

RESEARCH ARTICLE

Efficacy and Survival-associated Factors with Gefitinib Combined with Cisplatin and Gemcitabine for Advanced Non-small Cell Lung Cancer

Hong Fang*, Rong-Yan Lin, Ming-Xia Sun, Qian Wang, Yu-Liang Zhao, Jing-Lin Yu, Yan Tian, Xiao-Yun Wang

Abstract

Objective: To analyze the efficacy and survival associated factors of gefitinib combined with cisplatin and gemcitabine for advanced non-small cell lung cancer. **Materials and Methods:** A total of 57 patients with advanced non-small cell lung cancer (NSCLC), who received platinum-based chemotherapy regimens for more than 1 cycle, were treated with gefitinib combined with cisplatin and gemcitabine until disease progression. Efficacy, survival time and adverse reactions were observed. The Kaplan-Meier method was adopted for analysis of survival and Cox regression for associated influencing factors. **Results:** The patients were followed up until October 31, 2013, and the median follow-up time was 19 months. Of 57 patients, there were 4 (7.0%) with complete remission (CR), 8 (14.0%) with partial remission, 31 (54.4%) with stable disease, and 14 (24.6%) with disease progression. The remission rate was 21.1% and the disease control rate was 75.4%. The median progression-free survival (PFS) time and the median overall survival time were 10 months and 15.2 months. The one-year, two-year and three-year survival rates were 47.4%, 23.3% and 10.0%. Gender and pathological types were the independent risk factors influencing PFS time ($P=0.028$, $P=0.009$). Tumor pathological type and early efficacy were independent factors for the prognosis ($P=0.018$, $P=0.000$). Adverse reactions were mostly rashes of I~II degree and diarrhea and slightly increasing level of aminophosphatase. The skin adverse event incidence of III degree or above was 1.8% (1/57) and brain metastasis was found in 31.6% (18/57). **Conclusions:** Gefitinib combined with cisplatin and gemcitabine, is effective for patients with IIIb~IV NSCLC who received multiple cycles of chemotherapy.

Keywords: NSCLC - gefitinib - cisplatin - gemcitabine - adenocarcinoma - survival - associated influencing factors

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Introduction

Lung cancer, one of most common malignant tumors in the respiratory system, has become the common death cause of malignant tumors in many developed countries, in which non-small cell lung cancer (NSCLC) accounts for 80% and ranks the first death cause of malignant tumors in large and medium-sized cities in our country (Fukuoka et al., 2011; Chen et al., 2013; Huang et al., 2014). Because they have not obvious symptoms and signs in early stage of lung cancer, more than 50% patients develop into locally or completely advanced cancer when diagnosed and lose the opportunity of surgery, even after surgery and chemoradiotherapy, their 5-year survival rate is only 12%~15%, while advanced NSCLC has worse prognosis. Platinum-based chemotherapy in clinic can reduce the mortality risk of patients of stage IIIb~IV to 26%~32% (Scagliotti et al., 2010; Yu et al., 2014). Moreover, with the use of molecular targeted therapy, chemotherapy combined biological target therapy has become a hot

issue of present researches for enhancing clinical efficacy. In this study, gefitinib combined cisplatin, gemcitabine was employed for treating advanced NSCLC and the associated factors of influencing the efficacy and survival were analyzed.

