J Nepal Health Res Counc 2023 Apr-Jun;21(59): 330-5

Outcome of Epidermal Growth Factor Receptor Mutated and Non Mutated Adenocarcinoma Lung to Standard Therapy

Soniya Dulal,[1] Akshat Mishra,[1] Aarati Shah,[2] Bibek Acharya,[3] Ramila Shilpakar,[3] Sandhya Chapagain Acharya,[3] Ambuj Karn,[3] Rajeev Sharma,[1] Balram Gautam,[4] Bishnu Dutta Paudel[5]

[1]B. P. Koirala Institute of Health Sciences, Dharan, Nepal, [2]Medical Education Commission, Sanothimi, Bhaktapur, Nepal, [3]NAMS, Bir Hospital, Kathmandu, Nepal, [4]Decode Genomics and Research Center, Sinamangal, Nepal, [5]Bhaktapur Cancer Hospital, Nepal.

ABSTRACT

Background: Asian patients with adenocarcinoma of lung have higher incidence of epidermal growth factor receptor mutations which predict increased response and survival in patients to oral tyrosine kinase inhibitors. This study was conducted to study the frequency of epidermal growth factor receptor mutation in patients in Nepal and compare the outcome in epidermal growth factor receptor mutated versus non-mutated patients receiving standard therapy.

Methods: This is an observational study conducted among newly diagnosed patients with stage IV adenocarcinoma of lung in Bir Hospital from April 2017 to June 2018. Demographic and clinical data collection along with epidermal growth factor receptor mutation testing was done. Patients with epidermal growth factor receptor mutations received Gefitinib while non-mutated patients received systemic chemotherapy. Response evaluation, progression free survival at 1 year, objective response rate and quality of life were compared. Follow up period was for 1 year.

Results: Eighty three (33%, n=253) patients were diagnosed with adenocarcinoma of the lung with mean age at diagnosis being 59.4 years. epidermal growth factor receptor mutations were found in 29% patients. Complete response was achieved in 9.1% vs 3.0 % (p=0.46), objective response rate was 27.3% versus 15.2% (p=0.23), progression free survival at 1 year was 39% vs 27%, (p = 0.29) and mean score of global health status was 68.1 versus 61.6 in epidermal growth factor receptor mutated versus non-mutated (p = 0.036).

Conclusions: The frequency of epidermal growth factor receptor mutation in patients with adenocarcinoma of the lung was lower than in Eastern Asian studies, but higher than in western populations. epidermal growth factor receptor mutated patients had improved survival, better treatment response and quality of life in comparison with non-mutated.

Keywords: Adenocarcinoma of lung; EGFR; quality of life

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide. According to Globocan 2020, total number of new lung cancer cases in Nepal was 2,505 (12.2%) of all cancer cases and 16.8% of all cancer related deaths. Non-small cell lung cancer (NSCLC) comprises approximately 80% to 85% of all lung cancers and the majority of patients present with advanced or metastatic disease. Epidermal growth factor receptor (EGFR) is the somatic mutation in NSCLC, seen more frequently in certain population groups i.e. East Asian, including China, Japan, Mongolia, Korea; nonsmoking females with adenocarcinoma. The presence of activating or driver mutations in Exon 18 through Exon 21 of EGFR gene has been associated with better response to the anti-EGFR therapies (Tyrosine Kinase Inhibitors).[7] The transition in histologic profile from squamous to adenocarcinoma has also been observed in India in past decades following global trends. This study aims to determine the EGFR mutation frequency, prognostic significance and outcome to treatment with TKIs in EGFR mutated compared to standard platinum based therapy in EGFR non-mutated patients in our population.

METHODS

A prospective observational study was carried out in Bir Hospital from April 1 2017 to July 1, 2018 after ethical

Correspondence: Dr Soniya Dulal, B. P. Koirala Institute of Health Sciences, Dharan, Nepal, Email: soniyadulal@hotmail.com, Phone: +9779841584293.

clearance by the Institutional Review Board, NAMS. Informed written consent was taken from all participants before enrolling in the study.

