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Survival of gefitinib treated advanced non-small cell lung cancer patients harbouring EGFR mutations

Abstract

Context: The addition of gefitinib to first-line chemotherapy treatment in EGFR mutated patients maylead to improvement in overall survival in advanced non-small cell lung cancer (NSCLC).

Aims: This study aimed to investigate the relationship of epidermal growth factor receptor (EGFR) mutations with clinical features of non-small cell lung cancer patients and to determine overall survival (OS) of EGFR mutated adult NSCLC patients after gefitinib treatment.

Settings and design: A retrospective observational study was done for 93 advanced NSCLC adult Malaysian patients at Radiotherapy and Oncology Clinic, Hospital Kuala Lumpur, Malaysia.

Methods and material: Demographic and medical data were recorded from the patient's medical record file.Statistical analysis used: Statistical analysis was performed using SPSS version 21.0. Kaplan-Meier, log-rank test andCox regression analysis have been performed.

Results: There were 93 adult NSCLC Malaysian patients who were examined for EGFR gene mutations. Approximately 35.48% (33/93) of the patients were detected to have EGFRmutations in their tumour tissue DNA. EGFR mutations were commonly observed in females,adenocarcinoma, non-smokers, stage IV NSCLC and patients taking first-line gefitinib treatment. Positive EGFR status of adult NSCLC patients was independently associated with intake of gefitinib therapy. There were 19 patients who received 250 mg/day gefitinib as the first-line treatment. The patients with positive EGFR status had increased median survivaltime as compared than those with negative EGFR status (834.863 vs 246 days).

Conclusions: Advanced NSCLC patients with mutated EGFR had a longer median survival time after first- line gefitinib treatment. EGFR mutation is an independent prognostic factor for adult NSCLC patients.

Keywords: non-small cell lung cancer, EGFR, survival, gefitinib

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Key messages

Adult Malaysian patients suffering from advanced Non-small cell lung cancer (NSCLC) with Positive EGFR status when underwent first line targeted therapy (Gefitinib) had improved survival.

Introduction

Lung cancer is a malignant tumour in the tissue of one or both of the lungs.[1] Lung cancer is the most common malignancy and leading cause of cancer-related deaths worldwide, including Malaysia. At diagnosis, 60 % of patients had locally advanced (stage IIIB) or metastatic (stage IV) non-small cell cancer (NSCLC) while only 12% of patients had surgically resected stage I and stage II NSCLC.[2] In about 40 % to 80 % of NSCLC cases, epidermal growth factor receptor-tyrosine kinase (EGFR- TK) was over-expressed.[3] This over-expression of EGFR-TK stimulated cell proliferation, survival, migration and angiogenesis.[4] Clinically, EGFR mutations showed association with patients' characteristics including female, non-smoker and adenocarcinoma histology.[5] Gefitinib, a small molecular tyrosine kinase inhibitor (TKI) disrupts EGFR-TK activity by binding the adenine tyrosine phosphate (ATP) pocket within EGFR intracellular TK domain.[6] Somatic mutations in the EGFR correlated with improved survival in patients with NSCLC treated with gefitinib.[7] This retrospective study aimed to determine overall survival in gefitinib treated advanced NSCLC patients having EGFR mutation and to ascertain the relationship of EGFR mutation with clinical predictors such as gender, smoking status and type of histology of NSCLC, stage of NSCLC and gefitinib therapy.

