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Original Research Article

Therapeutic efficacy of Gefitinib in advanced NSCLC patients

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ABSTRACT

Introduction: Lung cancer uprises from the respiratory epithelium cells is divided into two broad categories; Non–small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC), derived from cells exhibiting Neuro-endocrine characteristics which is highly malignant tumour. The current drug therapy of Gefitinib has little evidence for its efficacy and safety profile in Indian patients.
Aim: The research was focused to assess the efficacy of Gefitinib in advanced Non-small cell lung cancer.
Materials and Methods: It is a retrospective study, done during the study period January 2009 to June 2012, and the number of NSCLC patients was 25 cases.
Results: Of the 25 cases, 13 (52%) were males and 12 (48%) were females. The factors affecting survival have been studied there was a significant difference in survival between male and female sex (males 7.2 months; females 10.9 months). NSCLC patients were also having pleural effusion in 15 (60%) patients; fluid was hemorrhagic in 13 cases and straw coloured in 2 cases. The mean ADA level was 18.3 IU (5-43) and the Cell count was predominantly lymphocytic. The pleural fluid cytology was positive for malignant cells in 9 cases (60%) and the pericardial effusion was present in 4 patients. Calculating the objective response rate, there was no patients with complete response, 3 (16, 7%) with partial response, 9 (50%) cases with Stable disease and 6 (33.2%) had progressive disease and the overall rate of survival was 10.9 months (range 8.2-13.6). The most common adverse effect observed was diarrhea reported in 5 cases (20%), followed by rash in 4 (16.7%) and mucositis in 4 (16.7%) of cases.
Conclusion: From the current study, it's likely that, its use may not rapidly move NSCLC from advanced late-stage disease to earlier and less-advanced stages, but it is observed as a well tolerated drug that shows significant survival advantage with minimal toxicity.

1. Introduction

Lung cancer, being one of the most common causes of cancer deaths, is not amenable to curative approaches. The majority of patients during their first diagnosis are being identified with advanced disease, especially Non-small cell lung cancer (NSCLC) with locally advanced inoperable or metastatic disease. NSCLC accounts for approximately 85% of all lung cancers.[1] Present treatment available is, platinum-based chemotherapy, which can improve the survival and overall quality of life of patients with locally advanced and metastatic lung cancer. Docetaxel monotherapy is a second line therapy available on failure of first line therapy, which reported improvement in the rate of resposnse, survival and quality of life. However, inspite of promising positive results, there are many limiting factors for Docetaxel such as high toxicities being reported, specifically occurrence of Grade 3-4 neutropenia reported in 85% population. Toxicities, adverse drug effects may render patients unable to accept cytotoxic chemotherapy resulting in poor therapeutic outcomes.[2,3]

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A therapeutic plateau has been reached with the current available chemotherapeutic regimens. There is a high demand of better treatment options in patients who relapse after first- and second-line chemotherapy. Consequently, targeted therapy gained a central place in current cancer therapeutics development with the discovery of the epidermal growth factor receptor (EGFR) found to be expressed or highly expressed in a variety of solid tumours.[4]

Molecular studies have uncovered the abnormal signal transduction in lung cancer cells and high EGFR expression, been associated with an unfavorable clinical outcome, making the receptor a promising target for anticancer therapy. Studies have shown that in patients with pulmonary adenocarcinoma who had a base-pair deletion at exon 19 (del746_A750) or a point mutation at exon 21 (L858R), the tumours were highly responsive to EGFR tyrosine kinase inhibitors, and subsequent studies of first-line therapy with these agents showed objective response rates of 54.8 to 81.6% and progression-free survival of 9.7 to 13.3 months among patients with these mutations including NSCLC.[5,6]

Gefitinib is the selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain, tyrosine kinase inactivates the anti-apoptotic Ras signal transduction cascade, and malignant cells are inhibited The target protein (EGFR) is a member of a family of receptors (ErbB) which includes Her1 (EGFR), Her2 (erb-B2), Her3 (erb-B3) and Her4 (Erb-B4). EGFR is over expressed in certain types of human cells in the lungs and breast cancers. This leads to inappropriate activation of the anti-apoptotic Ras signalling cascade, eventually leading to uncontrolled cell proliferation. Gefitinib is sensitive to non-small cell lung cancer mutation of EGFR tyrosine kinase domain also known as the adenocarcinoma, which is more prominent in the Asians. FDA approved Gefitinib in May 2003 for non-small cell lung cancer (NSCLC) as monotherapy in the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. Gefitinib has the following pharmacokinetic data; it has a half life of 6–49 hrs, oral bioavailability 59%, protein binding 90%, hepatic metabolism via CYP3A4 and final excretion through faecal.[7,8]

Gefitinib, a synthetic anilinoquinazoline, is an orally available inhibitor of the tyrosine kinase domain of the EGFR. But little is known about how its efficacy and safety profile in Indian patients. Hence, an attempt was made to find out the response of Gefitinib in terms of overall survival in advanced non small cell lung cancer and also assess the safety profile of the drug by a retrospective study in a tertiary care cent er and the regional cancer center of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) Puducherry.