Materials and Methods

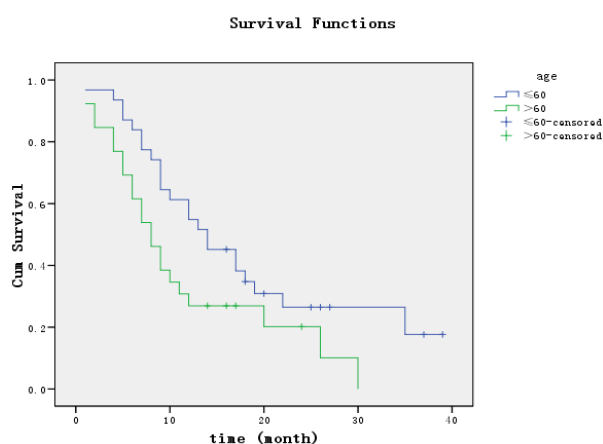
General data

The data of 57 patients with advanced NSCLC at the Department of Oncology Chemotherapy in Peking University First Hospital from April, 2009 to May, 2011 were collected, in which, 34 cases were males and 23 females, aged 21~86 years old with the median age being 59 years; 36 smokers (>100 cigarette in the lifetime) and 21 nonsmokers (≤ 100 cigarette in the lifetime). All patients were diagnosed by pathology and cytology as adenocarcinoma (33 cases), bronchioloalveolar carcinoma (8 cases), squamous carcinoma (10 cases) and large cell undifferentiated carcinoma (6); at stage IIIb (19 cases)

Department of Oncological Chemotherapy, Peking University First Hospital, Beijing, China *For correspondence: fanghongdexiang@sina.com

Table 1. Analysis of Short-term Efficacy in Subgroups and Baseline Characteristics [n (%)]

Items		n	CR+PR (%)	χ^2	P	CR+PR+SD (%)	χ^2	P
Gender	Male	34 (59.6)	3 (8.8)	5.868	0.015	22 (64.7)	5.238	0.022
	Female	23 (40.4)	9 (39.1)			21 (91.3)		
Age	≤60	31 (54.4)	10 (32.3)	5.134	0.023	28 (90.3)	8.126	0.004
	>60	26 (45.6)	2 (7.7)			15 (57.7)		
Clinical stage	IIIb	19 (33.3)	6 (31.6)	1.900	0.168	16 (84.2)	0.580	0.446
	IV	38 (66.7)	6 (15.8)			27 (71.1)		
Pathological type	Adenocarcinoma	33 (57.9)	10 (30.3)	4.035	0.045	29 (87.9)	6.546	0.011
	Non-adenocarcinoma	24 (42.1)	2 (8.3)			14 (58.3)		
Smoking	Yes	36 (63.2)	4 (11.1)	4.300	0.038	24 (66.7)	4.058	0.044
	No	21 (36.8)	8 (38.1)			19 (90.5)		
Local treatment	Yes	13 (22.8)	2 (15.4)	0.326	0.568	6 (46.2)	0.001	0.975
	No	44 (77.2)	10 (22.7)			37 (45.7)		
Brain metastasis	Yes	18 (31.6)	3 (16.7)	0.304	0.581	11 (61.1)	1.894	0.169
	Other	39 (68.4)	9 (23.1)			32 (82.1)		
Family history	Yes	10 (17.5)	4 (40.0)	1.419	0.233	6 (60.0)	0.713	0.398
	No	47 (82.5)	8 (17.0)			37 (78.7)		

**Figure 1. The Relationship Between Age and PFS Time**

and IV (38); with normal blood routine examination and renal function. Physically KPS score were more than 60. Patients had at least one measurable lesion and received at least 1 cycle of cisplatin-based chemotherapy regimen but no valid response to it, with the expected lifetime >3 months. All patients were followed up at least 6 months without loss.

Therapeutic method

All patients were given intravenous drip of gemcitabine (Hansoh Pharmaceutical, Jiangsu, H20030105, 200 mg each) on day 1, 8, 1 000 mg/m², intravenous drip of cisplatin during 1~3 days, 25 mg/m², oral administration of gefitinib (Iressa, AstraZeneca, 250 mg/tablet) 1 h after breakfast from day 10 to day 24, once daily, 4 weeks as 1 cycle, and chest CT was reviewed every 4 weeks. The regimen was stopped until the onset of severe adverse reactions or the presence of disease progression, or stopped by patients' requires or doctor' advice that it was not conducive to the conditions of the patients. Azasetron was routinely used for preventing gastrointestinal adverse reactions such as nausea and vomiting during chemotherapy.

