RESEARCH ARTICLE

Clinical Observation and Prognostic Analysis of Pemetrexed plus Platinum as First-line Treatment in Patients with Advanced Non-small Cell Lung Cancer

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Abstract

Objective: To determine clinical efficacy, safety and prognostic factors of pemetrexed plus platinum as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC). Materials and Methods: Clinical characteristics, short-term efficacy, survival and adverse reactions of 47 advanced non-squamous NSCLC patients who had received pemetrexed plus platinum as first-line treatment in Shanghai Pulmonary Hospital from January 2009 to June 2011 were retrospectively analyzed. The Chi-squared test was applied to statistically analyze the overall response rate (ORR), disease control rate (DCR) and toxicity reactions in both groups, while survival data wereanalyzed by Kaplan-Meier and logrank methods, and the COX proportional hazards model was adopted for a series of multi-factor analyses. Results: Only two patients were lost to follow-up. The ORR, DCR, medium progression-free survival time (PFS) and medium overall survival (OS) were 31.9%, 74.5%, 5 months and 15.2 months, while 1- and 2-year survival rates were 63.8% (30/47) and 19.2% (9/47), respectively. Single-factor analysis showed that tumor pathological patterns and efficacy were in association with medium PFS ($P<0.05$), whereas tumor pathological patterns, smoking history and efficacy were closely connected with medium OS ($P<0.05$). Multi-factor analyses demonstrated that pathological patterns and efficacy were independent factors influencing OS ($P<0.05$). The rate of toxicity reactions in degree III/IV was low, including hematologic toxicity marked by decline in white blood cell count and decrease in the platelet count (PLT), and non-hematologic toxicity manifested by gastrointestinal reactions, such as nausea and vomiting. Conclusions: Pemetrexed plus platinum as first-line treatment has excellent efficacy and slight adverse reactions with favorable drug-tolerance in patients with advanced non-squamous NSCLC.

Keywords: Tumor - non-small cell lung cancer - chemotherapy

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Introduction

Lung cancer is one of the most common causes in cancer-associated deaths, in which non-small cell lung cancer (NSCLC) accounts for 85% and most patients are in middle and advanced stage when being diagnosed (Li et al., 2012; Liu et al., 2013). Chemotherapeutic regimens are still the main therapeutic protocols and the third generation of chemotherapeutic drugs plus platinum has become the standard first-line therapeutic protocol. The famous clinical studies of JMDB, JMEI and JMEN, etc, showed that pemetrexed played an important role in first second-line maintenance treatment of NSCLC in that it was a cytotoxic drug with high efficacy and low toxicity (Hanna et al., 2004; Scagliotti et al., 2008; Ciuleanu et al., 2009). In 2009, pemetrexed plus platinum were included in the first-line treatment of NSCLC by National Comprehensive Cancer Network (NCCN), and has been widely prescripted in China (Deng et al., 2013; Lu et al., 2013). Therefore, this study retrospectively analyzed the efficacy, survival and toxicity reactions of pemetrexed plus platinum on 47 patients with advanced NSCLC, hoping to obtain the application data and study the characteristics of effective population, so as to further explore the prognostic factors.

Materials and Methods

Study objects

A total of 47 patients with chemotherapy-native advanced NSCLC in phase IIIB/IV in Shanghai Pulmonary Hospital from January, 2009 to June, 2011 were selected as study objects and retrospectively analyzed, in which 12 were in phase IIIB and 35 in phase IV. All patients were confirmed by histopathology or cytology, in which 34 were with adeno-carcinoma, 5 with large cell carcinoma and 8 with squamous adeno-carcinoma. When being diagnosed, the patients were 34~79 years old with medium age being 67 years, and the 19 female and 28 male had all received

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Table 1. Efficacy Analysis of 47 Advanced NSCLC Patients

Characteristic	N(%)	RR(%)	*P*	DCR(%)	*P*
Age			0.211		0.444
<65years	16(34.04)	43.75		81.25	
≥65 years	31(65.96)	25.81		70.79	
Gender			0.217		0.919
Male	28(59.57)	25.00		75.00	
Female	19(40.430	42.11		73.68	
ECOG score			0.112		0.705
0	11(23.41)	18.18		81.82	
1	24(51.06)	45.83		75.00	
2	12(25.53)	16.67		66.67	
Histological patterns			0.015		0.219
Large cell carcinoma	5(10.64)	0.00		80.00	
Adeno-carcinoma	34(72.34)	44.12		79.41	
Squamous adeno-carcinoma	8(17.02)	0.00		50.00	
TNM stages			0.401		0.414
IIIB	12(25.53)	41.67		83.33	
IV	35(74.47)	28.57		71.43	
Malignant pleural effusion			0.046		0.324
No	34(72.34)	23.53		70.59	
Yes	13(27.66)	53.85		84.62	
Smoking history			0.037		0.036
No	24(51.06)	45.83		87.50	
Yes	23(48.94)	17.39		60.87	
Chemotherapeutic protocols			0.058		0.110
PP	25(53.19)	44.00		84.00	
PC	22(46.81)	18.18		63.64	

