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Original Article

Docetaxel-based doublet versus pemetrexed-based doublet as second-line therapy in TKI treated advanced NSCLC patients with EGFR mutations: a multicenter retrospective study

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Abstract: This research aimed to investigate the effectiveness and safety of docetaxel-based versus pemetrexed-based doublet as second-line therapy in TKI treated NSCLC patients with EGFR mutations. Sixty-nine patients without T790M mutation who failed EGFR TKI therapy received second-line chemotherapy. Thirty-eight patients treated with a docetaxel-based doublet and 31 patients were treated using pemetrexed-based doublet. Little difference of overall response rate could be found between the two arms (docetaxel-based doublet vs pemetrexed-based doublet: 15.79% vs 19.35%; P = 0.473). No complete responses were observed in both arms. Median progression free survival was 3.5 months in the docetaxel-based doublet group and 5.1 months in the pemetrexed-based group (P = 0.0029). There was no statistical difference of OS between the two groups (P = 0.1019). No significant differences were observed between the two arms in terms of hematological toxicity, with the exception of leucopenia which was more pronounced in the docetaxel-based doublet (P = 0.007). Our findings in this study indicated that the Pemetrexed-based doublet showed an improvement in PFS compared with docetaxel-based doublet in NSCLC patients with EGFR mutations who failed first-line EGFR TKI treatment.

Keywords: Docetaxel, pemetrexed, EGFR mutations, tyrosine kinase inhibitors

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and is often diagnosed at an advanced stage. With first-line platinum-based chemotherapy, the median survival of NSCLC was reported to be only 7-10 months [1, 2]. In recent years, targeted therapies have been developed to improve survival of NSCLC patients with EGFR mutation. Mutations in exon 19 (Del19) and exon 21 (L858R) of EGFR gene were found to be correlated with a 70% response rate as well as a striking PFS prolongation in patients who received gefitinib or erlotinib treatment. However, no difference in OS could be detected [3-5]. EGFR mutation has been found in about 10% in the European patients with NSCLC, while it was reported to be as high as 30-40% in patient from East Asian patients. Particularly, the overall survival of NSCLC patients with EGFR mutations is potentially longer than those patients with wild type EGFR. Therefore, TKIs targeting EGFR has been approved as the first-line treatment for NSCLC patients with EGFR mutations.

Second-line treatments are indicated after disease progression. Until now, many clinical trials have been conducted to evaluate the efficacy and safety of docetaxel-based or pemetrexed-based doublets therapies in NSCLC patients those were previously treated with first-line platinum-doublet chemotherapy. Metaanalyses showed that both doublet combination therapy significantly improved progression free survival (PFS) and overall response rate (ORR) compared with single agent chemotherapy, although it did not improve the overall survival (OS) [6]. To date, no randomized prospective studies have

Table 1. Baseline characteristics of the study population

Patient characteristics	Docetaxel-based doublet (38)	Pemetrexed-based doublet (31)	t/x^2 value	*p* value
Age-(year)				
Mean	57.6	59.2	-1.22	0.24
Range	38-68	36-69		
Sex				
Male	19 (50%)	20 (64.5%)	1.46	0.17
Female	19 (50%)	11 (35.5%)		
Histologic feature of tumor				
Adenocarcinoma	36 (94.7%)	31 (100%)	1.67	0.30
Squamas cell	2 (5.2%)	0		
EGFR statue				
L858R	16 (50%)	13 (41.9%)	0.00	0.59
19DEL	22 (57.8%)	18 (58.0%)		
Disease stage				
IV	38 (100%)	31 (100%)	-	-
Site of metastasis				
Brain	10 (26.3%)	8 (25.8%)	0.02	0.59
Liver	1 (2.6%)	1 (3.3%)	0.02	0.70
Bone	14 (36.8%)	22 (70.9%)	7.97	0.06
Suprarenal gland	2 (5.2%)	3 (9.6%)	0.06	0.41
WHO performance status				
0-1	34 (89.4%)	25 (80.6%)	0.48	0.24
2-3	4 (10.5%)	6 (19.3%)		
WC < 3.5×10^9	2 (5.2%)	2 (6.4%)	0.04	0.61
Neutrophils < 2×10^9	1 (2.6%)	1 (3.2%)	0.02	0.70
Platelets < 100×10^9	3 (7.8%)	3 (9.6%)	0.07	0.56
Haemoglobin < 11.5 g/dl (woman), 13 g/dl (man)	14 (36.8%)	13 (41.9%)	0.57	0.31
ALP	4 (10.5%)	15 (48.3%)	12.26	0.00