Subjects and methods

Patients

Ninety three adult Malaysian patients (≥18 years old) with histological confirmation of locally advanced or metastatic NSCLC, from January 2009 through December 2012 in the Department of Radiotherapy and Oncology at Hospital Kuala Lumpur (HKL), Malaysia, were reviewed. The study was approved by Research Management Institute (RMI), UiTM, Shah Alam (600-RMI (5/1/6) and the Medical Research and Ethics Committee (MREC) via National Medical Research Registry (NMRR), Ministry of Health (MOH), Malaysia (NMRR-14-1010-20612 (IIR)). All patients were examined for age, gender, smoking status and EGFR mutation. EGFR status was collected at the initial diagnosis of the disease. NSCLC was staged using the TNM staging system of American Joint Committee on Cancer.[8] NSCLC histology was defined according to the World Health Organization (WHO) pathology classification.[9] Out of 93

patients, 19 patients received 250 mg/day gefitinib as the first- line therapy. Overall survival (OS) was calculated as the time from the beginning of chemotherapy to death or date of last follow-up. OS was calculated for patients undergoing gefitinib therapy.

Statistical analysis

The relationship between EGFR mutation and patient characteristics was analyzed by Pearson's χ^2 test.Potential prognostic factors were incorporated in binary logistic regression models to identify factors that might independently predict EGFR mutation. Survival curves were plotted by Kaplan-Meier survival test and the differences in survival curves were compared using log-rank test. For multivariateanalysis of survival, Cox proportional hazard regression model was performed to identify the most important independent prognostic factor predicting OS. Two-sided p-values less than 0.05 were considered significant. All analysis were performed using the SPSS software version 21.0.

Results

Patients' characteristics

Table 1 shows clinical characteristics of 93 adult NSCLC patients. The majority of patients (78.49 %) fall in age group of 41-64 years old. Fifty eight patients (62.36%) were male and 35 (37.63%) were female. Adenocarcinoma was the predominant histological type of NSCLC (79.56%). Thirty nine patients (41.93%) were non-smokers, 30 patients (32.25%) were ex-smokers while 24 patients (25.8%) were smokers. The majority of patients (72%) had stage IV NSCLC. Gefitinib was the first- line therapy in 19 patients (20.43%). EGFR gene mutations were found in 33 out of 93 patients (35.48%).

Table 1 Patient characteristics (n = 93) and EGFR mutation

Variable	No	EGFR mutation n (%)	Univariate analysis p	Multivariate analysis	
				Exp (B)	P
Age (years old)					
18 - 40	11	5 (45.4)			
41 - 64	73	25 (34.2)	0.762	1.931	0.282
≥65	9	3 (33.3)			
Gender					
Male	58	13 (22.4)	0.001*	0.343	0.132
Female	35	20 (57.1)			
Histopathology					
Adenocarcinoma	74	32 (43.2)	0.002*	0.111	0.073
Squamous carcinoma	19	1 (11.1)			
Smoking status					
Smoker	24	5 (20.8)			
Non-smoker	39	22 (56.4)	0.002*	1.33	0.754
Ex-smoker	30	6 (20.0)			
NSCLC stage					
IIIA	12	0 (0)			
IIIB	14	2 (14.2)	0.002*	2.471	0.247
IV	67	31 (46.2)			
Gefitinib therapy					
No	74	16 (21.6)	0.000*	20.643	0.000*
Yes	19	17 (89.4)			

*p<0.05

Relationship of EGFR mutations with clinical features

The relationship between the EGFR status and several important parameters was found using Pearson's χ^2 test. Results found that the EGFR gene mutations were frequently presented in females, adenocarcinoma, non-smokers, stage IV NSCLC and patients who underwent gefitinib therapy. Multivariate analysis showed that patients on gefitinib therapy (odds ratio 20.643, *P 0.000*) were independently associated with positive EGFR status (Table 1).

Impact of EGFR gene mutation on overall survival after gefitinib treatment

The OS for 19 adult gefitinib treated NSCLC patients was 802.498 days (95% C.I, 621.679 - 983.316 days). The median survival time

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for patients with positive EGFR status was 834.863 days (95% C.I, 656.494 - 1013.232) whereas 246 days (95% C.I 76.917 - 415.083) for patients with negative EGFR status. The difference in the survival curves of positive and negative EGFR status was insignificant (*P 0.091*, by log-rank test). The cumulative survival probability in survival curve appeared higher for positive EGFR status indicating that patients having positive EGFR status significantly extended the time until death or more likely to survive as compared to patients having negative EGFR status (Figure 1).

