutation positive report came and later started on first line TKIs as monotherapy, were enrolled in the study and were evaluated clinically and radiologically.

Primary data collection done after filling informed consent and patient information sheet. Details of clinicopathological status, EGFR mutation kinase domain status, TKI used, effects and side effects related to TKIs noted with help of study proforma. QOL of patients analysed at baseline and during treatment at 3-4 months by EORTC QLQ C30 version 3 scoring Questionnaire.

Performance status (PS) was assessed as per ECOG performance scale (0-5) and patients with PS >2were excluded from study. BSA was calculated as per Mosteller formula.

### EGFR Mutation Analysis:

The molecular laboratory of our Apollo Speciality Hospital performed DNA extraction and mutation analysis. Tumour DNA was extracted using The QiagenQIAamp DNA Mini Kit and used PCR method to determine kinase domain subtyping of EGFR mutation status in patients. Exons 18-21 of EGFR were analysed by using polymerase chain reaction (PCR).

All the specimens were formalin-fixed paraffin-embedded (FFPE) archival tissue blocks obtained by biopsy, cell block.

### Treatment:

These patients were started on TKIs as first line monotherapy orally with Gefitinib 250 mg od, continuously until objective disease progression, intolerable toxicity. These were re-assessed after 46 weeks, 3-4 months and then 6th month until disease progression / end of study. Baseline assessment done before start of treatment and then the response assessed clinically and Radiologically (RECIST version 1.1) periodically. Quality of life of these patients assessed at baseline before start of therapy and at 3-4 months of therapy by EORTC QLQ C-30 Version 3 questionnaire.

### Response Assessment:

Tumor response assessment was determined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1

### DEFINITIONS:

**Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.

**Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

**Overall response rate, ORR** (CR + PR) was also determined by RECIST 1.1.

**Progression Free Survival (PFS) –** Time from start of the study treatment to date of objective tumour progression, was determined by RECIST 1.1.

Safety and tolerability were assessed by adverse events (AEs), classified according to Common Toxicity Criteria (CTC) version 4.

**QOL ASSESSMENT:**

QOL assessment was done by EORTC QLQ C-30 version 3 questionnaire scoring. The QLQ-C30 is a questionnaire made up of 30 questions distributed in five scales of functionality (physical, cognitive, emotional, social and role performance); three scales of symptoms (fatigue, pain, nausea and vomiting); six items assessing symptoms associated with patients (dyspnoea, lack of appetite, insomnia, constipation and diarrhoea); a scale for global quality of life and health, and a scale for assessing the financial impact of the treatment and of the disease.

This proforma of questionnaire was attached with the main proforma and data was collected at base line and at follow up after 3 months of treatment with TKIs. Data will be interpreted after scoring these scales.

**Raw score:**

Raw score was calculated by doing average of the items that contribute to scale.

Raw Score = RS= $(I_1 + I_2 + I_3 + .... + I_n)$ /n.

**Linear transformation:**

Linear transformation was applied to standardize the raw score to a range of 0 to 100 to obtain the score.

For **Functional scale**:
Score = {1- (RS-1)/Range} x100 and

For **Global health status/QOL and symptom scale/items**:
Score = {(RS- 1)/range} x100.

Mean score was calculated at base line and during treatment at 3 months and correlated.

A high mean score more than 10% of baseline represented a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

## 6. STATISTICAL ANALYSIS

- Results statistically analysed using appropriate methods.
- All the continuous variables were assessed for the normality using Shapiro – wilk's test.
- If the variables were normally distributed, they were expressed as Mean ± SD otherwise Median (IQR). All the categorical variables will be expressed as either percentage or proportion.
- Comparison of normally distributed continuous variables were done by independent sample t test or ANOVA.
- Comparisons of non normally distributed continuous variables were done by Mann Whitney U test or Kruskal-Wallis H test.
- All other categorical variables were compared by either Chi square test or Fishers exact test.
- Data entry was done in MS-Excel sheet.
- Data validation and analysis was carried out by SPSS version 25.0.
- Median progression free survival was calculated by Kaplan Meier survival curve.
- All p values $<0.05$ were considered as statistically significant.

## 7. SALIENT FINDINGS OF THE STUDY

**AGE DISTRIBUTION:**

In our study, among 80 patients, 51% (n=41) were $\leq$60 years and 49% (n=39) were >60 years which showed slight higher percentage of EGFR positivity in adults than older age group. Mean Age of patients in our study was 61 Years (SD ±11); youngest patient was 32 year and oldest 84 years old.

**GENDER DISTRIBUTION:**

In our study, among 80 patients with EGFR mutation positivity, 51% (n=41) were females and 49% (n=39) were males showing slight higher percentage of EGFR positivity in females than males.

**SMOKING STATUS:**

Our study observed that among 80 EGFR mutation positive patients, 81% (n=65) were non smokers and only 19% (n=15) were smokers/former, showing higher positivity in non smokers than smokers.

**PERFORMANCE STATUS:**

Among 80 EGFR positive patients, 82% (n=66) were in good performance status (0-1) while only 18% (n=14) were in PS-2.