Patients of age > 18 with pathologically confirmed adenocarcinoma stage IV giving informed consent were eligible for the study. Patients with deranged liver function test (grade 2) or deranged renal function tests (grade 2) were excluded from the study.

Convenience Sampling was done as all patients who were eligible for the study were enrolled in the study. The estimated sample size using $n = Z^2 P (1-P)/ d^2$ was 66 and considering a dropout rate of 10% a total 72 patients were enrolled in the study.

All patients eligible for the study presenting to Oncology Out-Patient (OPD) or In-Patient or Emergency Department during the study period were enrolled in the study. Eligibility criteria were judged during the initial clinical evaluation of the patient. An informed written consent was obtained before the study was carried out. Demographic data of patients were collected. Standardized data collection sheets were used to record the data. Samples for EGFR mutation, i.e. [Exon 18 (G719C/S/A), Exon 19 - del/ins, Exon 20 (V765A/ T783A), Exon 21 (L858R/ L861Q] analysis were obtained from primary or metastatic lesions by imaging or bronchoscopic guided biopsy or pleural fluid cytology or blood. EGFR mutation analysis was not available in Bir Hospital. So, these tests were done in Decode Genomics and Research Center, Sinamangal, using Real Time PCR technique for detection of mutations on EGFR gene using FDA approved TheraScreen EGFR mutation kit. Routine blood investigations including complete blood count, random blood sugar, renal function test, liver function test were sent before starting treatment. The Tyrosine Kinase Inhibitor (TKI) (Tab. Gefitinib 250 mg, once a day till disease progression or unavoidable toxicity) was prescribed to EGFR mutation (Exon 18,19,21) positive patients and mutation negative patients were given standard chemotherapy (Pemetrexed 500mg/ m^2 and Cisplatin 75 mg/ m^2, every 21 days for 4 to 6 cycles or Cisplatin 25 mg/ m^2 for 3 days and Etoposide 100 mg/m^2 for 3 days for 6 cycles) following treatment protocol of Department of Clinical Oncology, NAMS. Patients were given options to choose between these two chemotherapy regimens as per their choice. In case of disease progression, patients were allowed to receive second line treatment as per the protocol of Department of Clinical Oncology. Patients were counseled about their disease status and treatment procedures. Clinical outcomes including response to targeted therapy, response to standard chemotherapy, disease progression, survival outcome (Progression free survival at 1 year), quality of life and assessment of adverse effects were evaluated. The patients were followed up for 1 year.

RECIST version 1.1 criteria was used for measuring treatment response in both standard platinum-based chemotherapy and TKI arm. Progression free survival at 1 year was evaluated for all patients to determine disease progression following treatment. EORTC QLQ-C 30 (version 3) questionnaires, a multidimensional general cancer specific questionnaire, were validated and used as a tool for evaluating quality of life, after taking permission from the EORTC Quality of life department, Brussels. The raw score was then converted to the linear score between range of 0 to 100 as per the EORTC Scoring manual. These questionnaire modules were used at the time of diagnosis that is baseline, and 1 month after treatment completion in patients receiving standard chemotherapy and after 3 months in patient receiving Gefitinib. The QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, nausea and vomiting); a global health status/ QoL scale; number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia) and perceived financial impact of the disease. Assessment of adverse effect was done using CTCAE version 5 criteria.

Data collection was done on a standardized data collection sheet. Patient's identification number, age, sex, ethnicity, address, education status, height, weight, body surface area, occupation, smoking status, date of enrollment, AJCC stage, EGFR mutation status and type of mutation, treatment regimen, treatment response as per RECIST criteria, disease progression, adverse effects and quality of life using EORTC QLQ-C30 questionnaire were recorded in the sheet. EORTC QLQ C30 was available in Nepali format. So, questions were asked verbally to the understanding of the patient and were recorded in the sheet.

