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Differential efficacy of gefitinib across age groups in treatment of advanced lung adenocarcinoma

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Objective: To compare the efficacy of gefitinib monotherapy across different age groups of patients with advanced lung adenocarcinoma. *Methods*: Clinical data of patients (mostly Chinese) with advanced lung adenocarcinoma who were non-smokers or light smokers and had received oral gefitinib (250 mg/d) between October 2006 and December 2009 were reviewed retrospectively. The 93 enrolled patients (25 male and 68 female; median age, 62.5 years), were divided into three age groups: $\leq$ 49 years (n = 22), 50–69 years (n = 53), and $\geq$ 70 years (n = 18). Among them, 84 patients had received at least one chemotherapy regimen previously. The objective response rate (ORR), time to disease progression (TTP), median overall survival (MOS) and adverse effects in response to gefitinib treatment were analyzed in the above age groups. *Results*: Out of 93 patients, a complete response was seen in 5 patients, partial response in 43 patients, stable disease in 36 patients, and disease progression in 9 patients. ORR was 51.6%, and the disease control rate (DCR) was 90.3%. No significant correlation was observed between ORR of gefitinib treatment and the baseline clinical characteristics of the patients. The median TTP was 12.6 months, and median overall survival (MOS) was 23.4 months. Gefitinib treatment-related TTP was prolonged with increasing age: 8.2 months, 14.2 months and 18.2 months in the age groups of $\leq$ 49-years, 50–69-years and $\geq$ 70-years, respectively (log-rank P = 0.002). MOS in the three age groups was 20.4 months, 23.6 months and 22.0 months, respectively ($P > 0.05$). The most common adverse effects were rash and diarrhoea, and rash seemed to be correlated with ORR (ORR = 2.631; p = 0.044, 95% CI: 1.025–6.753). *Conclusions*: In Asian patients with advanced lung adenocarcinoma who were non-smokers or light smokers and were treated with gefitinib, progression-free survival was correlated with age. Elderly patients ($\geq$ 70 years) seemed more likely to benefit from gefitinib treatment.

1. Introduction

Lung cancer, the most common cause of cancer-related deaths in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004 (WHO 2006). The two most prevalent histological types of lung carcinoma, categorized by the size and appearance of the malignant cells after microscopic examination by a histopathologist, are small cell and non-small cell lung carcinomas (Travis et al. 1995). Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancers, while small cell lung cancer accounts for the remaining 20% (Breathnach et al. 2001; Carney 2002; Oze et al. 2009).

Gefitinib is an oral, anti-cancer drug. Biochemically, it is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (Gibson 2002), which interrupts signalling through the EGFR involved in tumour cell growth, proliferation and tumour metastasis (Woodburn 1999). Gefitinib inhibits EGFR tyrosine kinase by binding to its adenosine triphosphate (ATP)-binding site. Thus it can inhibit the function of the EGFR tyrosine kinase in activating the anti-apoptotic Ras signal transduction cascade, and thereby the development of malignant cells (Takimoto CH 2008). Molecular studies (Lynch et al. 2004; Paez et al. 2004) on gefitinib-sensitive NSCLC have shown that mutations in the region encoding the EGFR tyrosine kinase domain are responsible for activating anti-apoptotic pathways (Pao et al. 2004; Sordella et al. 2004). These mutations tend to confer increased sensitivity to tyrosine kinase inhibitors such as gefitinib and erlotinib. Of the different types of NSCLC histologies detectable under a microscope, adenocarcinoma is one that harbours these mutations most often. These mutations are more commonly seen in Asians, women, and non-smokers who also tend to develop adenocarcinoma more often.

Among the new cases of lung cancer, 30% of the patients are older than 70 years (Havlik et al. 1994). For this elderly population optimal supportive care and single-agent chemotherapy using third generation drugs constitute the standard regimen

Table 1: Baseline characteristics of study group of patients with advanced NSCLC (N = 93) classified according to age

Characteristics	n	< 49 yr. (n = 22)	50–69 yr. (n = 53)	> 70 yr. (n = 18)	P value
Gender					
Female	68	8	12	5	0.473
Male	25	14	41	13	
Stage					
IIIB	16	3	7	6	0.130
IV	77	19	46	12	
Smoking status					
non-smoker	85	20	49	16	0.893
light smoker	8	2	4	2	
Surgery					
Yes	19	3	15	1	0.078
No	74	19	38	17	
Radiotherapy					
Yes	24	5	17	2	0.199
No	69	17	36	16	
Chemotherapy					
Yes	84	21	47	16	0.648
No	9	1	6	2	
ECOG PS					
0–1	52	16	24	12	0.055
2–3	41	6	29	6	