been reported to evaluate the efficacy and safety of docetaxel-based or pemetrexed-based doublets therapies in EGFR TKI treated NSCLC patients. A retrospective analysis showed that second-line pemetrexed singlet therapy significantly prolonged PFS compared to platinum-based doublet chemotherapy for NSCLC patients with EGFR mutations who failed in treatment of first-line EGFR TKI [7]. Here, we retrospectively investigate the effectiveness and safety of docetaxel-based versus pemetrexed-based doublet as second-line therapy post EGFR TKI treatment in NSCLC patients with EGFR mutations.

Patients and methods

Patients

One hundred and ninety-eight EGFR mutation positive patients with metastatic NSCLC (stage IV) were treated with TKIs between January 2008 and December 2014 at West China Hospital of Sichuan University, the Second Peoples Hospital of Sichuan, Sichuan province and Enshi Tujia and Miao Autonomous Prefecture Central Hospital. The study protocol was approved by the Institutional Review Board of Enshi Tujia and Miao Autonomous Prefecture Central Hospital. Patients who were eligible for inclusion in this study at the age of 18 or older were confirmed with advanced NSCLC (stage IV). Other inclusion criteria are as below: activating EGFR mutations including microdeletion at exon 19 or point mutation in site of L858R at exon 21, having received first-line EGFR-TKIs treatment and at least 1 measurable tumor lesions as evaluated by imaging detection. Exclusion Criteria are: a) Any evidence of severe or uncontrolled systemic diseases (unstable respiratory, cardiac, hepatic, or renal disease or other serious internal diseases or uncon-

Table 2. Response between docetaxel-based doublet and pemetrexed-based doublet groups

Response	Docetaxel-based doublet group	Pemetrexed-based doublet group	*P* value
CR	0	0	-
PR	6 (15.8%)	7 (22.6%)	0.473
SD	4 (10.5%)	5 (16.1%)	0.492
PD	28 (73.7%)	19 (61.3%)	0.720
DCR	10 (26.3%)	12 (38.7%)	0.308

CR: complete remission, PR: part remission, SD: stable disease, PD: progressive disease, DCR: disease control rate.

trolled infection); b) Any pregnant or lactating woman; c) Severe hypersensitivity to docetaxel, cisplatin, carboplatin, and pemetrexed. A total of 69 patients without T790M mutation failed first-line TKI treatment was enrolled in the study.

Treatment

Among the 198 patients, 69 NSCLC patients with EGFR mutations who failed first-line TKI were enrolled. Thirty-eight patients were treated with a docetaxel-based doublet (docetaxel/cisplatin, n = 17; docetaxel/carboplatin, n = 21) and 31 patients were treated using pemetrexed-based doublet (pemetrexed/carboplatin, n = 30; pemetrexed/cisplatin, n = 1). The administered dose of each drug are as below: docetaxel (75 mg/m^2)/pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC = 5) on day 1, repeated every 3 weeks. All chemotherapy drugs were administered intravenously.

Treatment assessments

The primary outcome was PFS after second-line chemotherapy. PFS was defined as the time from the start of docetaxel-based or pemetrexed-based doublet therapy till disease progression under the targeted therapy or death. The secondary outcome was OS in these patients. OS was defined as the time from the start of docetaxel-based or pemetrexed-based doublet therapy till the death of any cause. During treatment, tumor response was assessed every 2 months. Tumor response was performed using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. Safety and tolerability were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Statistics analysis

This analysis is based on the data obtained during the follow-up from January 2008 to December 2014. The survival time was calculated from the date of treatment initiation to that of death from any causes or to the last date of confirmation of survival. PFS and OS were assessed using the Kaplan-Meier method and compared between risk groups using the log-rank test. *P* values less than 0.05 were considered as statistically significant. Adverse events were assessed according to the NCI-CTCAE version 4.0. The significance of differences in adverse events and treatment response between the two arms was calculated by chi-square test. The statistical software SPSS16.0 (SPSS Inc., Chicago, Illinois) was used for all the statistical analysis.

