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Original Article

GEFITINIB IN PRETREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): ANALYSIS OF EFFICACY

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ABSTRACT

Introduction: To evaluate the efficacy and tolerability of gefitinib (Iressa (ZD 1839); Astrazeneca, Willington, DE), a novel epidermal growth factor receptor tyrosine kinase inhibitor, in patients with pretreated advanced non-small cell lung cancer (NSCLC).

Materials and Methods: Patients with pretreated advanced NSCLC received gefitinib at a daily dose of 250 mg orally until disease progression. Patients included in this study all had measurable, locally advanced or metastatic NSCLC, pretreated with at least one line of platinum based chemotherapy.

Results: From June 2004 to February 2006, 18 consecutive patients were enrolled onto the study, the overall disease control rate was 66.7% (partial response (PR), 11.1%; stable disease (SD) 55.6%), median TTP was 2.9 months (95% confidence interval 2.3 to 3.2 months) and median PFS was 3 months (95% confidence interval 2.4 to 3.6 months), median OS from start of gefitinib was 8.4 months (95% confidence interval 5 to 11.8 months). Univariete analysis of prognostic factors revealed that, response to gefitinib and longer duration of gefitinib treatment showed a better PFS, while only longer duration of gefitinib treatment showed a better OS.

Conclusion: Gefitinib showed clinically meaningful anti-tumor activity and provided symptom relief as second and third line treatment in pre-treated advanced NSCLC. Gefitinib is tolerable and had favorable adverse events.

Key Words: Gefitinib in pretreated, advanced, non-small, cell Lung, cancer (NSCLC).

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INTRODUCTION

Lung cancer is the most common cause of cancer deaths in both men and women worldwide[1]. Despite advances in treatment, such as combination chemotherapy and chemo-radiation, survival has improved very little over the past few decades[2]. A meta-analysis demonstrated that the median survival time for patients with advanced disease receiving cisplatin-based chemotherapy is around 6 months[3]. The five-year survival rate for all stages is less than 15%[4]. Prognosis is particularly poor for patients who have progressive disease following chemotherapy; for Non-Small Cell Lung Cancer (NSCLC) patients receiving best supportive care (BSC) after 1 or more prior chemotherapy regimen, median survival time is just 16 weeks, with 1- year survival rate of 16%[3-5]. It has become generally accepted that systemic chemotherapy is beneficial in terms of improved survival and quality of life (QOL) in those with advanced NSCLC[3-6]. As more patients receive 1st line chemotherapy, the need for effective second-line therapy is increasing. Currently, docetaxel and pemetrexed, having demonstrated survival benefits over BSC for patients who have been failed after previous platinum-based chemotherapy[7,8].

Gefitinib (ZD 1839, Iressa, Astra Zeneca, London, United Kingdom)is an orally active, selective EGFR-TKI that demonstrated antitumor activity against a variety of human cancer cell lines expressing EGFR, including ovarian, breast and colon and it is active in a range of xenograft models, including colon, prostate and NSCLC[9-11]. Phase I studies evaluating the safety and tolerability of gefitinib identified rash and diarrhea as unique and dose related toxicities. Notably, an 11% response rate (RR) has been observed among the 100 NSCLC patients enrolled onto these trials[11]. In phase II trial gefitinib showed a RR of 16% with overall disease control rate was 58.7%[12]. In phase III trial In the Iressa Survival Evaluation in Lung Cancer (ISEL), gefitinib failed to show survival benefit over BSC, but in, planned subset analyses in never smokers and those of Asian ethnicity, gefitinib showed significantly longer survival compared to placebo[13,14].

In current trial we planned to investigate the use of gefitinib in patients with pretreated advanced or metastatic NSCLC.

MATERIALS AND METHODS

The 18 patients included in our study were pathologically proven NSCLC in King Faisal Specialist Hospital and Research Center (KFSHRC) during the period 2004-2007.

All patients included in this study had measurable, locally advanced or metastatic NSCLC, pretreated with at least one line of platinum based chemotherapy. Patients with locally advanced disease were considered eligible if they were pretreated with front line platinum-based chemotherapy and ± radiation. Patients were older than 18 years of age and had an Eastern cooperative group (ECOG) performance status of 2 or less, a life expectancy of at least 12 weeks, EGFR expression by immunohistochemistry, a normal complete blood picture with accepted hemoglobin of 9gram/liter or more, bilirubin less than 1.5 –fold of the upper limit of normal (ULN), ALT or AST less than 3-fold of the ULN and normal renal profile. Patients were ineligible if they had evidence of prior/concurrent malignancy. The study was conducted after the approval from our institutional review board.

