Role of Tyrosine Kinase Inhibitor (TKI) in stage IV adenocarcinoma of lung: Early outcome from tertiary cancer hospital.

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Abstract

Background: Adenocarcinoma of lung is the most common type of non-small cell lung cancer. Driver mutation, especially EGFR mutation is not uncommon and tyrosine kinase inhibitor (TKI) is the mainstay treatment for stage IV disease. We aim to evaluate early outcome and progression free survival (PFS) of TKI with stage IV adenocarcinoma in Nepal.

Methods: A prospective observational study was carried out in 20 patients with stage IV adenocarcinoma harboring mutations (EGFR, ALK, ROS-1). Clinicodemographic details, molecular status, type of TKI, PFS and survival outcomes were analyzed.

Results: A total of 20 patients were included. The mean age was 57.4 years (range 31–76); 60% were female, and 75% were smokers. EGFR exon 19 deletion was the most frequent mutation (70%), followed by exon 21 (25%). Osimertinib was prescribed to 55% of patients, gefitinib to 40%, and crizotinib to 5%. At 2 years, overall survival was 78%, PFS was with a median survival of 14.6 months.

Conclusion: TKIs demonstrated promising short-term survival outcomes in stage IV adenocarcinoma lung within the Nepalese population. Continued follow-up and larger cohorts are needed to define long-term outcomes and resistance mechanisms in this setting.

Keywords: *Tyrosine kinase inhibitor, EGFR mutation, Stage IV lung adenocarcinoma, Targeted therapy*

Introduction

More than 80% of cases of lung cancer are Non-small cell lung cancer (NSCLC)[1] with 40% incidence of adenocarcinoma.[2] Pulmonary adenocarcinoma may be associated with driver mutation, namely Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1(ROS-1) in 40-60%, 5-3% and 1-3%, respectively.[3] At the time of presentation, patients usually have metastatic or locally advanced disease. TKI has been recommended as a first line therapy for such cases. First-generation EGFR-TKIs, such as gefitinib and erlotinib, as well as second-generation agents like dacomitinib and afatinib which irreversibly inhibit multiple members of the human EGFR (HER) family—are currently in clinical use[4]. Due to the development of resistance, particularly through the acquired T790M mutation, Osimertinib, a third-generation EGFR-TKI, was developed. While frontline Osimertinib has shown superior survival outcomes compared to standard treatments such as erlotinib or gefitinib[5 6], first- and second-generation TKIs continue to be widely used in clinical practice. Alectinib and Crizotininb have been recognized as a first line TKI for ALK and ROS-1 rearrangement, respectively.[7] The aim of this study is to evaluate the symptoms and signs of disease with 2-year overall survival (OS) and progression free survival (PFS) in stage IV adenocarcinoma of lung at a tertiary care cancer center.

Materials and methods

This was a single centered, prospective study conducted in the department of thoracic surgery, B.P. Koirala memorial cancer hospital (BPKMCH) from June,2023 to May,2025. This study included 20 consecutive patients with confirmed stage IV adenocarcinoma lung harboring driver mutation. Pathological confirmation was done by bronchoscopic biopsy, VATS biopsy or image guided biopsy. EGFR mutation was done using PCR test. ALK and ROS-1 rearrangements were confirmed by Immunohistochemistry (IHC) and/or Fluorescence In Situ Hybridization (FISH).

Patients were either considered directly for TKI or chemotherapy (pemetrexed and carboplatin) followed by TKI. Pre-TKI chemotherapy was started if there was a delay in obtaining reports of molecular testing. Clinical stage IV was confirmed by CT findings. For patients with EGFR mutation, Gefitinib or Osimertinib were prescribed whereas for ALK/ ROS-1 rearrangement cases – Crizotinib was used. Patient was followed up every 3 month and response to therapy was monitored by clinico-radiological evaluation as per RECIST guideline 1.1.[8] At least a 30% decrease and 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum diameters was classified as partial response (PR) and progressive disease (PD), respectively. The rest were classified as stable disease.

Primary and secondary outcomes assessed were PFS and 2-OS, respectively.

Statistical analysis was done using SPPS version 26. Demographics, symptoms and signs, types of driver mutation, TKI used were analyzed. Kaplan–Meier survival estimation for PFS and OS was calculated. P <0.05 was taken as statistically significant.

Ethical approval was taken from the Institutional Review Committee of BPKMCH.

Results

A total of 20 patients with stage IV adenocarcinoma of the lung were included in the study. The mean age was 57.4 years (range 31–76 years), with a female predominance (60%). Most patients (75%) had a history of smoking, averaging 29 pack-years. The predominant clinical symptom was cough (95%), followed by shortness of breath (55%), and hemoptysis (5%) (Table 1).

The tumor sites were mainly in the upper lobe (65%), followed by lower lobe (25%), middle lobe (5%), and multiple lobes (5%) evenly distributed between right and left lungs. Bronchoscopy was normal in 15 patients, while 5 showed abnormalities in main or lobar bronchi. Histological diagnosis was obtained mainly through image-guided biopsy (n=9) and video-assisted thoracoscopic surgery (VATS) biopsy (n=8), with few diagnoses from bronchoscopy (n=2) and supraclavicular node biopsy (n=1) (Table 2).