Data analysis was done upon completion of the study. The data were entered using SPSS version 20 statistical software. Statistical analysis was also done using SPSS software after entering the data on a master chart. Frequencies and percentages were obtained for each of the categorical variables. Mean and median was performed for continuous variables. Comparisons between the two groups were assessed using Chi square x2 test. Subgroup analysis were performed using crosstabs to evaluate the study outcomes. A two-tailed level of significance at P value of < 0.05 was considered significant and applied to all statistical tests.

RESULTS

Over the period of 1 year, a total of 253 patients were diagnosed with lung cancer. Out of these, 83 (33%) patients were diagnosed with adenocarcinoma via biopsy or cytology reports. 72 patients were enrolled in the study after confirming eligibility. Two EGFR mutated patients did not take the allocated treatment and three non mutated patients defaulted after one month.

Of the 83 patients diagnosed with adenocarcinoma 45 (54%) were males and 38 (46%) were females. The mean age at diagnosis was 59.4 years. Age at which adenocarcinoma of the lung was most commonly observed was between 61-70 years, which was 31.8%. Fifty eight percent of the study population had history of smoking of which 63% had a pack year of less than 10. Majority of the patients were illiterate (61%). EGFR mutations were found in 29% of all the patients.

For the sake of the comparison, 33 patients were taken each in EGFR mutated and non- mutated arms for further analysis. Majority of the patient had tissue biopsy sample for EGFR mutation analysis (21 patients in mutated and 18 patients in non mutated). 60% of the non- mutated patients were smokers whereas 55% of EGFR mutated patients were smokers. Amongst the EGFR mutated patients, Exon 21 (L858R) mutation was the most common mutation, followed by Exon 19 deletion. Among EGFR non mutated, 26 patients received Pemetrexed/ Cisplatin regimen and 7 patients received Cisplatin/ Etoposide regimen. All EGFR mutated patients received Gefitinib.

In our study 9% of the EGFR mutated patients had a complete response which was higher than non-mutated patients (3%) however the difference was not found to be statistically significant (p=0.46). EGFR non mutated patients had more progressive disease than mutated patients as seen in Figure 1.

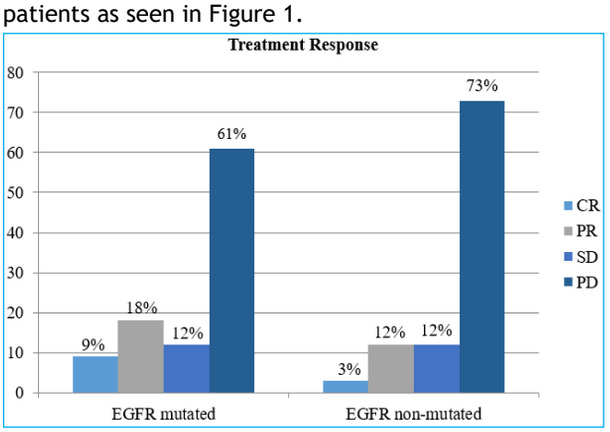

Figure 1. Comparison of treatment response among EGFR mutated and non-mutated patients.

The percentage of EGFR mutated patients versus non-mutated patients with progression free survival at 1 year was 39% [95% CI (25-56)%]vs 27% [95% CI (15-44)%] (p = 0.29). The median PFS was 11 and 9 months for EGFR mutated and non-mutated respectively (p = 0.045). A time to event graph is shown in Figure 2.

