



## A RETROSPECTIVE STUDY OF TYROSINE KINASE INHIBITOR INDUCED ADVERSE DRUG REACTION IN ADVANCED LUNG CANCER PATIENTS

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**ABSTRACT** **Background:** Tyrosine kinase inhibitors (TKIs) are a mainstay in the management of advanced lung cancer with specific molecular alterations. However, these agents are frequently associated with adverse drug reactions (ADRs), which may impact treatment compliance and outcomes. **Objective:** To assess the incidence and types of ADRs associated with various TKIs used in patients with lung carcinoma. **Methods:** A retrospective observational study of 84 patients was conducted in the Department of Medical Oncology, Amrita Institute of Medical Sciences. The demographic profile, treatment regimens, and adverse events were documented and analyzed. **Results:** The majority were males (72.6%) and had adenocarcinoma histology. EGFR mutation was the most common driver mutation (50.6%). Skin rash, abdominal pain, and gastrointestinal symptoms were among the leading ADRs. Osimertinib was the most used TKI, followed by erlotinib and gefitinib. **Conclusion:** ADRs related to TKIs are common and need proactive monitoring and management. Tailored supportive care and early recognition can improve patient adherence and outcomes.

**KEYWORDS :** Tyrosine Kinase Inhibitor, Adverse Drug Reaction, Lung Cancer, Driver Mutation

### AIM OF THE STUDY

The aim of this study was to analyze the onset of adverse drug reactions (ADRs) related to TKIs in lung carcinoma through a spontaneous reporting system (SRS) database.

### INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC) accounts for almost 85 % of all lung cancer cases. About 1.8 million cancer-related death cases and 2.2 million new cases of lung cancer were reported by International Agency for Research on Cancer in 2020, and the majority of these cases were diagnosed at an advanced stage. With the rapid development of molecular biology, the categorizing of NSCLC is mainly by distinct molecular subtypes nowadays, which have replaced traditional histological subtypes. It is paramount for precision therapy to identify specific molecules or gene alternation at the initial NSCLC diagnosis. Numerous driver genes have been discovered in NSCLC, including genes encoding epidermal growth factor receptor (EGFR) and anaplastic lymphoma.

Kinase (ALK). More importantly, specific TKIs targeting these genomic alterations are the therapeutic usefulness of TKIs is not limited despite their outstanding potency. The care of patients undergoing TKI therapy presents notable problems, including treatment resistance, off-target effects, and emergence of drug-related toxicities. This also highlights the necessity of continuing research efforts to improve treatment durability and overcome therapeutic resistance. Resistance mechanisms, such as secondary mutations or activation of alternate signaling pathways, have emerged. Our goal is to provide a thorough overview of multi-TKIs, including information on their safety profiles, therapeutic effectiveness, clinical indications, and mechanisms of action. Our aim was to make a valuable contribution to the field of precision oncology and better clinical management of cancer patients by clarifying the molecular basis of TKI therapy and exploring new approaches to improve treatment results that inhibit chloride channels. EGFR-TKIs inhibit the negative regulation of chloride secretion by EGFR; this results in excessive chloride movement into the lumen, which causes secretory diarrhea normal cardiopulmonary functions. The first-line treatment methods include oxygen.

A proportion of the patients enrolled in the crizotinib trials developed focal progression. In these cases, if a clinical benefit was maintained, patients were allowed to continue crizotinib beyond further systemic

progression, and to receive local treatments. Median duration of crizotinib post progression was 10 weeks in the patients enrolled in the Phase II PROFILE 1005. Different second generation ALK-TKIs, have been recently evaluated in Phase I studies, and results seem promising.

### MATERIALS AND METHODS

Study with retrospective data collected from files. The Amrita Institute of Medical Sciences, Kochi's Department of Medical Oncology, was the site of this investigation. This study included patients currently seen in the Medical Oncology OPD who were undergoing TKIs therapy for lung carcinoma.

### RESULT

TKI induced ADR in advanced lung cancer in our study 84 patients showed that male are more predominately affected compare to female. Median age of diagnosis is 63 years. Percentage of male is (72.6%), while in female is (27.4 %). Percentage of patient with comorbidities is 47.6%. In these study showed that right lung carcinoma is 58.3% and left lung carcinoma is 40.5 %. Most common driver mutation accounting for about is EGFR= 50.6%. In our study most of the patient received first line TKIs. Adverse events accounting for about diarrhea is 9.5%, skin toxicity is 23.8%, vomiting is 10.7%, abdominal pain is 21.4% respectively. Adenocarcinoma lung is the commonest histology we noted in these study. Among 84 patients' complete response was obtained in 7.1%.