Molecular analysis revealed EGFR mutations in 19 patients (95%), predominantly exon 19 deletions (70%) and exon 21 mutations (25%). ALK rearrangement was detected in 1 patient (5%). (Table 2).

Twelve patients (60%) received tyrosine kinase inhibitor (TKI) monotherapy, while eight patients (40%) were treated with a combination of chemotherapy and TKI. The chemotherapy regimen consisted primarily of carboplatin and pemetrexed. Among TKIs used, osimertinib was the most common (55%), followed by gefitinib (40%) and crizotinib (5%). (Table 3).

Table 1. Baseline characteristics of patients.

Characteristic	Value
N	20
Mean age (range)	57.4 years (31–76)
Sex	Female: 12 (60%) Male: 8 (40%)
Smokers	15 (75%) Mean pack-years: 29
Symptoms	Cough: 95%, Dyspnea: 55% Hemoptysis: 5%
Location of primary tumor	Upper lobe: 65% Middle lobe: 25% Lower lobe: 5%

Table 2. Molecular profile

Mutation Type	Frequency (%)
EGFR exon 19 deletion	14 (70%)
EGFR exon 21 mutation	5 (25%)
ALK rearrangement	1 (5%)

Table 3. Treatment distribution

Treatment	n (%)
Osimertinib	11 (55%)
Gefitinib	8 (40 %)
Crizotinib	1 (5%)
Chemotherapy + TKI	8 (40%)

The study recorded a 2-year survival rate of 78% (Fig.1). The median survival time was not reached.

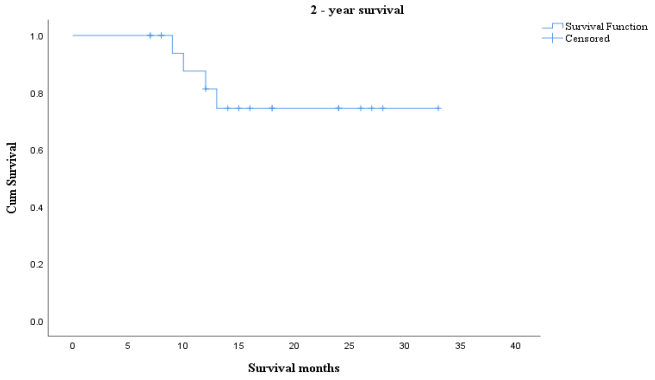

Fig.1. Kaplan-Meier Overall survival curve.

PFS was 80% at one year for the whole group (Fig.2).

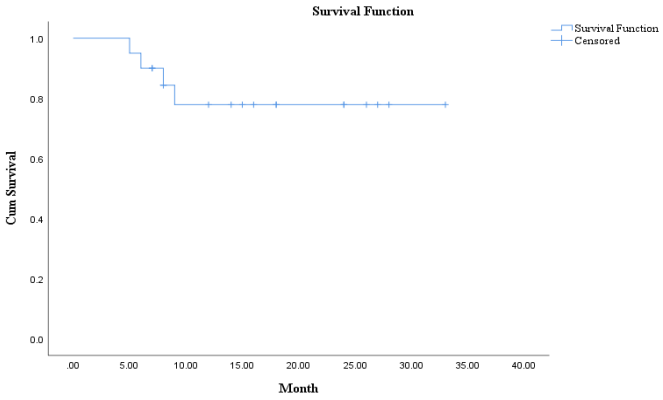

Fig.2. Overall PFS.

Table 5. Overall Comparison of PFS

	Chi-Square	df	p-value
Log Rank (Mantel-Cox)	25.003	2	<0.001
Test of equality of survival distributions for the different levels of disease status.			

The overall comparison of PFS using the Log-Rank (Mantel-Cox) test revealed a highly significant difference in survival distributions across the three disease status groups ($\chi^2 = 25.003$, df = 2, $p < 0.001$) (Table 5, Fig.3).

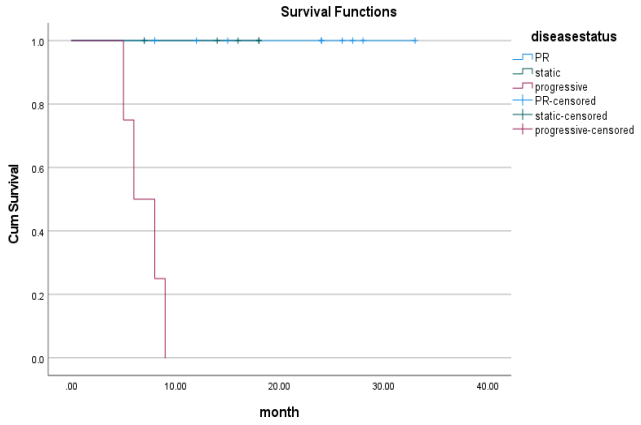

Fig. 3. Kaplan-Meier curve for PFS.