Therapeutic evaluation

Tumor curative effect was evaluated by Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0): curative effects include complete remission (CR),

partial remission (PR), stable disease (SD) and disease progression (DP). The response rate (RR)= CR+PR/Total cases×100%. The disease control rate (DCR)= (CR+PR+SD)/Total cases×100%. The influence of gender, age, pathological type, clinical stage, smoking, brain metastasis, local treatment and family on RR and DCR were analyzed.

Overall survival (OS) started from the first day of drug use to the last follow-up. Progression-free survival (PFS) referred to the time between drug administration and disease progression or onset of new lesions.

Statistical data analysis

SPSS17.0 statistical software package was employed for data analysis. X² and Logistic multi-factor regression analysis were used for analyzing the differences of RR and DCR among different factors. Kaplan-Meier method was adopted for survival analysis and Log-rank test for analyzing survival differences in different baseline characteristics and therapeutic response. Cox regression was used for survival associated factors analysis of PFS and OS.

Results

Short-term efficacy and associated factors analysis

Of 57 patients, there were 4 CR (7.0%), 8 PR (14.0%), 31 SD (54.4%) and 14 PD (24.6%). The RR was 21.1% and DCR was 75.4%. Clinical efficacy was closely related to gender, age, smoking and pathological types but not associated with clinical stage, local treatment, brain metastasis and family. The RR and DCR were higher in female, ≤60 years old, non-smoking, adenocarcinoma subgroups ($P=0.015, 0.023, 0.045, 0.038; P=0.022, 0.004, 0.011, 0.044$), as shown in Table 1, Figure 1 and 2.

PFS and associated influencing factors

The median PFS time was 10 months (95%CI, 7.310~12.690). Log rank Test showed that age, gender and pathological types could influence the PFS time of the patients. And PFS time was longer in ≤60 years, female, adenocarcinoma subgroups. The PFS time were 14 months in ≤60 years subgroup and 8 months in >60 years