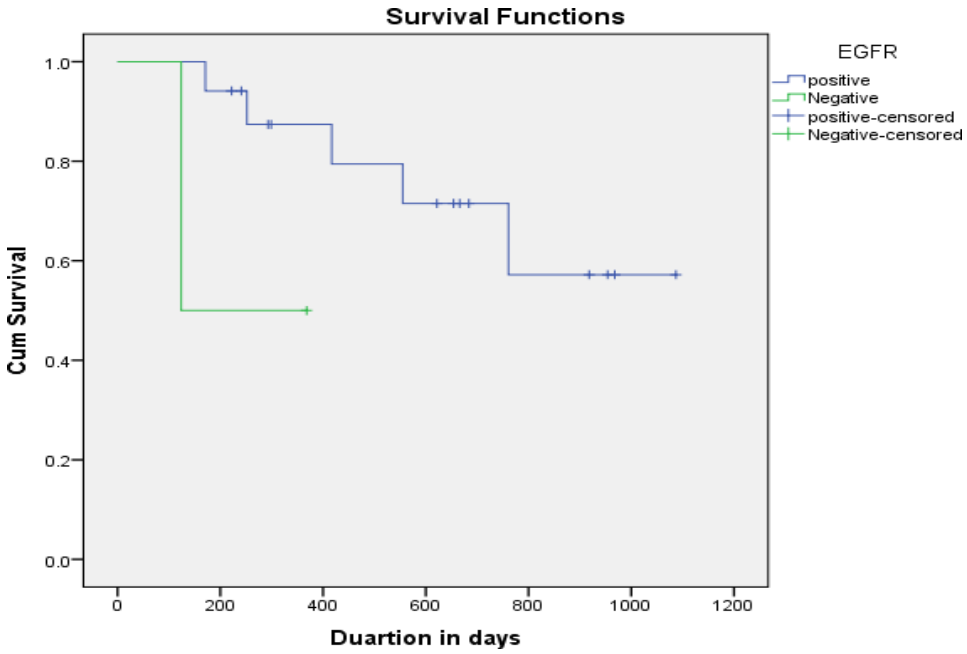

Figure 1 Kaplan-Meier survival curve for EGFR status.

Discussion

The results of present study showed that EGFR mutations were frequently presented among females, lung adenocarcinoma and non-smokers. Similar results were also reported by[10-12] that EGFR mutations were significantly presented in females versus males, adenocarcinoma versus squamous cell carcinoma, and non-smokers versus smokers or ex-smokers. Moreover, two groups of researchers in Boston and in New York reported that activating mutations of the EGFR gene were present in a subset of NSCLC, and that tumors with EGFR mutations are highly sensitive to EGFR TKI.[13,14] A review article by Mitsudomi & Yatabe (2007) similarly reported that EGFR mutations are predominantly found in females, non-smoking and adenocarcinoma patients of East Asian origin.[15]

The prevalence of EGFR-mutant NSCLC in appreciably higher females than in males. It is hypothesized that these disparate frequencies may be attributable to underlying genetic modifiers. Given that EGFR-mutated lung tumors occur more frequently in women, it might be due to the possibility that estrogen levels might contribute to the differences in EGFR mutation frequency Estrogen levels are maintained by a balance in estrogen biosynthesis and metabolism. These complex biochemical processes are regulated by a number of genes, some of which encode allozymatic variants with variable functional activities leading to inter-individual variation in estrogen levels. Altered estrogen levels could enhance the development of a form of lung cancer that is marked by the subsequent somatic acquisition of EGFR mutations. Alternatively, estrogen effects could directly modulate the functional properties of mutant EGFRs to enhance their tumorigenic properties.[16] The current study reported that female sex and never smokers showed higher prevalence for EGFR mutations. These current study findings were also consistent to the systemic review of ten relevant studies conducted in countries such as Lebanon, Egypt, Turkey, Saudi Arabia, Qatar and Morocco involving total of 1215 patients with NSCLC in the Middle East and African regions. Based on the male-female distribution of patients with NSCLC, 829 (68.2%) were male and 386 (31.8%) were females. Despite that, all ten studies reported higher frequency of EGFR mutation in female versus male NSCLC patients. The correlative analysis of all cases also showed that the prevalence of EGFR mutation was higher among females versus male patients (OR=1.87, 95% CI, 1.44-2.42).[17] Likewise a record of 35 patients with NSCLC retrieved from a hospital in Taipei, Taiwan comprising 18 female patients and 17 male patients. EGFR mutations were more frequent in women, 13 out of 18 patients (72%) than in men, 4 out of 17 patients (23%) (P=0.009].[18]