None of the patients with stable disease or partial responders had any event during the whole observation period, whereas none of patients with PD survived beyond 10 months. Median survival in percentiles for progressive disease has been shown in Table 4.

This percentile table shows estimates of survival times (in months) at different percentiles for patients with progressive disease. The 25th percentile survival time was 8 months (with SE = 1.299), the median survival time (50th percentile) was 6 months (with SE = 1.500), and the 75th percentile survival time was 5 months.

Table 4. Median survival time in percentiles for PD.

Disease status	Percentiles					
	25.0% (Q1)		50.0% (Q2)		75.0% (Q3)	
	Estimate	Std. Error	Estimate	Std. Error	Estimate	Std. Error
Progressive	8.000	1.299	6.000	1.500	5.000	

Discussion

Adenocarcinoma of lung harbor EGFR mutations in ~10–15% of Western patients whereas the prevalence as high as 30–50% has been reported in East Asian patients, and 25–45% of Indian patients. KRAS mutations are more frequent in Western populations (20–40%) compared with Asia (8–15%), while other driver alterations such as ALK, ROS1, BRAF, MET exon 14, RET, and HER2 are less common, each reported in ~1–7% of cases.[9 10 11 12]

The introduction of first-generation TKIs such as gefitinib and erlotinib marked a major advance in the management of EGFR-mutated lung adenocarcinoma. The landmark IPASS trial demonstrated that gefitinib significantly improved response rates and PFS compared with chemotherapy alone in East Asian patients with sensitizing EGFR mutations in stage IV lung adenocarcionoma.[13] Similar results were confirmed with erlotinib in the OPTIMAL[14] and EURTAC trials[15], the latter being the first study to establish the benefit of EGFR TKIs in a Caucasian population. Despite these benefits, most patients develop acquired resistance, with the secondary EGFR T790M mutation accounting for approximately 50–60% of cases within median time of 13 months, while other mechanisms include MET amplification, HER2 amplification, PIK3CA mutations, histologic transformation to small-cell carcinoma, and epithelial–mesenchymal transition.[16] To overcome T790M-mediated resistance, Osimertinib, a third-generation EGFR TKI, was developed and demonstrated superior efficacy in the phase III FLAURA trial, where first-line osimertinib achieved a median progression-free survival of 18.9 months versus 10.2 months with gefitinib or erlotinib, and significantly improved overall survival.[5]

Osimertinib demonstrates enhanced central nervous system (CNS) penetration, resulting in higher

intracranial response rates and reduced CNS progression compared with first-generation TKIs, thereby establishing it as the preferred agent for patients with baseline brain metastases.[17]

Studies from tertiary care centers show high initial response rates and meaningful symptom relief shortly after starting TKIs, but durability depends on mutation subtype and availability of subsequent targeted options.

A number of tertiary-center retrospective cohorts (including non-Western populations) documented exon-19 deletions and L858R as the common sensitizing alterations, high proportions of nonsmokers, and good early radiologic response to TKIs — supporting the external validity of randomized trials in routine practice.[18]

Our study revealed some extremely relevant findings. Two-year OS was 78%, which indicates excellent results in Nepalese patients with driver mutation. This is similar to the results from FLAURA phase III trial, where 556 patients with previously untreated, EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC in a 1:1 ratio received either Osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily) .18-months OS was 83% in Osimertinib group vs 71% in gefitinib group.[5]

A single observational study regarding use of TKI has been reported from Bir Hospital, Nepal.[19] In a cohort of 83 patients with stage IV lung adenocarcinoma, the incidence of EGFR mutations was 29%. Patients were given gefitinib in EGFR mutated cases and systemic chemotherapy in non-mutated patients. one-year PFS was 39% vs 29% favoring gefitinib. There have been so far no reports regarding use of Osimertinib in Nepal. Our study showed remarkably higher 1-year PFS (80%) than the result from Bir hospital.

In our study progressive disease had median survival of only 5 months at 75th percentile. These results indicate that patients with progressive disease had a very short survival duration, with half of them dying within 6 months of follow-up, and none surviving beyond 10 months. This indicates that progressive disease is associated with a markedly poor prognosis compared to other groups. PFS was statistically significant in stable and partially responders than in patients with disease progression ($p<0.001$). None of the patients in the latter group had the event at the end of two years.

Our study demonstrates that TKIs are effective in improving short-term outcomes in Nepalese patients with stage IV adenocarcinoma harboring EGFR/ALK mutations.

Our findings highlight challenges in resource-limited environments: affordability, drug access, and limited sequencing strategies. Despite this, the 2-year survival rate of 78% is encouraging and underscores the potential of TKIs as frontline therapy.

Limitations include small sample size, short follow-up, lack of detailed adverse effects and comparison of gefitinib vs osimertinib. However, this is the first report of its kind from Nepal, providing valuable local data regarding use of osimertinib as well as gefitinib.

Conclusion

TKI is effective targeted treatment in stage IV adenocarcinoma lung patients in Nepal. Early outcomes demonstrate significant survival benefits, supporting their integration into standard treatment pathways. Further large-scale studies are warranted to refine sequencing strategies, resistance monitoring, and cost-effectiveness in the Nepalese context.

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