Table 2: Logistic regression analysis of the response rate to gefitinib treatment in NSCLC patients

Characteristics	n	CR + PR	SD + PD	OR	95% CI
Gender					
Female	68	36	32	1.371	0.328–2.054
Male	25	12	13	1.00	
Age (yr)					
≤ 49	22	8	14	0.457	0.128–1.632
50–69	53	30	23	1.043	0.356–3.063
≥ 70	18	10	8	1.00	
Stage					
IIIb	16	10	6	8.341	0.193–1.767
IV	77	38	39	1.00	
ECOG PS					
0–1	52	30	22	1.364	0.251–1.312
2–3	41	18	23	1.00	
Surgery					
No	74	36	38	0.947	0.641–5.107
Yes	19	12	7	1.00	
Radiotherapy					
No	69	37	32	1.156	0.288–1.858
Yes	24	11	13	1.00	
Chemotherapy					
No	9	5	4	1.250	0.200–3.344
Yes	84	43	41	1.00	

under current guidelines, although the median survival time (MST) of patients is only 8–10 months (Gridelli 2001, 2003; Kudoh et al. 2006). As it is often difficult to obtain tissue biopsy samples during clinical treatment, it is very important to choose the right treatment on the basis of clinical characteristics of patients (Asahina et al. 2006; Douillard et al. 2010; Hirsch et al. 2006; Inoue et al. 2009; Mok et al. 2009; Sequist et al. 2008; Zhu et al. 2008). Increasing the efficacy of treatment in elderly patients with lung cancer, prolonging survival time and improving their quality of life are challenges for both clinicians and researchers.

Clinical efficacy of gefitinib was shown in clinical subgroup analyses of patients older than 70 years in earlier studies (Cappuzzo et al. 2004; Gridelli et al. 2003; Hotta et al. 2005). In these studies, the response rate was about 5%, and the MST was 4–7 months. A recent retrospective study by Na et al. (2010) who studied gefitinib treatment in female, Asian NSCLC patients also suggested that age was an important predictive factor for drug efficacy and patient survival. However, these studies did not clarify whether there are any differences in the objective response rate (ORR), time to progression (TTP) and overall survival (OS) between patients who are older than 70 years and those who are younger. There is still controversy about the age criterion for elderly lung cancer patients. For example, epidemiological studies often use 65 years as an age limit, while oncological studies use 70 years as the age limit (Hotta et al. 2004). A retrospective analysis (Gridelli and Shepherd 2005) found that there was an increase in chemotherapy-related toxic events in lung cancer patients older than 70 years, suggesting that the age criterion of 70 years seems more reasonable.

In this retrospective study, the NSCLC patients who had received gefitinib treatment were divided into three age groups using 50 and 70 years as the grouping criteria. This study was designed to explore whether or not age affects short-term efficacy of gefitinib, progression-free survival and OS through retrospective analyses of the clinical characteristics of gefitinib-treated Asian patients with advanced lung adenocarcinoma who are non-smokers or light smokers.

2. Investigations and results

2.1. Patient characteristics

The baseline characteristics of the study group are listed in Table 1. A total of 93 gefitinib-treated, NSCLC patients were enrolled, 68 women and 25 men, with ages ranging from 32 to 79 years and a median age of 62.5 years. The patients were classified into three age groups: ≤ 49 years (n = 22), 50–69 years (n = 53), and ≥ 70 years (n = 18). Out of 93 patients, 84 patients had an ECOG PS score of 0–2, and the remaining 9 patients scored 3. In all, 16 cases were classified as clinical stage III B and the other 77 cases as clinical phase IV. Of the 93 patients, 19 had previously received surgical treatment, 24 had received chest radiotherapy, 84 had received chemotherapy, and 9 had received no treatment.

