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Role of Gefitinib as First Line Treatment in Patients with Advanced Adenocarcinoma Lung

Authors
Jyothi E[1], Suraj KP[2], Gayathri Mohan[3]
[1]Assistant Professor, [2]Professor, [3]Junior Resident
Department of Pulmonary Medicine, Government Medical College, Kozhikode
Corresponding Author
Dr Suraj KP
Professor, Department of Pulmonary Medicine, Government Medical College, Kozhikode

Introduction

Lung cancer is the most common cause of cancer related deaths worldwide[1]. Even with advances in chemotherapy and surgical therapy, the overall 5-year survival in lung cancer remains dismal at 12% to 16%[2]. At present lung cancer therapy is in the path of a revolution toward personalised therapy. In the past decade, multiple advances have been made in understanding the underlying biology and molecular mechanism of lung cancer, especially adenocarcinoma. With the arrival of targeted therapy there has been significantly improved outcome in metastatic lung malignancy.

There are 2 broad categories of lung cancer- Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). Non-small cell lung cancer consists mainly of adenocarcinoma (38.5%), squamous cell carcinoma (20%) and large cell carcinoma. In the past several decades adenocarcinoma has replaced squamous cell carcinoma as the most prevalent histopathological type.

Due to the rapid advancement in the molecular diagnostic methods, various mutations have been discovered in adenocarcinoma lung and it is now possible to render personalised therapy for lung cancer based on the mutations. In 2004 driver mutations in the epidermal growth factor receptor (EGFR) gene, a membrane bound receptor tyrosine kinase, that regulates cell growth were discovered in NSCLC, especially adenocarcinoma[3]. This mutation was found to be associated with deregulated signalling, leading to cell growth and development of oncogenic phenotype. It also results in cellular dependence on EGFR tyrosine kinase signalling. The presence of this mutation was strongly associated with therapeutic sensitivity to tyrosine kinase inhibitor(TKI).

The first of EGFR TKI drug available for treatment were Gefitinib and Erlotinib. They bind to EGFR in competition with ATP, suppressing EGFR phosphorylation and downstream signalling. These are orally administered drugs with a good safety profile. Approximately 90% of observed EGFR gene mutations are either deletion in exon 19 or an amino acid substitution in exon 21. The EGFR gene mutations were more commonly found in females, never smokers of

East Asian origin with adenocarcinoma histology[4]. The incidence of EGFR mutation is 25-35% in Asians compared to approximately 15% in Western population.

Many retrospective series have shown that response to EGFR TKIs in EGFR mutation positive patients exceeds 60%, which is much higher compared to the 20% response to combination chemotherapy[5,6,7]. First line therapy with TKI have shown a progression free survival of 9.2 to 14 months in patients with EGFR mutation[5,8,9]. The IPASS trial, designed with progression free survival as the primary end point comparing gefitinib with carboplatin/paclitaxel, showed superiority of gefitinib for PFS, objective response rate and quality of life for the entire cohort[10]. But many patients who initially respond to gefitinib eventually may become resistant and develop progressive disease.

Aim of the study

1. To assess the progression free survival (PFS) of patients with adenocarcinoma lung with immunohistochemistry positive for EGFR, treated with gefitinib
2. To compare the response to gefitinib between smokers and non-smokers.

Materials and Methods

Patients with a diagnosis of inoperable adenocarcinoma lung, and immunohistochemistry showing EGRF positivity were enrolled for the study. The study was conducted in Institute of Chest Diseases, Government Medical College, Kozhikode.

Study Design: Prospective cohort study

Study Period: The study was conducted between July 2013 and June 2015

Inclusion Criteria: All cases of inoperable adenocarcinoma lung, with immunohistochemistry showing TTF1 and EGFR positive.

Exclusion criteria: a)Patients who have received standard chemotherapy as first line treatment

b)Age below 18 years

c) Presence of other significant systemic illness

d)Moribund patients

e) Not willing for the study.