In this study, consecutive patients with pretreated NSCLC received gefitinib at a daily dose of 250 mg administered until disease progression. Gefitinib was taken once daily in the morning, at approximately the same time each day. Baseline evaluation included a complete history and physical examination, complete blood cell count and serum chemistry analysis, urinalysis, chest x ray and total-body computed tomography scan. Other imaging modalities, such as magnetic resonance imaging and bone scintigraphy, were performed according to specific clinical indications. All baseline imaging procedures were performed within 4 weeks before study entry. Biochemical screening was performed every 4 weeks, assessing renal hepatic and electrolyte profiles. Toxic effects were assessed every 28 days according to the National Cancer Institute common toxicity criteria version 2. Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (RECIST)[15]. Tumor response was assessed by computed tomography scan every 2 months, with a confirmatory evaluation to be repeated in responding patients at least 4 weeks after the initial determination of response.

Statistical Analysis:

All statistics were Performed with SPSS soft ware (Statistical Package for Social Science, Version 14). Description statistics was presented as number and percentage (frequency distribution). Fisher's exact test was used to compare the results for significance with p value of <0.05 was considered as significant results. Over all survival (OS) was defined as time from date of start of gefitinib to date of last follow up or death. Progression free survival (PFS) was defined as time from date of start of gefitinib treatment to date of progression or death. Time to progression (TTP) is defined as time from date of achieving CR or PR to date of recurrence. Cox regression analysis was used for univariate and multivariate analysis of factors affecting survival, with a p-value of < 0.05 was used for significance. The Kaplan-Meire method was used to determine survival curves and the log-rank test was used to compare survival in different populations, log-rank P value was used with a significance of <0.05.

RESULTS

From June 2004 to February 2007, 18 patients with previously treated NSCLC patients were treated with gefitinib in KFSHRC. Characteristics of the patients are listed in (Table 1). The majority of the patients were male (72.2%), with a mean age of 51.2 years (range, 36 to 68 years) and with ECOG performance status (0 to 1 in 72.2%). Histology was adenocarcinoma in 77.8% of patients (one was broncho-alveolar) and squamous cell carcinoma in 22.2%. All patients included in the trial had received platinum-based chemotherapy and 33.3% of them had received two lines of chemotherapy including platinum, taxanes and gemcitabine. All stage IIIB patients were pretreated with mediastinal radiotherapy as part of a chemo radiation integrated approach.

Table 1: Patients Characteristics (18 Patients).

Factor		No	%
Age			
	Mean	51.22 +/- 8.822	
	Range	38-68	
Sex			
	Male	13	72.2
	Female	5	27.8
Smoking			
	Yes	13	72.2
	No	3	16.7
	Unknown	2	11.1
Histology			
	Adenocarcinoma	14	77.8
	Squamous	4	22.2
Stage			
	IIIB	7	38.9
	IV	11	61.1
ECOG PS			
	1	13	72.2
	2	5	27.8
Prev. Chemotherapy			
	1, including platinum	12	66.7
	2, including platinum and taxanes	6	33.3

Response to treatment was evaluated in all 18 patients. Gefitinib was administered orally, with median treatment duration of 3 months (range 2-15 months). We observed 2 partial response (PRs; 11.1%) and 10 stable diseases (SDs; 55.6%), for an overall disease control rate of 66.7% (95% confidence interval 59.2% to 74.3%)

(Table 2). For the entire population, median TTP was 2.9 months (95% confidence interval 2.3 to 3.2 months) and median PFS was 3 months (95% confidence interval 2.4 to 3.6 months) (Figure 1), median OS from start of gefitinib was 8.4 months (95% confidence interval 5 to 11.8 months) (Figure 2). Univariate analysis of prognostic factor revealed that only duration of gefitinib treatment as a constant factor showed a significant impact on OS. There was no impact on OS from the following factors, PS, gender, smoking, histology and stage, response to primary treatment and response to gefitinib. On the other hand both response to gefitinib and duration of treatment of gefitinib showed a significant impact on PFS, adenocarcinoma subtype and PS 1 showed trend to have an impact on PFS, while other factors including gender, smoking, stage and response to 1st line treatment didn't show impact on PFS (Table 3).