pemetrexed plus platinum for ≥2 cycles. According to Eastern Cooperative Oncology Group (ECOG) scores, 11 patients were with 0 score, 24 with 1 score and 12 with 2 scores. In addition, 23 patients were smokers and 13 were accompanied with malignant pleural effusion.

Study methods

7 d before the administration of pemetrexed, 400μg/d folic acid was orally given and 1 000 μg vitamin B12 was intramuscularly injected to all patients once every 9 weeks until the third week of the terminal chemotherapy. Pemetrexed (500 mg/m^2, on day 1) plus cisplatin (25 mg/m^2, on days 1-3) were performed to 26 patients, while pemetrexed (500 mg/m^2, on day 1) plus carboplatin (AUC=5, on day 1) were given to the others, 3 weeks as a cycle. And 4 mg/time dexamethasone was orally given 1 d before, the day of and the second day after the administration of pemetrexed, bid..

Evaluation criteria

(1) The short-term efficacy evaluation of chemotherapy referred to Response Evaluation Criteria in Solid Tumors (RECIST), including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). RR=(CR+PR)/total cases×100%; DCR=(CR+PR+NC)/total cases×100%. The efficacy was evaluated after drug administration for ≥2 cycles and conformed 4 week later if disease remised. (3) Long-term efficacy: Progression-free survival (PFS) was defined as the time from NSCLC progression to death and overall survival (OS) from diagnosis of NSCLC to death or the terminate follow-up. (4) Adverse reactions were evaluated and divided into 0~IV degrees based on Grading Criteria of Toxicity Reactions of WHO Anti-tumor Drug.

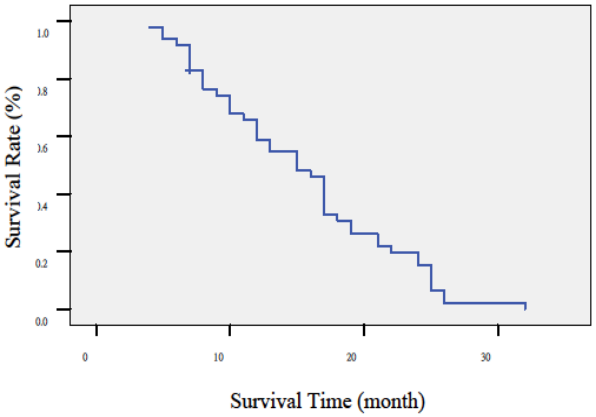

Figure 1. OS Curve of 47 NSCLC Patients in Phase IIIB/IV

Follow up

Follow-up was performed every 3 months until June, 2013. The follow-up rate was 95.74% as 2 patients lost their follow-ups, but the short-term therapeutic evaluations were finished.

Statistical analysis

All data were analyzed by SPSS13.0 statistical software. Chi-squared test was applied to statistically analyze the ORR, DCR and toxicity reactions in each group, while survival date was analyzed by Kaplan-Merier and logrank methods, and COX proportional hazards model was adopted for a series of multifactor analyses. $P<0.05$ was regarded as significant.

Results

Short-term efficacy analysis

Of all patients, the medium chemotherapeutic cycle was 4 weeks, in which there were 15 PR, 20 SD and 12 PD, with total RR and DCR being 31.91% and 74.47%, respectively. Chi-squared test indicated that age, gender, ECOG score, TMN stages and chemotherapeutic protocols had no relation with chemotherapeutic efficacy. 15 patients with adeno-carcinoma reached PR, whereas the short-term efficacy of patients with large cell carcinoma and squamous adeno-carcinoma did not, and there was no significant difference in DCR (P=0.219); patients accompanied with malignant pleural effusion were better than the others (P=0.046), but DCR still had no significant difference (P=0.324); and smoking history was associated with efficacy, but no differences were found in ORR and DCR (Table 1).