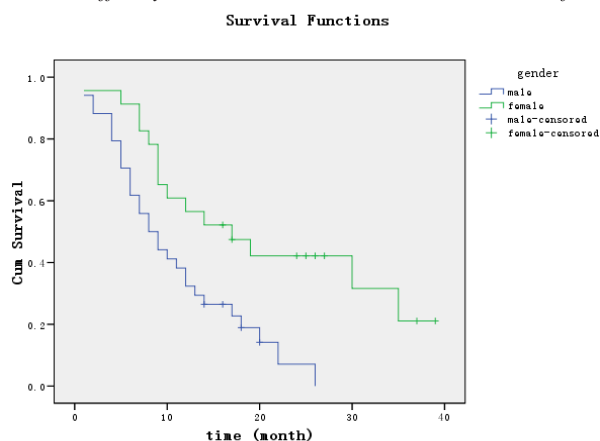


Figure 2. The Relationship Between Gender and PFS Time

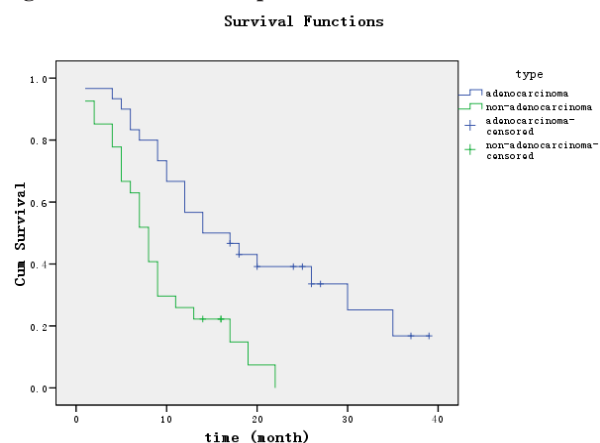


Figure 3. The Relationship Between Pathological Type and PFS Time

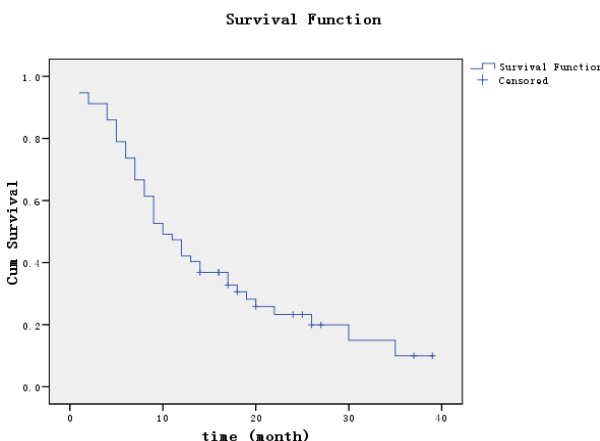


Figure 4. Overall Survival Curve

subgroup; 17 months in female subgroup and 8 months in male subgroup; 14 months in adenocarcinoma subgroup and 8 months in non-adenocarcinoma subgroup, as shown in Figure 3, 4 and 5. However, PFS time had no association with clinical stage, smoking, the history of local treatment and brain metastasis, and family history. Cox regression analysis revealed that gender and pathological type were independent risk factors of influencing PFS time ($P=0.028$, $P=0.009$), the mortality risk in female subgroup could reduce to 47.8% of male patients and the mortality risk of non-adenocarcinoma patients was 2.363 times as many as adenocarcinoma patients.

OS and associated influencing factors

The patients were followed up until October 31,

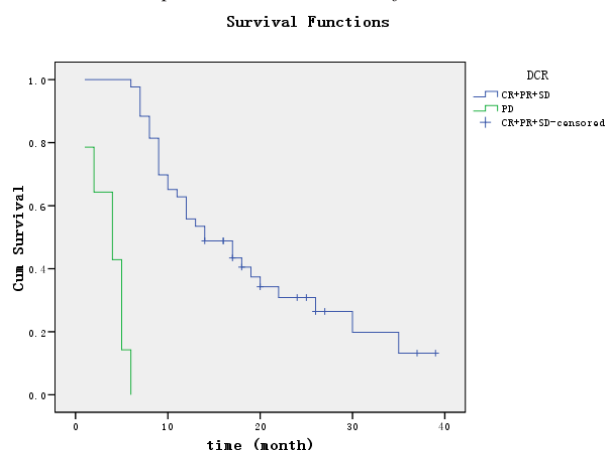


Figure 5. The Relationship Between DCR and OS Time

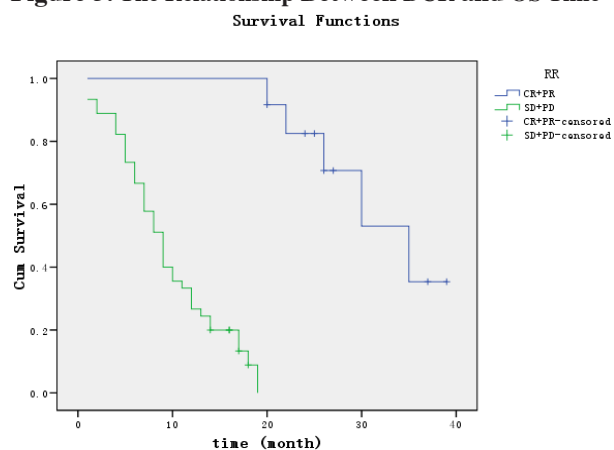


Figure 6. The Relationship Between RR and OS Time

2013, and the median follow-up time was 19 months. There were 45 cases of death and 2 cases loss to follow up (more than 13 months). The median OS time was 15.2 months (95%CI, 11.940~18.397). The one-year, two-year and three-year survival rates were 47.4%, 23.3% and 10.0%. Figure 6 was the OS curve. Log rank Test showed that different pathological types, gender, age and early efficacy could affect OS time, of which, OS time was longer in patient with adenocarcinoma, lung cancer resection, female, and obviously early efficacy, while had no relationship with clinical stage, smoking, brain metastasis and family history.