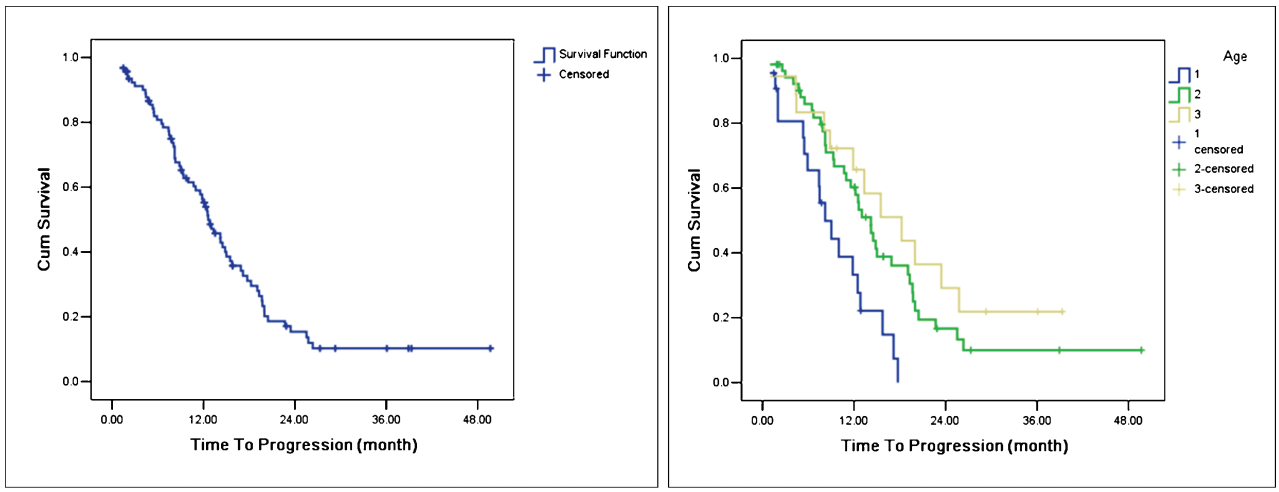
2.2. Objective response rate (ORR)

Out of the 93 cases, CR was observed in 5 cases (5.4%), PR in 43 cases (46.2%), SD in 36 cases (38.7%), and PD in 9 cases (9.7%). ORR (CR + PR) was 51.6%, and disease control rate (DCR) (CR + PR + SD) was 90.3%. ORR in the age groups ≤ 49-years, 50–69-years and ≥ 70-years was 36.3%, 56.6% and 55.5%, respectively. There appears to be a lower ORR in younger patients (≤ 49-years) compared to the elderly (≥ 70-years), but the difference was not statistically significant (p = 0.228, OR [odds ratio] = 0.457, 95% CI [confidence interval]: 0.128–1.632).

The response rate was also analysed in terms of other parameters such as sex, age, PS score, clinical stage and previous treatments (Table 2). Logistic regression analysis of the relationship between the basic clinical characteristics and the response rate failed to show any statistically significant correlations (Table 2).

2.3. Time to progression (TTP)

The follow-up period ranged from 1.0 to 49.7 months with a median of 15.8 months. The median TTP for the 93 patients was 12.6 months, and the 1-year progression-free survival (PFS)



(A) (B)

Fig. 1: Disease progression in NSCLC patients receiving gefitinib treatment. Kaplan–Meier curves for time to disease progression in all 93 patients (Panel A), or as stratified into age groups of ≥ 70-years (1), 50–69-years (2) and ≤ 49-years (3) (Panel B). Tick marks indicate patients for whom data were censored at the data cut-off point which was the day of the last follow-up (early May 2010, 5 months after end of treatment period)

was 32%. The median TTP in the age groups ≤ 49-years, 50–69-years and ≥ 70-years was 8.2 months, 14.2 months, 18.2 months respectively, and the differences between the three age groups were statistically significant (log-rank, p = 0.002) (Fig. 1). The 1-year PFS for the three groups was 3%, 37% and 52% respectively (Wilcoxon p = 0.022).

Univariate Cox regression analysis showed that there were significantly more TTP benefits from gefitinib treatment in patients older than 70 years when compared with patients younger than 49 years (hazard ratio [HR] = 3.410, p = 0.002, 95% CI: 1.579–7.365). Patients older than 70 years seemed to benefit similar to those aged 50–69 years, because the difference in TTP was not statistically significant (HR = 1.437, p = 0.278, 95% CI: 0.747–2.764).

Similarly, multivariate Cox regression analysis also indicated that TTP after gefitinib treatment was associated with age, and patients in ≤ 49 age group were more prone to disease progression (HR = 2.870, p = 0.020,95% CI:1.180–6.976).

2.4. Median overall survival (MOS)

The MOS for the 93 patients was 23.4 months, with 67% of the patients showing a 1-year overall survival and 31% of the patients showing a 2-year survival. The OS was 20.4 months in ≤ 49-years age group, 23.6 months in 50–69-years age group, and 22.0 months in ≥ 70-years age group, and there was no statistically significant difference between the three age groups (log-rank p = 0.257) (Fig. 2). The 1-year survival for the three group was 59%, 66% and 75%, and the 2-year survival was 9%, 32% and 42% respectively (Wilcoxon p = 0.487).