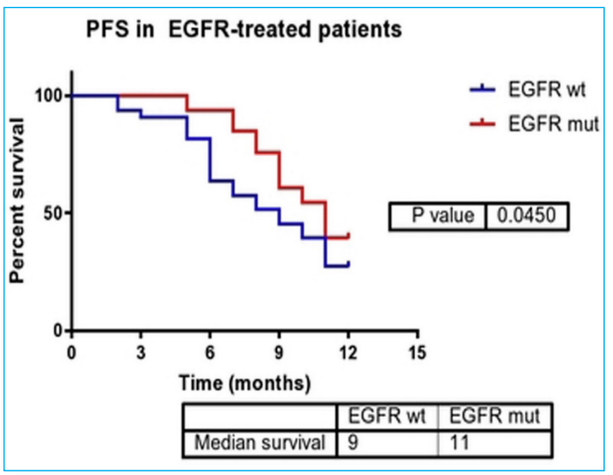

Figure 2. Time to event graph of progression free survival in Mutated (EGFR-mut) versus non-mutated (EGFR-wt).

There were five functioning scales that were assessed before and after 1 month of chemotherapy completion or after 3 months of targeted therapy. In the non-mutated arm receiving chemotherapy, there was clinically significant (difference (Δ) >10) improvement in all 5 scales and there was a statistically significant difference ($p<0.05$) in Emotional functioning. Similarly in the targeted therapy arm, after three months all 5 scales showed clinically significant improvement and statistically significant improvement in Emotional functioning ($p<0.05$) as seen in Table 1.

In targeted therapy after 3 months, there was statistically significant improvement in fatigue ($p<0.05$) and clinically significant improvement in all other symptoms. There was clinically significant difference in physical functioning in the targeted therapy arm (difference (Δ)>10) compared to the chemotherapy arm. There was clinically and statistically greater improvement in nausea, insomnia and appetite loss ($p<0.05$) in the targeted therapy arm as seen in Table 1.

There was a statistically significant improvement of Global health status calculated according to the EORTC QLC-30 in the Gefitinib arm as compared to the chemotherapy arm ($p<0.05$) as seen in Table 2.

Table 1. Mean scores(standard deviation) and mean difference of quality of life scales for functioning and symptom scales, after chemotherapy (1 month after treatment completion) and after Targeted Therapy (3 months after starting treatment).

EORTC QLQ-C30	After Chemo-therapy	After Targeted therapy	Mean Difference (Δ)	P value
Physical functioning	55.55 (17.05)	66.66 (10.80)	+ 11.11	0.213
Role functioning	48.48 (14.04)	56.25 (23.77)	+ 7.77	0.060
Social functioning	49.49 (14.11)	53.73 (22.65)	+ 4.24	0.211
Emotional functioning	67.98 (21.96)	68.68 (14.43)	+ 0.7	0.731
Cognitive functioning	48.98 (13.78)	56.25 (23.77)	+ 7.27	0.073
Pain	18.68 (14.88)	16.66 (16.66)	- 2.02	0.670
Fatigue	37.03 (20.90)	26.59 (20.01)	- 10.44	0.338
Nausea	19.18 (15.09)	7.06 (10.22)	- 12.12	0.010
Dyspnoea	24.24 (23.96)	14.14 (18.68)	- 10.1	0.144
Insomnia	60.60 (28.20)	18.18 (22.18)	- 42.42	0.005
Appetite loss	60.60 (28.20)	18.18 (22.18)	- 42.42	0.005
Financial Difficulties	47.47 (25.04)	43.43 (24.27)	- 4.04	0.870

Table 2. Mean scores (standard deviation), difference of global health quality of life after chemotherapy (1 month after treatment completion) and after Targeted Therapy (3 months after starting treatment).

EORTC QLQ-C30	After Chemotherapy	After Targeted therapy	Mean Difference (Δ)	P Value
Global Health Score	61.61(27.47)	68.07 (22.95)	+ 6.46	0.036

One patient receiving gefitinib had grade 3 skin toxicity. Chemotherapy induced nausea and vomiting, myelosuppression and peripheral sensory neuropathy (either grade 1 or grade 2) were the most common toxicities in patients receiving standard chemotherapy.