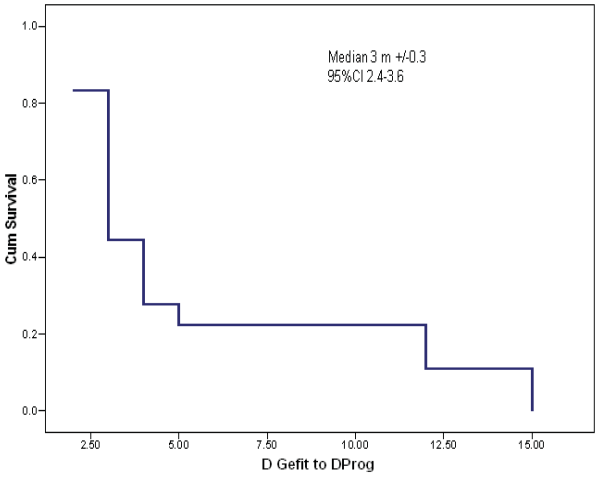

Figure 1: Progression Free Survival (18 Patients).

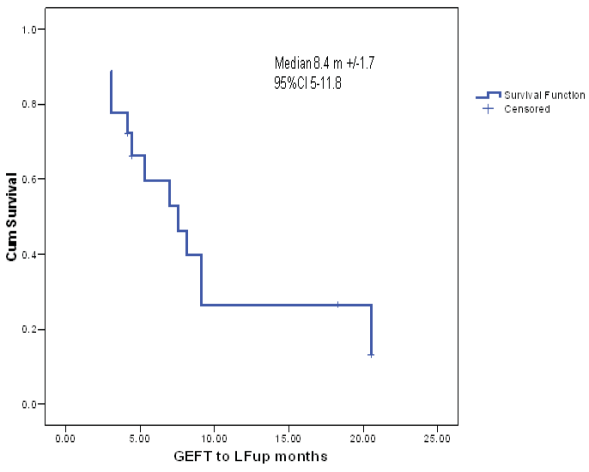

Figure 2: Overall Survival After Start of Gefitinib (18 Patients).

Table 2: Response to Gefitinib (18 Patients).

Response	No.	%
CR	0	0
PR	2	11.1
SD	10	55.6
Disease Control Rate	12	66.7
PD	6	33.3

Table 3: Univariete Analysis of Prognostic Factors.

Factor		PFS		OS	
		Median	P	Median	p
PS					
	1	5	0.067	18.6	0.36
	2	2.9		22.5	
Gender					
	Male	3	0.83	18.6	0.65
	Female	3		22.5	
Smoking					
	Yes	3	0.34	20.1	0.54
	No	3		22.5	
Histology					
	Adenocarcinoma	4	0.079	18.6	0.23
	Squamous	3		23.1	
Stage					
	IIIB	4	0.41	23.1	0.32
	IV	2.9		18.6	
Response 1st line			0.31		0.25
Response Gefitinib			0.001		0.13
Duration Gefitinib			0.00001		0.035

All 18 patients were evaluated for toxicity. Side effects were generally mild and considered of grade 2 and 3 skin toxicities, reported in 33.3% of patients and pruritus in 11.1% of patients, grade 2 and 3 diarrhea reported in 16.7% of patients and nausea and vomiting reported in 11.1% of patients (Table 4). Symptom outcome was observed in all 18 patients and symptomatic improvement and symptom stabilization were observed in 24.7% and 49% of patients, respectively.

Table 4: Grade 2 and 3 Toxicities (18 Patients).

Toxicity		No.	%
Skin			
	Rash	6	33.3
	Pruritus	2	11.1
GIT			
	Diarrhea	3	16.7
	Anorexia	1	0.6
	Nausea/Vomiting	2	11.1
Metabolic			
	ALT	2	11.1
	AST	1	0.6
Whole Body			
	Asthenia	1	0.6

DISCUSSION

Treatment of patients with advanced non-small cell lung cancer (NSCLC) who have relapsed after an initial chemotherapy regimen for advanced disease is a difficult problem. Small molecule epidermal growth factor receptor (EGFR) inhibitors (gefitinib, erlotinib) were initially developed for use as second-line therapy after failure with a cytotoxic chemotherapy regimen[12,16].