Univariate Cox regression analysis showed that OS in patients ≥ 70-years was slightly better when compared with ≤ 49-years age group (HR = 2.198, p = 0.108, 95% CI: 0.842–5.739) and 50–69 age group (HR = 1.421, p = 0.338, 95% CI: 0.640–3.157).

2.5. Adverse effects

The major adverse effects were rash (72/93 patients) and diarrhoea (34/93 patients), with an occurrence of 77.4% and 36.6%, respectively. The rash was mainly present as acne-like and vesicular rash on face and the upper half of the trunk, without an itching sensation, and with a severity of I-II. The rash could be relieved by symptomatic treatment. Diarrhoea was mostly mild and was resolved by symptomatic treatment. The drug dose was reduced to 250 mg every other day instead of daily in two patients with rash and in one patient with diarrhoea, and was resumed to the normal dosage 7 days later. With treatment the symptoms of rash and diarrhoea gradually subsided or disappeared, though they recurred in some patients.

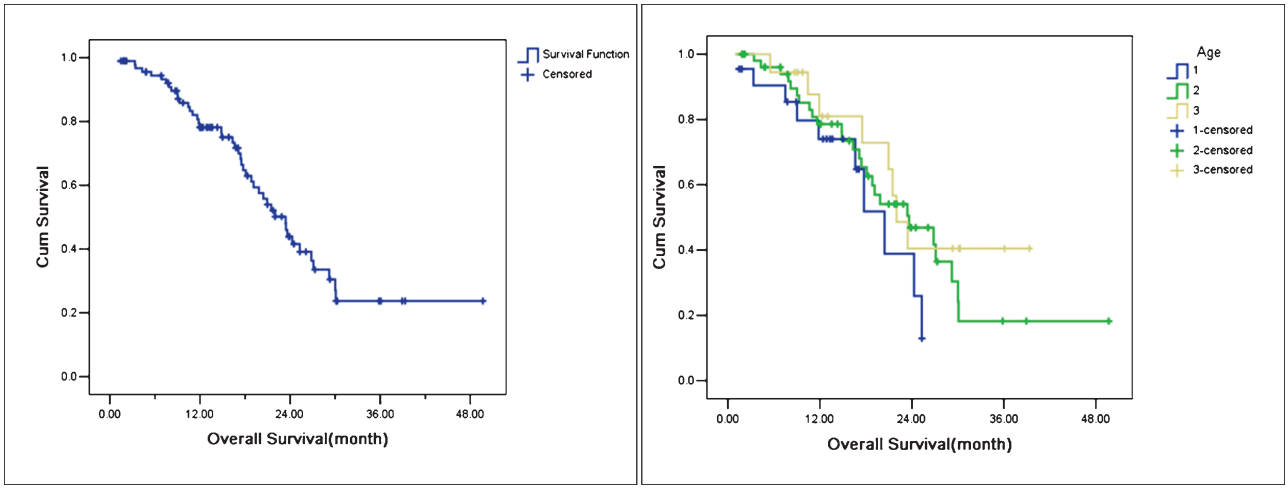
Liver transaminase elevation was observed in 6 patients during gefitinib treatment, and controlled within 2-fold upper limit of the normal range via oral administration of hepatoprotective drug(s), without dose reduction or discontinuation from gefitinib treatment. There were no cases of renal impairment or serious complications such as interstitial pneumonia.

Interestingly, logistic regression analysis showed that the onset of rash was associated with ORR. Patients with rash showed a better outcome (ORR = 2.631, p = 0.044, 95% CI: 1.025–6.753), while no such association was observed with diarrhoea (HR = 0.622, p = 0.274, 95% CI: 0.266–1.455).

3. Discussion

The main purpose of this study was to evaluate the efficacy of gefitinib treatment in advanced lung adenocarcinoma patients across different age groups and determine the survival in patients who were Asian (mainly Chinese) non-smokers or light smokers. It is interesting to find that patients older than 70 years could achieve better prognosis with gefitinib treatment than those in the other age groups, while gender was not an independent predictive factor for TTP benefits associated with gefitinib treatment (HR = 1.822, p = 0.114, 95%CI: 0.866–3.834).