2. Materials and Methods

2.1. Study setting

The research was focused to assess the safety and efficacy of Gefitinib in advanced non small cell lung cancer in Indian patients. The study location was a teaching cum research based super specialty & tertiary care hospital and a regional cancer centre of, Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) located at Puducherry, Tamil Nadu state in south India.

2.2. Study design

It is a retrospective study, done during the period of January 2009 to June 2012. After the approval from the Institutional Review Board of JIPMER, all clinical data were collected retrospectively from the Regional Cancer Centre of JIPMER in association with the Dept of Pulmonary Medicine of JIPMER.

2.3. Drug profile

Gefitinib 250 mg tablets manufactured by Cipla Ltd by the brand name "GEFTICIP", being supplied by the state government was prescribed for all the patients in the study. Duration of treatment is six months to one year depending on the patient's response and there is no fixed schedule. Every month the patients are intended to take medication for 21 days and 7 days w ere scheduled as wash out period.

Gefitinib is the selective inhibitor of epidermal growth factor receptor's (EGFR), tyrosine kinase domain, Gefitinib tyrosine kinase inactivates the anti-apoptotic Ras signal transduction cascade, and malignant cells are inhibited The target protein (EGFR) is a member of a family of receptors (ErbB) which includes Her1 (EGFR), Her2 (erb-B2), Her3 (erb-B3) and Her4 (Erb-B4). EGFR is over expressed in certain types of human cells in the lungs and breast cancers. This leads to inappropriate activation of the anti-apoptotic Ras signalling cascade, eventually leading to uncontrolled cell proliferation. Gefitinib is sensitive to non-small cell lung cancer mutation of EGFR tyrosine kinase domain also known as the adenocarcinoma, which is more prominent in the Asians. FDA approved Gefitinib in May 2003 for non-small cell lung cancer (NSCLC) as monotherapy in the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. Gefitinib has the following pharmacokinetic data; it has a half life of 6–49 hrs, oral bioavailability 59%, protein binding 90%, hepatic metabolism via CYP3A4 and fnal excretion through faecal.[7,8]

2.4. Inclusion criteria

Patients of age $\geq$ 18 years, who are finally diagnosed with stage IV advanced NSCLC and received Gefitinib therapy.

2.5. Exclusion criteria

Patients who have not received any previous therapy other than Gefitinib therapy.

Data collected from medical records of all patients admitted with NSCLC during the study period, January 2009 to June 2012 and received Gefitinib during treatment. Data collected includes, complete medical history, physical examination, laboratory tests (whole blood counts, urine analysis, liver and renal functions), electrocardiogram, thorax computed- tomography (CT) scans, ultrasonography of the abdomen and radionuclide bone scan. All the symptomatic affects before and after the initiation of Gefitinib treatment was recorded. Changes in key symptoms of lung cancer, both objective and subjective evidences were recorded before and during the treatment, are used for the assessment of the overall progress of the patient. Subjective evidences include, chest pain, cough, etc., and laboratory tests, CT scan etc., are objective evidences. EGFR mutation analysis of most important genes that is common in NSCLC (exon 18-20) is suggested to be done in all the patients.

The primary end point for the study was survival, and the secondary end points were progression free survival (PFS) and symptom relief. Improvements in the key symptoms related to lung cancer including, cough, dysponea, chest pain and laboratory investigations were recorded. Both subjective as well as objective changes were used in the assessment of NSCLC patient's response to the Gefitinib. All adverse events during the therapy were recorded. Analysis was done using SPSS software version 14 and survival analysis was calculated using Kaplan meier curve.

3. Results and Discussion

In the present observation and a retrospective study carried out in the Department of Pulmonary Medicine, JIPMER, Puducherry, we have observed a variation in response to the given Gefitinib therapy. During the study period only 25 patients were identified with NSCLC at the study setting, hence the sample size was limited. Table 1 indicates out of 25 cases, 13 (52%) were males and 12 (48%) were females. The age distribution at presentation was within a range of 34 to 70 and the mean age in males was 58.92 $\pm$ 14.59 and in females was 56.58 $\pm$ 13.68.

The NSCLC risk prediction analysis developed by Spitz and colleagues was used which incorporated multiple variables such as smoking history, exposure to environmental tobacco smoke, occupational exposures to dusts and to asbestos, and family history of cancer. In our study out of 25 patients, 7 patients (28%) had smoking history of 20.2 $\pm$ 9.3 mean pack years and all were male. The factors affecting survival have been studied and there was a significant difference in survival between male and female sex (males 7.2 months; females 10.9 months). There was no significant difference in survival between smoking status, duration of smoking, performance score or the age of the patient (Table 1).