Cox regression analysis showed that only pathological type and early efficacy, which were related to OS time, were the independent factors for the prognosis ($P=0.018$, $P=0.000$). OS time were longer in patients with adenocarcinoma than patients with non-adenocarcinoma, were longer in CR+PR+SD patients when compared with PD patients and prolonged in CR+PR patients when compared with SD patients ($P=0.027$), as shown in Figure 7 and 8.

Adverse reactions

The adverse reactions of 57 patients were mostly rash of I~II degree and diarrhea and slightly increasing level of aminopherase. The skin adverse event incidence of III degree above was 1.8% (1/57) and brain metastasis accounted for 31.6% (18/57). 1.8% (1/57) had sense of piercing pain and dry cough but the symptom disappeared after drug discontinuance.

Discussion

Lung cancer is one of the most common malignant tumors in respiratory system in our country. Epidermal growth factor receptor (EGFR), highly expressed in patients with lung cancer, is closely related to the cell proliferation, angiogenesis and metastasis of tumors, thus, can be regarded as the target of treating lung cancer (Heukamp, et al., 2010). Gefitinib, EGFR tyrosine kinase inhibitor and aniline quinazoline compounds with low molecular weight, can competitively bind to EGFR tyrosine kinase and block EGFR-mediated tumor cell signaling, thus inhibiting the proliferation and metastasis, and angiogenesis of tumor and promoting the apoptosis of tumor cells (Fukuoka et al., 2011; Lee et al., 2013). With the application of new chemotherapeutics such as navelbine, paclitaxel, erlotinib and gefitinib in clinic in recent years, the chemotherapy regimens of combined with cisplatin can greatly enhance the survival rate of advanced NSCLC (Heinermann, et al., 2009; Mill, et al., 2011; Natukula et al., 2013; Di et al., 2014). At present, gemcitabine combined with cisplatin is one of the standard first-line regimens for advanced NSCLC, but with the most common adverse reactions of combined chemotherapy such as myelosuppression and part of late patients difficult to tolerate (Giorgio et al., 2008). Previous study showed that gefitinib, as the representative drug of molecular targeted therapy for tumors with the advantages of convenience, high specificity, quickly relieved toxicity, had been widely used as second or third line for treating advanced NSCLC in clinic (Mei et al., 2008).

Mok et al (Mok et al., 2009) used gemcitabine, cisplatin combined with erlotinib to treat advanced NSCLC and the response rate was 35.5%, with the median OS time being 7.2 and hazard ratio being 0.57. Guo et al (Guo et al., 2012) adopted gemcitabine combined cisplatin sequential to gefitinib in the treatment of advanced NSCLC and observed the efficacy and toxic and side effect, and the results showed that observational group (gemcitabine combined cisplatin sequential to gefitinib) had better effect than control group (gemcitabine plus cisplatin) (36.1% vs 14.3%). The median OS time and PFS time were 12.1 months and 10.8 months, respectively and there was statistical difference ($P < 0.05$), which revealed gemcitabine combined cisplatin sequential to gefitinib was effective and safe in treatment of advanced NSCLC.

In this study, gefitinib combined cisplatin, gemcitabine was used for treating patients with IIIb~ IV NSCLC. The remission rate was 21.1% and the disease control rate was 75.4%. The median progression-free survival (PFS) time and the median overall survival time were 10 months and 15.2 months. The one-year, two-year and three-year survival rates were 47.4%, 23.3% and 10.0%. Cox regression analysis showed only pathological type and early efficacy, which were related to OS time, were the independent factors for the prognosis ($P = 0.018$, $P = 0.000$). OS time were longer in patients with adenocarcinoma than patients with non-adenocarcinoma, were longer in CR+PR+SD patients when compared with PD patients and prolonged in CR+PR patients when compared with SD patients ($P = 0.027$).

The adverse reactions in this study were mostly rash of I~II degree and diarrhea and slightly increasing level of aminophosphatase. The skin adverse event incidence of

III degree above was 1.8% (1/57) and brain metastasis accounted for 31.6% (18/57). In addition, all patients were well tolerated, which revealed gefitinib combined with cisplatin and gemcitabine is safe for treating advanced NSCLC, and the samples can be enlarged for the further study.

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