Long-term efficacy analysis

At the end of the follow-up, 16 patients were survived and 2 lost their follow-ups, with medium PFS, medium OS, 1- and 2-year survival rates being 5 months, 15.2 months, 63.83% (30/47) and 19.15% (9/47), respectively, as shown in Figure 1. Single-factor analysis influencing PFS and OS demonstrated that tumor pathological patterns and

Table 2. Single-factor Analysis of OS in 47 NSCLC Patients in Phase IIIB/IV

Characteristic	N(%)	Medium PFS (month)	*P*	Medium OS (month)	*P*
Age			0.187		0.074
<65years	16(34.04)	6.2		15.7	
≥65 years	31(65.96)	5.1		14.0	
Gender			0.825		0.798
Male	28(59.57)	5.1		15.0	
Female	19(40.430	6.3		15.5	
ECOG score			0.588		0.100
0	11(23.41)	5.4		15.6	
1	24(51.06)	6.3		17.1	
2	12(25.53)	4.5		10.6	
Histological patterns			0.047		0.015
Large cell carcinoma	5(10.64)	3.9		11.4	
Adeno-carcinoma	34(72.34)	6.5		17.1	
Squamous adeno-carcinoma	8(17.02)	3.1		9.5	
TNM stage			0.116		0.224
IIIB	12(25.53)	6.0		17.2	
IV	35(74.47)	5.1		14.4	
Malignant pleural effusion			0.270		0.287
No	34(72.34)	5.0		15.5	
Yes	13(27.66)	5.6		14.7	
Smoking history			0.144		0.048
No	24(51.06)	6.3		15.8	
Yes	23(48.94)	5.0		14.0	
Chemotherapeutic protocols			0.063		0.051
PP	25(53.19)	5.9		15.7	
PC	22(46.81)	4.2		11.5	
Efficacy			0.020		0.003
PR	15(31.92)	8.4		18.6	
SD	20(42.55)	4.1		12.5	
PD	12(25.53)	3.1		9.5	

efficacy were in association with medium PFS ($P<0.05$) whereas tumor pathological patterns, smoking history and efficacy were in connection with medium OS ($P<0.05$). COX regression model, including gender, age, group, tumor pathological patterns, TMN stages, ECOG score, with/without malignant pleural effusion and smoking history, etc., was statistically analyzed, suggesting that pathological patterns and efficacy were the independent factors impacting OS ($P<0.05$), as shown in Table 3.

Adverse reactions

As shown in Table 4, hematological toxicity reactions were mainly manifested by declined white blood cell count and decreased PLT, including declined white blood cell count in degree III/IV in 4 patients, fever due to granulocytopenia in 1 and decreased PLT in degree III/IV in 3, while non-hematological toxicity reactions were marked by gastrointestinal reactions, such as nausea and vomiting, etc.. The other adverse reactions were low in rate and slight in severity, which could be favorably tolerated.

Discussion

As a mutil-target anti-metabolic cytotoxic drug and a folic acid antagonist, pemetrexed could suppress tumor development and progression via inhibiting

Table 3. Multi-factor Analyses of OS in 47 NSCLC Patients in Phase IIIB/IV

Programs	B	SE	Wald	df	Sig	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	0.200	0.454	0.194	1	0.659	1.222	0.502	2.974
Gender	-0.085	0.437	0.038	1	0.846	0.919	0.390	2.163
ECOG	0.477	0.291	2.688	1	0.101	1.612	0.911	2.853
Stages	-0.198	0.503	0.155	1	0.694	0.821	0.306	2.198
Smoking	-0.352	0.489	0.518	1	0.472	0.703	0.269	1.835
Protocols	-0.018	0.474	0.001	1	0.970	0.982	0.388	2.489
Efficacy	0.684	0.320	4.584	1	0.032	1.982	1.060	3.708
Pleural effusion	-0.722	0.459	2.468	1	0.116	0.486	0.197	1.196
Pathology	0.542	0.382	4.073	1	0.045	1.407	0.810	2.444

Table 4. Toxicity Reactions Analyses of 47 NSCLC Patients in Phase IIIB/IV(n)

Toxicity	0	I	II	III	IV	Rate(%)
Leukopenia	15	20	8	3	1	8.51
Anemia	14	21	11	1	0	2.13
Thrombocytopenia	23	12	9	2	1	6.38
Nausea/vomiting	11	22	9	5	0	10.64
Diarrhea	45	2	0	0	0	0
Constipation	42	4	1	0	0	0
Transminase increase	36	10	0	1	0	2.13
Serum creatinine increase	44	2	1	0	0	0
Peripheral nerve toxicity	46	1	0	0	0	0