The subjective and objective symptoms of NSCLC patients were recorded before initiation of Gefitinib therapy and the improvement of the same were used for assessment of the response. The symptoms include cough 19 (76%) patients, chest pain in 18 (72%); dysponea in 12 (48%); hemoptysis in 6 patients (24%); hoarseness in 4 patients (18%) and.SVC obstruction in 3 (12%) patients. And some of the patients also found with a past history of ATT intake in 3 cases (12%), diabetes mellitus in 5 (20%) and both diabetes mellitus with essential hypertension in 2 (8%) patients (Table 2). The NSCLC patients were also having pleural effusion in 15 (60%) patients, fluid was hemorrhagic in 13 cases and straw coloured in 2 cases. The mean ADA level was 18.3 IU (5 -43) and the Cell count was predominantly lymphocytic. The pleural fluid cytology was positive for malignant cells in 9 cases (60%) and the pericardial effusion was present in 4 patients.

From Table 3 indicates metastasis conditions in all the patients. All 25 (100%) patients are presented with adenocarcinoma with mediastinal nodal metastasis of lymph node, which was observed as the most common in NSCLC. Patients with cervical node, bilateral cervical nodes, contra lateral cervical node, axillary node and both axillary & cervical nodes were 8 (34%), 4 (16%), 23 (92%), 4 (17%), and 3 (13%) respectively. And patients with skeletal, liver, adrenal, brain, and contra lateral lung metastasis were 7 (30%), 3 (13%), 2 (8.6%), 2 (8.6%) and patients and the percentage respectively.

Table 4 depicts the over-all response rates, while no patient was reported with complete response, 3 (16, 7%) patients responded partially, 9 (50%) patients stable disease condition and 6 (33.2%) had progressive disease and the overall median survival was 10.9 months (range 8.2-13.6). Based on the willingness of the patients mutati on analysis is being performed in only 4 patients. Out of them, 2 patients showed mutations in Exon 18, 20, one patient in Exon 19 and one patient got a negative result (Table 5).

The most common adverse effect was diarrhea seen in 5 cases (20%), followed by rash in 4 (16.7%) and mucositis in 4 (16.7%) of cases and n one of the cases developed pneumonitis. 7 patients out of 25 reported death while on treatment and hence not able to recover the complete data. Only 2 patients in the study have brain metastasis and none of them received drugs such as warfarin, phenytoin ect., hence possible drug interactions were not observed in the study population.

Table 1: Results of distribution of the studied cases according to different parameters in NSCLC patients

S.no	Observation		Assessment
1.	Total number of patients		25(100%)
2.	Males		13 (52%)
3.	Females		12 (48%)
4.	Mean age	Males	58.92 ± 14.59
		Females	56.58 ± 13.68
6.	Non-smokers		18 (72%)
7.	Smokers		7(28%)
8.	Mean smoking (Yrs)		20.2 ± 9.3
9.	Median survival (months)		10.9 (Range 8.2-13.6)
10.	Median survival	Male	7.2 (months)
		Female	10.9 (months)

Table 2: Results of distribution in the observation of disease / disorders in NSCLC patients

S.no	Symptoms / Disease / Disorders		Number of patients and its %
1.	Cough		19 (76%)
2.	Chest pain		18 (72%)
3.	Dysponea		12 (48%);
4.	Hemoptysis		6 (24%);
5.	Hoarseness		4 (18%).
6.	Svc Obstruction		3 (12%)
7.	Antitubercular therapy		3 (12%).
8.	Diabetes mellitus		5 (20%)
9.	Both diabetes mellitus and essential hypertension		2 (8%)
10.	Pleural effusion15 (60%)	Hemorrhagic colour fluid	13 (86.6%)
		Straw colour fluid	2 (13.4%)
12.	Adenosine diaminase level		18.3 IU (5-43).
13.	Pleural fluid cytology (positive for malignant)		9 (36%).
14.	Pericardial effusion		4 (16%).