This open label pilot study conducted in King Faisal specialist hospital and research center evaluated the efficacy and safety of daily oral dose of 250 mg of gefitinib in patients with locally advanced or metastatic NSCLC who had previously received either one or more chemotherapy regimens (at least one of them contained platinum). This study demonstrated 2 partial response (PRs; 11.1%) and 10 stable diseases (SDs; 55.6%), for an overall disease control rate of 66.7% (95% confidence interval 59.2% to 74.3%) with no CR reported in our study. These results are similar to those reported in multiple phase II trials; Cappuzzo et al.[12] reported 15.9% partial responses and 42.8% stable disease, for an overall disease control rate of 58.7%. Another phase II trial randomizing 2 doses of gefitinib (250 mg versus 500mg), reported 17.5% partial responses and 35.9% stable disease, for an overall disease control rate of 53.4%[16]. A third phase II trial showed a lower response to gefitinib, of 172 patients evaluable for efficacy, 7 (4.1%; 95% CI; 1.7–8.2%) experienced a partial response (PR); 60 patients (34.9%) had stable disease (SD) as their best response[17]. The results in current trial compared to the previously mentioned phase II trials demonstrated that the current trial had more patients with stable disease.

After a median follow-up of 11.2 months, the median TTP was 2.9 months (95% confidence interval 2.3 to 3.2 months) and median PFS was 3 months (95% confidence interval 2.4 to 3.6 months), median OS from start of gefitinib was 8.4 months (95% confidence interval 5 to 11.8 months). These survival data are higher than that reported in most of the phase II trials; Cappuzzo et al[12] reported median TTP of 3.3 months and median OS of 4.1 months which is lower than that reported in current trial (8.4 months). Fukuoka et al.[16] reported survival data equivalent to ours in gefitinib dose of 250 mg with median PFS of 2.7 months and median OS 7.6 months. In the Iressa Survival Evaluation in Lung Cancer (ISEL) trial, 1692 patients were randomly assigned to gefitinib or placebo[13]. All patients had failed prior systemic chemotherapy and were not considered candidates for additional chemotherapy. The trial failed to demonstrate a statistically significant improvement in median survival gefitinib (5.6 versus 5.1 months with placebo), even when the analysis was restricted to patients with adenocarcinoma (6.3 versus 5.4 months). In contrast, planned subset analyses in never-smokers and those of Asian ethnicity showed significantly longer survival compared to placebo (8.9 versus 6.1 months and 9.5 versus 5.5 months, respectively)[13,14]. In the Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) trial, 1466 patients were randomly assigned to gefitinib or docetaxel, which has been a standard drug use for second-line chemotherapy[18]. Survival in patients treated with gefitinib was not statistically significant different from docetaxel (median 7.6 versus 8.0 months, hazard ratio 1.02, 95% CI 0.91-1.15). These results fulfilled the predefined conditions for noninferiority. Similar findings were noted in a smaller Japanese trial comparing gefitinib and docetaxel[19]. There were no statistically significant differences in progression-free or overall survival. However, the trial was not designed to demonstrate noninferiority and a clinically significant inferiority to docetaxel could not be excluded[20]. Gefitinib may prolong survival in Asian patients with adenocarcinoma and characteristic EGFR mutations[21]. In a historical comparison of 330 Asian patients with advanced adenocarcinoma before and after the commercial introduction of gefitinib, the median survival was significantly increased in patients with an EGFR mutation once gefitinib was available (27.2 versus 13.6 months prior to its commercialization). In contrast, survival was not significantly increased in those without an EGFR mutation (13.2 versus 10.4 months). Better outcomes in Asian patients were also noted in the ISEL trial[14]. On the other hand erlotinib, which is the second EGFR TKI, showed a survival benefit over best supportive care[22]. In this trial, 731 such patients were randomly assigned to treatment with erlotinib or placebo.The following significant benefits were noted with erlotinib; an increase in the objective response rate (9 versus <1 percent with placebo), an increase in overall survival (6.7 versus 4.7 months).

Although the overall objective response rate in previously treated patients given EGFR inhibitors is low, many patients achieve stable disease that can be associated with a survival benefit[23]. Multiple phase II studies[17,24-26] and a phase III randomized trial[22] identified a series of clinical parameters associated with clinical responsiveness. These include the following; adenocarcinoma including bronchoalveolar, women, nonsmokers and Asians.