**BODY SURFACE AREA:**

In our study, maximum patients 91% (n=73) had a BSA $\geq$ 1.45 $m^2$ while only 9% (n=7) had BSA <1.45 $m^2$ which showed that higher EGFR positivity is seen in patients with higher BSA.

**STAGE OF DISEASE:**

In our study, most of the patients 81% (n=65) were in Stage IV (metastatic disease) while only 19% (n=15) were in Stage III (locally advanced). It shows that EGFR mutation positive patients usually presents in more advanced disease stage.

**HISTOLOGY IN NSCLC:**

Adenocarcinoma was the predominant histologic subtype in 92% (n=74) among all NSCLC EGFR mutation positive patients while adenosquamous and squamous were seen in only 8% (n=6) patients.

**EGFR MUTATION KINASE DOMAIN SUBTYPES:**

Among total 80 patients with EGFR mutation positivity, 67% (n=54) patients were positive for Exon 19 deletions, 29% (n=23) were positive for Exon21/ L858R frame shift mutation while only 4% (n=3) of patients were positive for Exon 18/ G719X. Exon 20 and complex mutations were not found in any of the patients.

**GENDER DISTRIBUTION AMONG KINASE DOMAIN EGFR MUTATION SUBTYPES:**

In our study, among patients with Exon 19 deletion, 59% (n=32) were females, in Exon 18/G719X, 67% (n=2) were females while among Exon 21/L858R, maximum 71% (n=16) patients were males which shows that Exon 19 deletions and

Exon 18 mutations are more common in females than males.

**SMOKING STATUS AMONG KINASE DOMAIN EGFR MUTATION SUBTYPES:**

In our study, 78% (n=42) in exon19, 87% (n=20) in exon 21 and 100% (n=3) in exon 18 were non smokers, showing higher percentage of EGFR positivity in non-smokers.

**TYROSINE KINASE INHIBITORS USED AS FIRST LINE MONOTHERAPY:**

Among total 80 patients with EGFR mutation positive NSCLC, 37% (n=30) patients were started on Gefitinib, 54% (n=43) on Erlotinib and 9% (n=7) on Afatinib as first line monotherapy agents.

None of the patient received Osimertinib as first line agent as FDA approved osimertinib as first line agent in April 2018 and our study enrollment cut off was Feb 2018.

**RESPONSE ASSESSMENT OF TKIS:**

Among 80 patients enrolled in our study, 6 patients were lost to follow up and hence response assessment and QOL assessment was carried out on 74 patients only. In our study, among 74 patients on TKIs, 4% had complete response, 32% had partial response, and 23% had stable disease while 40% patients progressed on first line TKIs with overall response rate (ORR) of **36 %** and disease control rate (DCR) of **59 %.**

Among patients with age >60 years, 52% (n=19) patients had progressive disease, 14% (n=1) had stable disease, 31% (n=11) had partial response while only 3% (n=1) patient had complete response. Patients with Age ≤60 years, 29% (n=11) had progressive disease, 32% (n=12) had stable disease, 34% (n=13) had partial response while 5% (n=2) patients had complete response. This shows that age group doesn't affect the Efficacy of TKIs.

In our study, 6% (n=2) female patients on TKIs have complete response while only 3% (n=1) male had CR. But in males, 37% (n=14) had partial response, and 26% (n=10) had stable disease. More percentage of females (47%) (n=17) progressed on TKIs than male (34%) (n=13). It showed that TKIs gives mixed response amongst male and females which was not statistically significant (p= 0.570).

In our study, Non smokers showed an initial good response to TKIs with complete response in 5% (n=3) patients, partial response in 30% (n=18) patients, stable disease in 18% (n=11) patients. But later disease progressed in 47% (n=28) patients. Whereas Smokers had 43% (n=6) partial response, 43% (n=6) had stable disease and 14% (n=2) progressed on therapy. It showed that TKIs gives mixed response amongst non smokers and smokers which was not statistically significant (p= 0.066).

When we compared response as per BSA, our study showed mixed response to TKIs in patients with BSA $\geq 1.45m^2$ and BSA $<1.45m^2$ which was not statistically significant (p= 0.413).

**RESPONSE ASSESSMENT AMONG KINASE DOMAIN EGFR MUTATION SUBTYPES:**

In our study, Exon 19 del patients responded well to treatment with 4% (n=2) patients in CR, 36% (n=18) in PR, 24% (n=12) had stable disease and 36% (n=18) progressed on therapy. Among Exon 21 mutation patients, 4% (n=1) had CR, 24% (n=5) had PR and SD each but 48% (n=10) patients progressed on therapy. Exon 19 Del patients had better response with ORR of 40% while Exon 21 mutation had ORR of 28% only. It shows that patient with Exon19 deletion had better response to TKIs than Exon 21 mutation.

In our study TKIs showed mixed response among various subgroups like age, sex, smoking status, BSA except EGFR mutation subtypes subgroup. It showed that efficacy of TKIs is not dependant on Age, Sex, Smoking status and BSA, but depends upon EGFR mutational kinase domain subtypes.