Table 3: Results of distribution in the observation of histology by metastasis condition in NSCLC patients

S.no	Histology by metastasis condition	Number of patients and its %
1.	Adenocarcinoma and metastasis of lymph node	25 (100%)
2.	Mediastinal nodal metastasis	25 (100%)
3.	Cervical node	8 (34%)
4.	Bilateral cervical nodes	4 (16%)
5.	Contra lateral cervical node	23 (92%)
6.	Axillary node	4 (17%)
7.	Both axillary and cervical node	3 (13%)
8.	Skeletal metastasis	7 (30%)
9.	Liver metastasis	3 (13%)
10.	Adrenal metastasis	2 (8.6%)
11.	Brain metastasis	2 (8.6%)
12.	Contra lateral lung metastasis	6 (24%)

Table 4: Results of distribution in the observation and the response assessment of disease status in NSCLC patients

S. no	Assessment of disease status	No. of Patients (n=18)	Percentage
1.	Complete Response (CR)	0	0%
2.	Partial response (PR)	3	16.7%
3.	Objective response (OR) (CR+PR)	3	16.7%
4.	Stable Disease (SD)	9	50%
5.	Progressive disease (PD)	6	33.2%
6.	Details not available**	7	33.2%

Details not available ** not accounted for above response assessment

Table 5: Results of distribution in the observation of mutation analysis in NSCLC patients

S.no	Mutation analysisNo. of Patients (n=04)	Number of patients and its %
1.	Exon 18,20	2 (50%)
2.	Exon 19.	1 (25%)
3.	Negative	1 (25%)

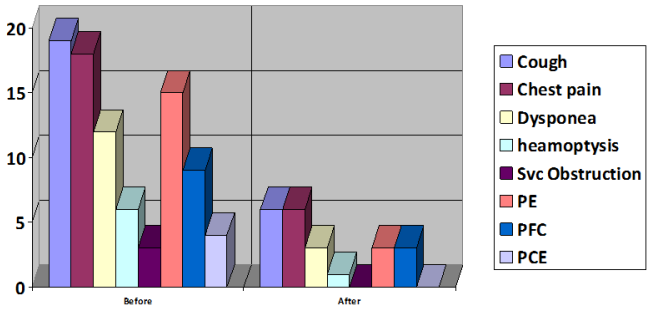

Fig. 1: NSCLC patients responded after the initiation of Gefitinib treatment

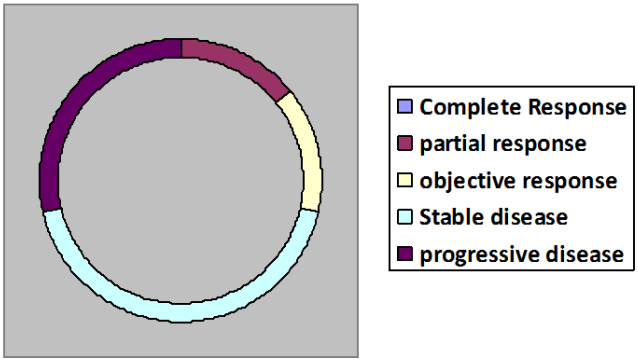

Fig. 2: Results of distribution in the observation and the response assessment of disease status in NSCLC patients

4. Discussion

In our study median survival was 10.9 month, which coincides with the 10.4 survival in a multi -centered study conducted at Japan and comparable to ISEL study, the median survival 9.5 months in patients with Asian origin and the median survival rate was high in females.[9,10]The objective response was 16.7% in our study which coincided with a study conducted over Indian patients in whom the objective response was 14% and ORR of 13.5% a higher ORR of 23%.[11,12] No significant difference in survival and response rate between smoking statuses, duration of smoking. Significant differences in performance score related to the age of the patient couldn't be identified due to smaller sample size. Overall results of the study coincided with a study done on efficacy if Gefitinib at Bulgaria.[13] The adverse effect seen in our series were mainly skin rashes and diarrhea, most of which were grades 1 or 2 and were well tolerated. Incidence of skin rash and diarrhoea were much less compared to other studies that ranged between 25- 57%. No incidence of interstitial lung disease in our study.[14] EGFR and ALK are 2 of the most important genes that get commonly mutated in NSCLC, adenocarcinoma patients which we have targeted therapies that can work very well. Exon 18-20 analysis directs in appropriate drug selection and better outcomes.[15]

However there are certain limitations in the study like, small sample size due to less frequency of NSCLC patients, and EGFR Mutations not being performed for all patients due to economic burden and lack of expertise in testing fine-needle aspiration cytopathology (FNAC) specimens.

5. Conclusion

The present study demonstrates, Gefitinib appear to be one of better treatment option for advanced NSCLC. However, from the results of current study, it's likely that, its use may not rapidly move NSCLC from advanced late-stage disease to earlier and less-advanced stages, but it is observed as a well tolerated drug that shows significant survival

advantage with minimal toxicity population particularly of Asian origin. Our data gives ground for recommendation of Gefitinib to be included as first or subsequent line of therapy in the NSCLC treatment schedules. However due to certain limitations in our study we would recommend further research to be performed with a bigger sample size and analysis of EGFR Mutations is strongly recommend.

6. Source of funding

None.

7. Conflict of interest

None.

8. Acknowledgement

None.

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