Many of these clinical parameters may be mediated through differences in the frequency of EGFR and k-Ras mutations. As an example, EGFR mutations are more common in those with adenocarcinoma and in Asian populations and k-Ras mutations are less frequent in both of these groups[27,28]. However, these factors are not absolute. Even for poor prognosis subsets (i.e., men, non-adenocarcinoma histology, non-Asian ethnicity and current or former smokers), there was a reduction in the hazard ratio for death among patients treated with erlotinib. The adverse effect of active cigarette smoking may be mediated in part by increased metabolism of erlotinib thereby decreasing exposure to the drug[29]. After a single dose of 150 mg, the total drug exposure (as reflected by the area under the curve) was 2.8-fold lower in smokers than in nonsmokers at a comparable dose. Although a single dose of 300 mg in smokers yields a plasma concentration similar to that at 150 mg in nonsmokers without an increase in toxicity, additional study is required to determine whether this dose escalation has any therapeutic value[30].

Clinical correlation studies have found that EGFR protein over expression, gene amplification and specific activating mutations in the TK domain of the EGFR

(exon 19 deletions, L858R point mutation in exon 21) are associated with increased responsiveness to either gefitinib or erlotinib[31,32]. The impact of EGFR mutations on prognosis may be modified by the presence of nuclear expression of estrogen receptor beta (ER-beta)[33]. Multiple studies have shown that ER-beta is expressed in more than one-half of patients with NSCLC[34,35]. In a Japanese study of 447 patients with resected adenocarcinoma of the lung, ER-beta expression was significantly more frequent in those with an EGFR mutation than in those with EGFR wild-type tumors (70 versus 37 percent). Furthermore, those with an EGFR mutation and strong ER-beta expression had a significantly better prognosis than those with an EGFR mutation but without ER-beta expression. ER-beta expression did not affect prognosis in those without an EGFR mutation.

Whether or not these molecular markers provide more information than clinical parameters is unclear. As an example, in the phase III trial comparing erlotinib to placebo, tissue from 325 of 731 patients was analyzed for over expression of the EGFR protein, gene amplification and mutations in the TK domain of the receptor[36].

Gefitinib may prolong survival in Asian patients with adenocarcinoma and characteristic EGFR mutations[21]. In a historical comparison of 330 Asian patients with advanced adenocarcinoma before and after the commercial introduction of gefitinib, the median survival was significantly increased in patients with an EGFR mutation once gefitinib was available (27.2 versus 13.6 months prior to its commercialization). In contrast, survival was not significantly increased in those without an EGFR mutation (13.2 versus 10.4 months). Better outcomes in Asian patients were also noted in the ISEL trial[14].

IPASS trial — in a phase III trial conducted in Asia, 1217 previously untreated patients with advanced NSCLC were randomly assigned to gefitinib or carboplatin plus paclitaxel[37]. Preliminary results were presented at the European Society for Medical Oncology (ESMO) meeting in 2008. Overall, progression-free survival was better with erlotinib compared to chemotherapy (HR 0.74, 95% CI 0.65-0.85), while overall survival was similar (HR 0.91, 95% CI 0.76-1.10). The objective response rate was significantly higher with gefitinib (43 versus 32 percent). In preplanned subset analyses, results were compared based upon EGFR mutation status. For patients whose tumors contained an EGFR mutation, PFS was markedly improved with gefitinib (HR 0.48, 95% CI 0.36-0.64). In contrast, for patients without an EGFR mutation, gefitinib was inferior to chemotherapy (HR 2.85, 95% CI 2.05-3.98).

Current trial did not show any survival significance in any of these factors and the only factor that showed prognostic influence in OS is duration of gefitinib treatment, may be because of small number of cases.

Gefitinib in current trial was tolerable and there was no major side effects to its use and most of these side effects were grade 2 and 3 and manageable. The most common toxicities were skin rash and diarrhea which is similar to that reported in most of the published trials.

CONCLUSION

Oral gefitinib at 250 mg/d provides clinically significant durable antitumor activity, accompanied by clinically meaningful symptom relieves second and third line treatment in patients with advanced NSCLC who have received previous platinum-based therapy.

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