Patients diagnosed with adenocarcinoma lung who gave informed consent were recruited for the study. Immunohistochemistry was done for TTF 1 and EGFR. Only those patients who had EGFR 2+ and 3+ status on immunochemistry staining were included in the study. 2+ and 3+ EGFR status refers to moderate membranous staining and strong membranous staining respectively to monoclonal antibodies directed against epidermal growth factor receptor. These patients were started on Gefitinib 250mg once daily after assessing baseline complete hemogram, random blood sugar, renal and liver function test. In the first two months twice weekly follow up was done, followed by monthly visits for the next two months and 3 monthly follow upto 1 year or till death.

During follow up Chest X-ray was repeated after 3 months and at the end of 1 year and as and when required in between. CT thorax was repeated at the end of first year or as and when required. Progression free survival (PFS) was assessed according to RECIST guidelines version 1.1 till completion of 1 year. Quality of life was assessed by ECOG scoring.

Results

During the study period 89 patients were recruited who met the inclusion and exclusion criteria. Out of this, there were 58 males and 31 females. Mean age of the study population was 60.4 years. Among the study population there were 43 smokers and 46 non-smokers. There were 7 female smokers in this group. The smoking index of the patients ranged from 800-1200.

Progression free survival was assessed base on RECIST guidelines. Among the 58 males started on gefitinib, at the end of 1 year 31 patients had progression free survival. While for the 31females 5 had disease progression at the end of 1 year.

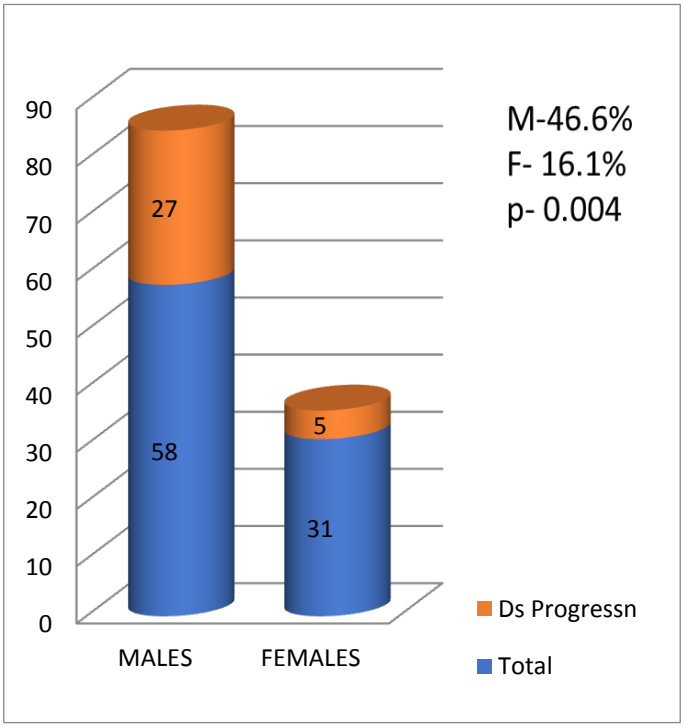

Fig 1 : Difference in disease progression between males and females.

Comparing the PFS between smokers and non-smokers, 26 smokers out of 43 (60.46%) had PFS at the end of 1 year. Among non-smokers 31 patients out of 46 (67.5%) had PFS at the end of 1 year, which is not statistically significant.