**Effectiveness of TKIs on survival:**

Overall Median Progression free survival with TKIs in our study was **13 months (**95% CI, 12.005-13.995).

Comparison among various TKIs for Progression free survival was not objective of our study and numbers of patients in each arm were different, we have not done overall comparison between these individual drugs.

In our study, out of interest but not as objective, when we individually calculated median PFS, Gefitinib showed Median PFS of **12 months** (95% CI, 8.47-15.52)

**SIDE EFFECTS RELATED TO TKIs:**

Rash was the most common side effect related to TKIs, present in 83% (n=62) of patients. Diarrhoea was the second most common side effect related to TKIs, present in 39% (n=29) of patients.

Nail disorder including paronychia was present in 26 % (n=19) of patients.

Nausea and vomiting was 4th most common side effect related to TKIs after nail disorder, present in 18% (n=13) of patients.

. Rash was present in 76% of patients on Gefitinib (P <0.05).

Nail disorders were present in 4% of patients on Gefitinib, (P <0.05).
Diarrhoea was present in 39% of patients on Gefitinib,

Nausea and vomiting was present in 18% of patients on Gefitinib, (P <0.05).

**QOL ASSESSMENT OF PATIENTS ON TKIs:**

In our study:
In Global QOL, there was an increment in mean score from baseline (55.85 ±7.64) to (85.13±13.46) on treatment, which was statistically significant (P <0.05), which shows that **TKIs improves Global QOL.**

Similarly there was an increment in mean score from baseline to on treatment score in physical, emotional and social functioning which was statistically significant (P <0.05) which shows that **TKIs improves Physical, Emotional and social functioning** while there is increment in role functioning and cognitive functioning but was not statistically significant.

In symptomatology scores, there was an increment in mean appetite loss score, fatigue score, nausea /vomiting score and diarrhoea score which was statistically significant (P <0.05), which shows that TKIs can cause some side effects which can hamper the QOL of patients while there was decrease in mean dyspnoea score which was statistically significant (P <0.05). There was also decrease in mean pain score but was not statistically significant (p=0.348).

There was decrease in mean insomnia score on treatment, which was statistically significant (P <0.05) which shows that TKIs slightly improve your Insomnia symptom. No patient in study group had constipation baseline and there was no change on treatment also.

Thus our study showed that TKIs improves QOL of patients in terms of Global health status, functioning scales, tumour related symptoms while causes some increment in symptoms which can be correlated with side effects of TKIs. There was increment in financial difficulties mean score because of

continuous use of therapy causing financial burden.

**STRENGTH OF OUR STUDY:**

1. This will be one of few studies from India who analysed the effectiveness of TKIs as first line monotherapy in EGFR mutation positive NSCLC patients at tertiary care centre with special focus on Effectiveness of TKI among different kinase domain subtypes.
2. We did clinicopathological correlation among Different kinase domain subtypes in EGFR mutation positive NSCLC patients.
3. We analysed QOL of patients on TKIs for which there are very studies in literature.

## 8. CONCLUSIONS

- EGFR mutations are significant drivers in NSCLC especially amongst Asian females, non smokers with adenocarcinoma histology. Our study also concluded that higher prevalence of EGFR mutations are found in age $<60$ years, females, non smokers, adenocarcinoma histology, PS 0-1 and BSA $\geq 1.45m^2$.
- Exon 19 deletions are the most common kinase domain mutational subtypes followed by Exon21/L858R among patients with EGFR mutation positive tumours.
- Our study concluded that Females have more Exon 19 deletion than Males.
- Our study also concluded that treatment with TKIs are an independent predictor to improve progression free survival in patients with EGFR mutation positive NSCLC.
- Exon 19 deletion patients respond better to TKIs than any other EGFR mutations subtype.
- Our study also concluded that Effectiveness of TKIs doesn't depend upon age, sex, BSA and smoking status as such but depends on kinase domain EGFR mutational subtypes.
- TKIs are well tolerable drugs with minimal side effects which are manageable.
- TKIs improve patient's quality of life in terms of Global health status, functional scales and improve tumour related symptoms.

Our study confirms and reinforces the efficacy of TKIs as first line monotherapy in EGFR mutation positive NSCLC patients and improves QOL of patients on TKIs.

## 9. RECOMMENDATIONS

1. We recommend TKIs – Gefitinib as First line monotherapy in EGFR mutation positive NSCLC patients.
2. All NSCLC patients should be tested for EGFR mutational testing. Results of tests should be in detailed format including kinase domain subtypes. We recommend Qiagen DNA extraction Minikit and PCR technique or similar standard approved PCR techniques to be used for kinase domain subtyping of EGFR mutations.
3. Side effects related to Tyrosine kinase inhibitors are manageable but may need diligent dose reduction in few patients.
4. We recommend EORTC C-30 questionnaire or similar tool for assessing QOL of all NSCLC patients on TKIs. We also recommend formulating dedicated specific tool for assessing QOL of NSCLC patients on TKIs on day to day basis.
5. We need more studies to address QOL of Patients on TKIs.