DISCUSSION

Our study showed that 33% of all lung cancer patients had adenocarcinoma. Majority of the patients were male and were either current or ex-smokers.This is contrary to the fact that adenocarcinoma is more common in non-smokers and women. This is similar to a study in India where 28.3% of the patients were diagnosed with adenocarcinoma within NSCLC and 86% were male with the ratio of men to women was 7.4. Majority of patients (78.3%) were current/ ex-smokers.

The incidence of EGFR mutation in our population was found to be 29% which is similar to a study done in Tata Memorial Hospital, India where they found the incidence to be 35%.

In the PIONEER study, the most common mutations were exon 19 deletion and L858R point mutation in exon 21. In contrary, the most common EGFR mutations found in our study was exon 21 (L858R) followed by exon 19 deletion.

Thus, the frequency of EGFR-mutation in adenocarcinoma of the lung in our study was lower than in Eastern Asian studies, but higher than in western populations and the frequency of Exon 21 mutation was higher than in western or eastern Asian studies.

In a study by Noronha V et al[18] the PFS for patients with EGFR mutation was significantly longer at 10 months, as compared to an estimated PFS of 2 months for EGFR negative patients. The estimated median OS of the patients with EGFR mutation was significantly longer at 21 months, as compared to 10 months for EGFR non-mutated. The response rate to TKI for mutation positive was 74%, while in mutation negative was 5%.

The trial called IPASS by Tony S. Mok et al provided strong evidence for testing for EGFR in the first-line setting where the objective response rate and progression-free survival (PFS) was significantly longer in EGFR patients treated with Gefitinib than it was among patients who received platinum-based chemotherapy.

In our study, complete response was high in EGFR mutated patients than non-mutated patients, while non mutated patients had more progressive disease than mutated patients.The median progression free survival for EGFR mutated patients was higher than in non-mutated (11 months versus 9 months)

Objective response rate was also high in EGFR mutated patients in comparison to EGFR non-mutated. Although the differences in survival were not statistically significant possibly due to our smaller sample size, this shows that there is a possibility that the presence of EGFR mutation and its subsequent treatment is associated with a favorable prognosis and it can be used as a prognostic biomarker.

We also observed in our study that there was significant improvement in physical, role, social, emotional and cognitive functioning scales, as well as quality of life on global health scale after Gefitinib.

Thus, EGFR mutated patients treated with gefitinib had improved quality of life in comparison with EGFR non mutated patients treated with chemotherapy.

Our study had, however, several limitations. The most important being that the sample size was small for comparison of outcomes. We also had a short follow up period to confidently interpret the survival outcome, drug induced long term toxicities, further change in different functioning scales of EORTC-QoL in a longer time frame. As the study was conducted in a single center, the study outcome could not represent the whole Nepalese population.

CONCLUSIONS

Our study confirms the importance of molecular testing in the adenocarcinoma patient subgroup with an aim to identify the exact molecular targets that can benefit from the newer generation of targeted therapies in our part of the world as well. The frequency of EGFR mutation in this study was lower than in Eastern Asian studies, but still higher than in western population. So, it is recommended to do pre-emptive EGFR testing in all patients diagnosed with advanced adenocarcinoma lung. Larger studies are needed to properly validate EGFR as a prognostic biomarker in adenocarcinoma lung.

ACKNOWLEDGEMENTS

Dr. Prakash Neupane, MD , The University of Kansas Medical Center, Westwood, Kansas, USA, Dr. Natasha B Leighl, MD, Princess Margaret Cancer Center, Toronto, Canada, Dr. Odd Terje Brustugun, MD, University of Oslo, Norway