Wingo et al. (2003) observed a downward trend in morbidity and mortality in lung cancer patients younger than 50 years, and an increasing trend in patients older than 70 years in the past 10 years. Previous epidemiological studies (Ries et al. 2010) reported that the mortality rate in lung cancer patients older than 70 years was 10-fold higher than in younger patients. However, our study indicates a decreased risk of death in elderly patients with advanced NSCLC who received gefitinib treatment, although there was no significant difference in OS of these patients compared with those in other age groups. Subgroup analysis of the three age groups produced no significant difference in ORR, but TTP showed significant differences after gefitinib treatment (8.2 months, 14.2 months and 18.2 months, respectively, log-rank P = 0.002). Cox regression analysis of multiple factors also suggested that older patients had a better TTP than the other groups. When compared with patients



(A) (B)

Fig. 2: Overall survival of NSCLC patients receiving gefitinib treatment. Kaplan–Meier curves for overall survival in all 93 patients (Panel A), or as stratified into age groups of ≥ 70-years (1), 50–69-years (2) and ≤ 49-years (3) (Panel B). Tick marks indicate patients for whom data were censored at the data cut-off point, which was the day of the last follow-up (early May 2010, 5 months after end of treatment period)

older than 70 years, the patients younger than 49 years had a higher risk of disease progression (HR = 2.628, p = 0.029), than the 50–69-years age group patients (HR = 1.25, p = 0.566).

Molecular analysis in IPASS study (Mok et al. 2009) indicated that the EGFR mutation rate was higher in patients older than 65 years. This may imply that the EGFR mutation rate increases with aging, which could explain why elderly lung cancer patients may obtain relatively more TTP benefits from gefitinib treatment.

In this study, age stratified analysis did not show any significant advantage in median OS in elderly lung cancer patients (log-rank P = 0.257). Thus, the advantage of TTP was not translated into an OS benefit. Recent studies by Maemondo et al. (2010) showed that gefitinib treatment or first-line chemotherapy could significantly improve the median TTP, PFS and ORR in NSCLC patients with EGFR mutations (adenocarcinoma accounts for 90% of all cases) when compared to chemotherapy (10.8 months *vs* 5.4 months, $p < 0.001$), and dramatically improved the response rate (73.7% *vs* 30.7%, $p < 0.001$). But there was no significant difference in MOS (30.5 months *vs*. 23.6 months, p = 0.31). It is noteworthy that the median age of patients in that study was more than 60 years, which is similar to that in our study. A study on Chinese Taipei population (Wu et al. 2010) also had investigated the efficacy of the second-line treatment in advanced NSCLC patients older than 70 years and younger patients, and found that the DCR and MOS were comparable between the two age groups of patients after receiving gefitinib treatment and second-line chemotherapy, and fewer adverse effects were observed in the gefitinib group.

Why could the advantage of TTP not be translated into OS benefit? Elderly lung cancer patients are prone to complications from other systemic diseases. Therefore, it is impossible to carry out further chemotherapy and multi-target drug therapy in the presence of EGFR-TKIs induced disease progression as they are more likely to die from complications. Complications can also be an important confounding factor influencing OS. In our study, out of the 18 patients ≥ 70-years, 8 patients died after last follow-up, of which only 4 deaths were attributed to tumour causes, and the other 4 deaths were attributed to unknown causes (2 cases) or massive ascites (1 case) or sudden death from heart disease (1 case).

Rash and diarrhoea were the most commonly adverse effects observed in all clinical trials of EGFR-TKIs (gefitinib and erlotinib). TALENT study (Gatzemeier et al. 2007) first demonstrated the relationship between the efficacy of erlotinib and rash, which was later confirmed by a large number of clinical studies. Interestingly, patients without rash were associated with a poor efficacy.

For non-selected NSCLC populations, gender is also an important factor affecting efficacy of gefinitib (Kaneda et al. 2004; Shepherd et al. 2005). The most common histological type of lung cancer in Asian women is adenocarcinoma (Hotta et al. 2009), and most of them do not have a history of smoking. As EGFR mutations have been found in more than 50% adenocarcinoma cases in non-smoking patients, female patients are more likely to benefit from gefitinib use. Women are also more likely to be enrolled in gefitinib studies. For example, women accounted for 70% of all enrolled patients in two recent clinical first-line gefitinib studies (Rosell et al. 2009; Yang et al. 2010). However, the results might vary if the enrolled population consisted of patients with adenocarcinoma who were non-smokers. The IPASS study (Mok et al. 2009) reported that female gender was not an independent prognostic factor for PFS benefit. Molecular analysis on smoking patients revealed that the EGFR mutation rate declined with the smoking duration (Paeze et al. 2004), while there was a strong positive correlation between the mutation rate of K-ras gene and smoking history (Ahrendt et al. 2001). Therefore, smoking history seems to be more important than gender as a predictive factor for the efficacy of gefitinib treatment. In this study, there was no evidence of the influence of gender on gefitinib-related ORR and survival. However, in this retrospective study, because of the lack of blinding and control groups, we could not obtain more convincing information about the validity of age on predicting the efficacy of gefitinib in selected patients with advanced lung adenocarcinoma.