### DISCUSSION

The introduction of several TKIs for the treatment of NSCLC has radically changed the management of these patients. Improvements in the identification of molecular subgroups of advanced NSCLC patients led to an increase in the number of molecular analyses requested in this setting. However, the use of TKIs is not free from the onset of AEs, even serious ones. In this study, ADRs related to the use of TKIs for the treatment of NSCLC were identified. Moreover, the higher number of reports related to ERL, AFT, and OSI, after their first authorization for NSCLC, is probably due to the inclusion in the AIFA monitoring registers platform; the monitoring was concluded for ERL in 2018, while the monitoring for AFT and OSI was started in 2014 and 2017, respectively, and is still ongoing. Furthermore, some active pharmacovigilance projects were conducted during the years to evaluate the use of biologic drugs in oncologic patients and, in particular, one with a focus on the use of TKIs in NSCLC performed in Campania and Lazio regions through "Pharmacovigilance Funds 2012-2013-2014" had an impact on ADR distributions.

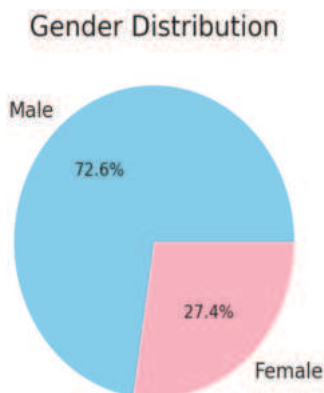
In these group of 84 patients shows the median age of the patients in this cohort was 63 years, with a range of 50.5 to 70 years, indicating a predominantly middle-aged to older population. The gender distribution revealed 23 (27.4%) female and 61 (72.6%) male patients, reflecting a slight male predominance in the sample. While 52.4 percentage have comorbidities and 47.6 percentage have no comorbid. NSCLC- Adenocarcinoma lung is the most predominant histology of lung cancer in our present study. Most of our patient received first line TKI which is Gefitinib. TKI induced several ADR as we mentioned above. In order to evaluate the response assessment of TKI by RECIST criteria. Despite these very encouraging results, the majority of patients develop resistance to crizotinib within a year of commencing treatment and several secondary resistance mutations have been described []. Recent data suggest that an even rarer molecular subtype of NSCLC harboring a translocation in ROS1 may also respond to crizotinib []. Of 121 patients undergoing tissue sampling, 104 (86%) were successfully analyzed and the resistant T790M mutation was detected in 68% of cases. Sequist et al. performed a genetic and histological analysis in 37 NSCLC patients with documented acquired resistance to EGFR-TKIs, who underwent multiple repeated biopsies over the course of their treatment. In our study showed small number of patients showed resistance to T790M out of 84 patients only 6% shown resistance. Patients those who are multiple comorbidities with poor performance status will develop life threatening events secondary to administration of TKI. In these data shows that 44.0 % patients developed TKI induced life threatening events while the 56% patients tolerated treatment well. Some patient develop Grade 2 or more ADR will need medical intervention or may need to adjust the TKI dose based on adverse events. Our study showed that 15.5% patients dose has been reduced, while the remaining 84.5% have better tolerance to standard dose of TKIs. If a very few patients will need to discontinue the TKI due to because of poor tolerance or severe ADR or some patient related factor. Our study shows that 34.5 % patients will lead to withhold the treatment, while the remaining 65.5% have a better tolerance to TKI.

**CONCLUSION**

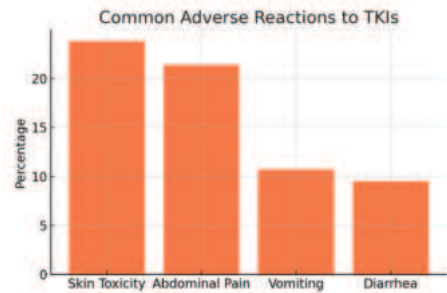
In conclusion, the study reinforces the significance of recognizing adverse drug reactions (ADRs) associated with tyrosine kinase inhibitors (TKIs) in patients with advanced lung carcinoma. While TKIs have revolutionized the management of lung cancer through personalized medicine, the incidence of ADRs necessitates a balance between efficacy and tolerability. Our findings highlight the importance of regular monitoring and timely interventions to optimize treatment outcomes. Multidisciplinary care, patient education, and pharmacovigilance programs are essential to ensure safe and effective cancer therapy.

**Table 1. Patient Demographics and Adverse Drug Reactions**

Parameter	Value
Median Age	63 years
Male	72.6%
Female	27.4%
Comorbidities	47.6%
EGFR Mutation	50.6%
Skin Toxicity	23.8%
Abdominal Pain	21.4%
Vomiting	10.7%
Diarrhea	9.5%



**Figure 1. Gender Distribution Among Patients**



**Figure 2. Most Common Adverse Drug Reactions**

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