folic acid-dependent enzymes, such as thymidylate synthase (TS), Dihydrofolate reductase (DHFR) and glycinamide ribonicleotide formyltransferase (GARFT), and disturbing the biosynthesis of thyminide and purine nucleoside. In 2004, FDA initially approved pemetrexed as the second-line treatment of NSCLC based on the study results of Hanna et al. Scagliotti et al., conducted a randomized control study (JMDB) in 2008, whose results demonstrated that pemetrexed plus cisplatin were better than gemcitabine plus cisplatin in efficacy (ORR: 30.6% vs. 28.2%), especially on patients with adeno-carcinoma and large cell carcinoma. Therefore, FDA approved pemetrexed plus cisplatin as the first-line treatment of NSCLC, except for patients with squamous carcinoma. JMDB subgroup analysis of East Asian revealed that in East Asian patients, such as Taiwan and Korean, etc., pemetrexed plus cisplatin was better in efficacy (ORR: 46.5% vs. 17.1%) and longer in survival time than gemcitabine plus cisplatin in patients with non-squamous carcinoma (Yang et al., 2010). Thus, this study analyzed the clinical effect, survival and relevant influence factors of pemetrexed plus platinum in treating NSCLC patients with non-squamous carcinoma.

This study retrospectively analyzed 47 advanced NSCLC patients with non-squamous carcinoma who had received pemetrexed plus platinum as the first-line treatment, and the results showed 31.91% RR and 74.47% DCR. ORR in this study was similar to that of IMDB, but lower than that in JMDB subgroups of East Asian. Chi-squared test indicated that age, gender, ECOG score, TMN stages and chemotherapeutic protocols had no relationship with chemotherapeutic efficacy; histological patterns showed that 15 patients with adeno-carcinoma reached PR, but those with large cell carcinoma and squamous adeno-

carcinoma did not, and there was no significant difference in DCR (P=0.219); RR in patients with malignant pleural effusion was better than the others (53.85% vs. 23.53%, P=0.046), and though there was no significant difference in DCR (P=0.324), imaging characteristics might become a potential research direction for the prognostic factors of pemetrexed. Further evaluation could not be conducted due to the small amount of cases in this study, so more samples are needed. Additionally, patients without smoking history had better total RR and DCR than those who smoke (P<0.05).

Medium PFS and OS in all patients were 5 months and 15.2 months, while 1- and 2-year survival rates were 63.83% (30/47) and 19.15% (9/47), respectively. Medium OS in patients with non-squamous carcinoma was better in this study than those in JMDB, which might relay on two reasons: firstly, the survival advantage of East Asians with NSCLC (including Chinese patients) was better than overall populations, which was consistent with JMDB subgroup analyses of East Asians, and secondly, the percentage of patients with smoking history was low in this study (23/47, 48.94%), whereas in JMDB, smokers accounted for 73%. Single-factor analysis influencing PFS and OS proved that tumor pathological patterns and efficacy were in association with medium PFS, and patients with adeno-carcinoma or favorable short-term efficacy had longer medium PFS (P<0.05), while pathological patterns, smoking history and efficacy were closely related with medium OS that was prolonged significantly in patients with adeno-carcinoma and favorable short-term efficacy, and without smoking history (P<0.05). COX multi-factor analyses showed that pathology and efficacy were the independent prognostic factors for OS (P<0.05), but further study was still needed to conform the influence of suqamous adeno-carcinoma in this study. At present, some researches demonstrated that pemetrexed was more effective in treating NSCLC patients with positive ALK, with longer PFS and OS, etc. (Altavilla et al., 2010; Jeong-Ok et al., 2011; D. Ross et al., 2011; Chang et al., 2013; Ho et al., 2013; Wang et al., 2013). Duan et al. (2012) reported that in the first-line treatment of NSCLC with pemetrexed, PS enzyme expression was in close connection with survival time. Therefore, study range should be further expanded to obtain prognostic factors from molecular and genetic levels (Hattori et al., 2013; Kim et al., 2013; Pereira et al., 2013).

Pemetrexed plus platinum proved favorable tolerance on adverse reactions, marked by low rate of toxicity reactions in degree III/IV, in which hematological toxicity reactions included reduced white blood cell count and decreased granulocytes, and non-hematological toxicity reactions included gastrointestinal responses, such as nausea and vomiting, etc. (Hattori et al., 2013; Patel et al., 2013). And further analysis showed that elderly patients (>65 years) also had favorable drug-tolerance, and there was no significant difference between PC and PR.

To sum up, as an effective and low-toxicity cytotoxic drug, pemetrexed plays an important role when combined with platinum as the first-line treatment of NSCLC, especially on patients with non-squamous carcinoma (de Marinis et al., 2013; Hatakeyama et al., 2013). With the continuous promotion and application of evidence-based medicine, the emphasis of our research focuses on finding out the relevant advantageous population for pemetrexed through clinical selection, pathological patterns of molecules and genetic detection, etc., so as to provide individual therapies and cytotoxic drugs with higher efficacy and low toxicity.

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