In conclusion, gefitinib treatment showed differential efficacy in NSCLC patients from different age groups. When compared with patients younger than 50 years, elderly patients ≥ 70 years, showed better prognosis after gefitinib treatment. Although this is a retrospective study with uneven distribution of the baseline characteristics between the three age groups, it indicates that choice of gefitinib treatment could be made on the basis of clinical characteristics, especially as histological examination is not possible. In addition, age may be an important predictive factor for the efficacy of gefitinib. These observations should be confirmed by future prospective cohort studies.

4. Experimental

4.1. Patients

Asian patients with advanced lung adenocarcinoma were selected from those admitted to the out- or in-patient wards at Henan provincial Tumour Hospital between October 2006 and December 2009. The main inclusion criteria were: 1) patients who were willing to sign informed consent 2) patients who were non-smokers or light smokers, classified according to Mok et al. (2009), where non-smokers are described as those who smoked fewer than 100 cigarettes in their lifetime, and light smokers, those who had quit smoking for more than 15 years and smoked fewer than 200 cigarettes yearly 3) patients whose diagnosis of lung adenocarcinoma had been confirmed by histology or cytology 4) patients whose clinical phase was IIIB or IV based on a TNM staging system (Mountain 2003); 5) patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–3 6) patients with at least one measured lesion according to the Response Evaluation Criteria In Solid Tumours (RECIST), and whose expected survival time was less than 12 weeks 7) patients without new central nervous system (CNS) metastasis 8) patients who did not need to receive other anticancer or biological therapies during the study period, although analgesic treatment in cases of bone metastases, and other symptomatic treatments were permitted 9) patients whose routine blood and biochemical tests were essentially normal (AST and ALT $\leq$ 100 U/L, total bilirubin $<$ 2.0 mg/dL). This study was approved by the Institutional Review Board of Tumour Hospital of Zhengzhou University (Zhengzhou, China) and written informed consent was obtained from each patient.

4.2. Drug administration

Gefitinib 250 mg was orally administered daily unless disease progression was observed or toxicity was intolerable. In patients who experienced severe toxic reactions, gefitinib treatment was either discontinued or the dosage was reduced. In patients who failed to respond to gefitinib treatment, other chemotherapy or treatments were considered.

4.3. Efficacy evaluation

The baseline examination was completed one week before start of gefitinib treatment. This included recording of medical history, physical examination, chest CT, head CT or MRI, abdominal CT/B-scan ultrasound, bone scan, and liver and kidney function test. Patients were monitored throughout the study period and the last follow-up was on May 10, 2010. The above examinations were repeated after four weeks of treatment for preliminary efficacy evaluation. Treatment efficacy was classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to RECIST criteria. In patients with CR, PR, or SD the examinations were performed at an 8-week interval for continued evaluation of efficacy. In patients who showed PD at the first evaluation, treatment was discontinued. In patients with CR and PR, the efficacy was re-evaluated once every four weeks.

Time to progression (TTP) was defined as the period from day 1 of oral administration of gefitinib to the day when the primary tumour progression or a new lesion was observed. Missing value was defined as patients who showed no signs of disease progression during the last follow-up.

Survival time was defined as the period from day 1 of oral administration of gefitinib to the day of patient death or the last follow-up. Missing value was defined as patients who were still alive during the last follow-up.

Adverse effects were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0.

4.4. Statistical analysis

All the data were processed by SPSS13.0 software package, and the relationship between the basic clinical characteristics of patients, the adverse effects of gefitinib treatment and treatment efficacy were analyzed by logistic multiple factor regression analysis. Univariate survival analysis and survival curve were obtained by the Kaplan-Meier method. Wilcoxon rank sum test was used to analyze progression-free survival. Multivariate survival analysis was performed by multiple Cox regression. In all the statistical analysis, p values less than 0.05 was considered to be significant.

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