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer Disparities by Race/Ethnicity and Socioeconomic Status. CA Cancer J Clin. 2004;54(2):78-93. doi:10.3322/canjclin.54.2.78
2. Globocan, International Agency for Research on Cancer: Nepal. Summary statistic 2020. [Download PDF]
3. Crinò L, Weder W, van Meerbeeck J, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;21(SUPPL.5). doi:10.1093/annonc/mdq207
4. Lynch TJ, Bell DW, Sordella R, Okimoto RA, Brannigan BW, Harris PL, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib. New England Journal of Medicine. 2004;350(21):2129-2139. doi:10.1056/NEJMoa040938
5. Usui K, Ushijima T, Tanaka Y, Tanai C, Noda H, Abe N, et al. The Frequency of Epidermal Growth Factor Receptor Mutation of Nonsmall Cell Lung Cancer according to the Underlying Pulmonary Diseases. Pulm Med. 2011;2011:1-5. doi:10.1155/2011/290132
6. Kim HR, Shim HS, Chung JH, Lee YJ, Hong YK, Rha SY, et al. Distinct clinical features and outcomes in never-smokers with nonsmall cell lung cancer who harbor EGFR or KRAS mutations or ALK rearrangement. Cancer. 2012;118(3):729-739. doi:10.1002/cncr.26311
7. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba I, et al. Clinical and Biological Features Associated With Epidermal Growth Factor Receptor Gene Mutations in Lung Cancers. JNCI Journal of the National Cancer Institute. 2005;97(5):339-346. doi:10.1093/jnci/dji055
8. Minna JD, Gazdar AF, Sprang SR, Herz J. A Bull's Eye for Targeted Lung Cancer Therapy. Science (1979). 2004;304(5676):1458-1461. doi:10.1126/science.1099578
9. Gazdar AF, Shigematsu H, Herz J, Minna JD. Mutations and addiction to EGFR: the Achilles 'heal' of lung cancers? Trends Mol Med. 2004;10(10):481-486. doi:10.1016/j.molmed.2004.08.008
10. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy. Science (1979). 2004;304(5676):1497-1500. doi:10.1126/science.1099314
11. Mohan A, Latifi AN, Guleria R. Increasing incidence of adenocarcinoma lung in India: Following the global trend?. Indian journal of cancer. 2016 Jan 1;53(1):92-5.doi:10.4103/0019-509X.180819
12. Li X, Ren R, Ren S, Chen X, Cai W, Zhou F, et al. Peripheral Blood for Epidermal Growth Factor Receptor Mutation Detection in Non-Small Cell Lung Cancer Patients. Transl Oncol. 2014;7(3):341-348. doi:10.1016/j.tranon.2014.04.006
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S,

Mooney M, Rubinstein L. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009 Jan 1;45(2):228-47.doi: 10.1016/j.ejca.2008.10.026

14. Pandey RA, Dhungana GP, Twi JT, Byanju S, Khawas B. Quality of life of patients undergoing cancer treatment in BP Koirala Memorial Cancer Hospital, Bharatpur, Chitwan, Nepal. American Journal of Cancer Prevention. 2015;3(2):35-44.[Download PDF]

15. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Quality of Life Research. 1996;5(6):555-567. doi:10.1007/bf00439229

16. Colevas AD, Setser A. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 is the new standard for oncology clinical trials. Journal of Clinical Oncology. 2004 Jul 15;22(14_suppl):609810.1200/jco.2004.22.90140.6098

17. Mohan A, Latifi A, Guleria R. Increasing incidence of adenocarcinoma lung in India: Following the global trend? Indian J Cancer. 2016;53(1):92. doi:10.4103/0019-509X.180819

18. Noronha V, Prabhash K, Thavamani A, Chougule A, Purandare N, Joshi A, et al. EGFR mutations in Indian lung cancer patients: Clinical correlation and outcome to EGFR targeted therapy. PLoS One. 2013 Apr 19;8(4):e61561. doi:10.1371/journal.pone.0061561

19. Shi Y, Li J, Zhang S, Wang M, Yang S, Li N, et al. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology–mainland China subset analysis of the PIONEER study. PloS one. 2015 Nov 23;10(11):e0143515. doi:10.1371/journal.pone.0143515

20. Mok TS, Wu YL, Thongprasert S, Nishiwaki Y, Ohe Y, Yang JJ et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. New England Journal of Medicine. 2009;361(10):947-957. doi:10.1056/NEJMoa0810699