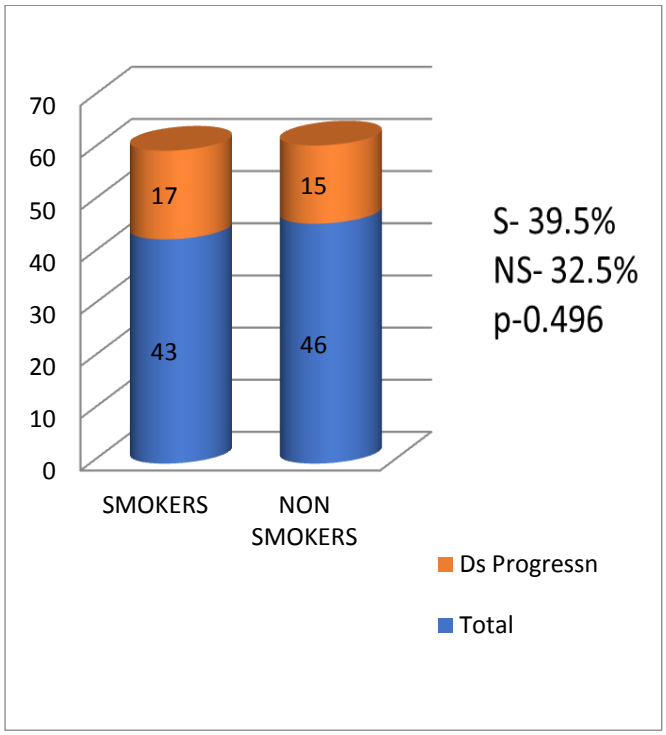

Fig 2: Difference in disease progression between smokers and non-smokers.

Quality of Life: The ECOG score at the beginning of the treatment was 3.4 and after 1 year of treatment with gefitinib, it was reduced to 2.5., with a P value of 0.03.

Mortality: Out of 89 patients 28 patients died during the study period which included 24 males and 4 females. Among this, 15 males were smokers and 3 females were smokers.

So finally, at the end of 1 year, 57 patients were continuing gefitinib. The proportion of patients who had a positive response at the end of 1 year is 64%, which is comparable to many of the previous trials[5-7]. During the 1 year period, 28 patients died and, treatment had to be stopped because of disease progression in 4 patients. The mean progression free survival in the study group is 8.38 months and the standard deviation is 2.72.

Adverse Events: The adverse events noticed in this study were diarrhoea in 10 patients, vomiting in 7 patients and skin rash in 6 patients. In one patient because of persistent vomiting treatment had to be stopped

Discussion

EGFR gene mutations are more common in non-smokers, females and people of Asian origin. But in this study, EGFR positivity demonstrated by immunohistochemistry in inoperable adenocarc-inoma patients was seen in a significant percentage of males and smokers. There was aalso a significant positive response to treatment. The study population consisted of more males than females. There were 58males and 31 females. There were 43 smokers and 46 non-smokers. There were 7 female smokers with adenocarcinoma in this study group. Disease progression was seen in 46.6% males compared to 16.1% females. There is a statistically significant disease progression among males compared to females with a P value of 0.004.In a study by Hayashibara et al, female gender was associated with prolonged survival[11]. Another significant observation in this study was the similar disease progression between smokers and non-smokers. The PFS was 60.46% for smokers and 67.5% for

non-smokers. This shows that in patients with advanced adenocarcinoma, based on the EGFR status patients may be started on gefitinib. In a study by Shinichi Toyooka et al it was found that only the EGFR mutation and not sex and smoking is associated with favourable prognosis.[12]

The commonly reported adverse events reported in patients on gefitinib include diarrhoea, vomiting, skin rash and interstitial lung disease.[13] In our present study, the reported adverse effects include diarrhoea in 10 patients, vomiting in 7 patients and skin rash in 6 patients. Compared to cancer chemotherapy, gefitinib has a very good safety profile.

The limitation of this study is that only immunohistochemistry was done to assess EGFR status and EGFR mutation analysis was not done. We need larger multicentre trials in India to assess response to gefitinib in our population.

Conclusion

In advanced inoperable adenocarcinoma lung, EGFR tyrosine kinase inhibitors do have a favourable therapeutic effect. Even though the response to gefitinib is better in females compared to males, a positive response to treatment at the end of 1 year was seen in 64% of patients. Similar to previous trials, good tolerability was also demonstrated for gefitinib, with very few severe adverse effects. The response to treatment in smokers was comparable to that of non-smokers. This is a significant observation of this study. Even though EGFR mutation analysis by direct sequencing is the most reliable method of predicting treatment response, we were able toget good treatment response in our study population in which gefitinib was started based on immunohistochemistry. Further larger studies are required with EGFR mutation analysis to assess response to treatment with EGFR tyrosine kinase inhibitors in patients with adenocarcinoma lung.

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