The efficacy of gefitinib for patients with non-adenocarcinoma NSCLC harboring EGFR mutations is still unclear because of low non-adenocarcinoma histological prevalence and only a small percentage of patients enrolled in the clinical trials to evaluate the efficacy of gefitinib for tumors harboring EGFR mutations were non-adenocarcinoma NSCLC. EGFR mutations can be detected in 30% of adenocarcinoma patients, however they are detected in only 2% of non-adenocarcinoma patients.[15] A pooled analysis conducted to extract and compile the data from the 15 published reports in the year 2005-2009 in the countries such as Japan, China, Korea, Taiwan, Greece and Switzerland to clarify the efficacy of gefitinib for non-adenocarcinoma NSCLC patients harboring EGFR mutations. This analysis included thirty-three patients with advanced or recurrent non-adenocarcinoma NSCLC who had EGFR mutations and were treated with gefitinib. On the other hand, among 199 adenocarcinoma

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patients, 167 patients (84%) had sensitive EGFR mutations. The pooled analysis of 15 published reports found that the difference between non-adenocarcinoma NSCLC and adenocarcinoma NSLC in the proportion of patients harboring EGFR mutations was statistically significant in the v2 test (P=0.0059). The response rate of gefitinib in adenocarcinoma versus non-adenocarcinoma NSCLC patients harboring EGFR mutation was also found statistically significant (P=0.000028).[19]

In Asian countries, about 60–80% of female patients with lung cancer are never smokers. Similar trend has been observed in the present study findings. It seems that in non-smokers patients with NSCLC, the EGFR signaling pathway can be selectively activated. The possible explanation could be that never-smokers have a higher rate of activating EGFR-mutations in exons 18–21. Tumors harboring these mutations are dependent on the EGFR signaling pathway for their survival and proliferation.[20] Also, similar results were testified in the meta-analysis of twenty six studies involving 3,688 NSCLC patients. The analysis showed that the incidence of EGFR mutations in NSCLC differs according to smoking status. The odds ratio for the EGFR mutation in non-smokers relative to smokers was 4.829 (95% C.I: 3.598–6.482; P < 0.001).[21]

In the current study, analysis of OS showed that patients with EGFR mutation exhibited longer OS as compared to patients without EGFR mutation, which were similar to another study that also observed prolonged survival among patients having EGFR mutation.[22] In view of the substantial survival benefit of treatment with gefitinib in patients with EGFR mutation, all NSCLC patients; especially those with adenocarcinoma, female and non-smokers are highly suggested to be tested for EGFR mutational status, and for patients with EGFR mutation, gefitinib must be considered as the treatment choice.

In summary, these predictive factors and patient characteristics can assist clinicians in assessing the probability of EGFR mutations, and sensitivity to gefitinib in patients with NSCLC using histological type and smoking history. Lung cancer in never smokers is likely to be an assemblage of molecularly defined subsets which would be a good candidate for personalized diagnostic and therapeutic approaches.

Conclusion

Patients with advanced NSCLC treated by gefitinib and bearing EGFR mutations have significantly better overall survival. EGFR status is an independent prognostic factor for advanced NSCLC.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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