Results

Patient characteristics

A total of 69 patients with PS score of 0-1 (85.5%) were enrolled in this retrospective study. The majority of patients had histological diagnoses of adenocarcinoma (97.1%). Male patients are more than female (60.8% vs. 39.2%). All patients were confirmed with EGFR mutation by PCR performed at the central laboratory in our hospital. Among the 69 patients, 36 patients were found to bear with bone metastases, while 18 patients with brain metastases, 5 patients with adrenal metastases, and 2 patients with liver metastases. Thirty eight patients were treated with a docetaxel-based doublet (docetaxel/cisplatin, n = 17; docetaxel/carboplatin, n = 21) and 31 patients were treated with a pemetrexed-based doublet (pemetrexed/carboplatin, n = 30; pemetrexed/cisplatin, n = 1). Baseline clinical and pathological characteristics are presented in **Table 1**.

Overall response rate to the chemotherapy was similar in the two groups

The overall response rates were close to each other in the two arms (docetaxel-based doublet vs pemetrexed-based doublet: 15.79% vs

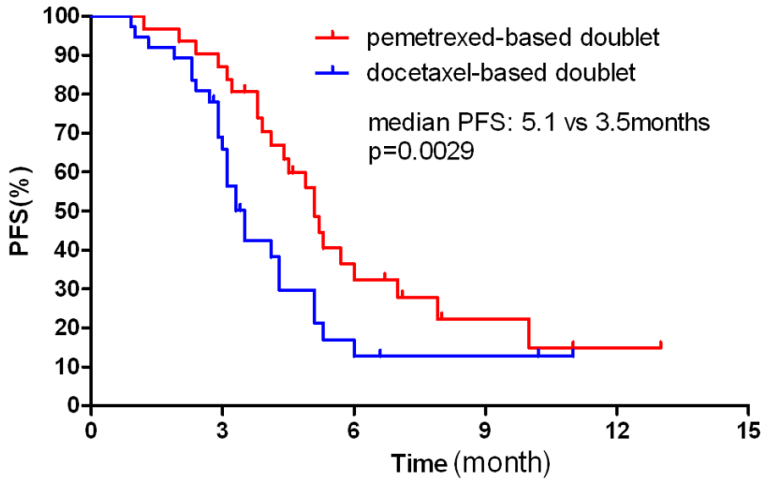

Figure 1. Kaplan-Meier curves showing progression-free survival, stratified by the use of second-line chemotherapy.

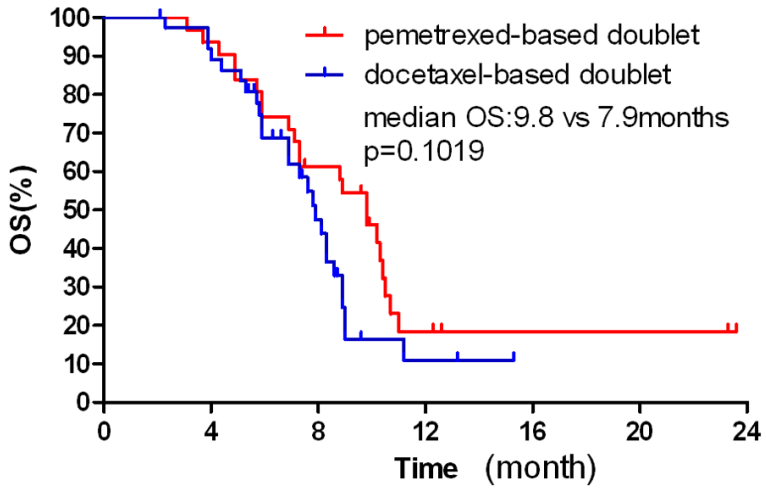

Figure 2. Kaplan-Meier curves showing overall survival, stratified by the use of second-line chemotherapy.

19.35%; P = 0.473). No patient with complete response were observed in both arms, while 6 (15.79%) and 7 (19.35%) patients achieved a partial response (PR) in the docetaxel-based doublet and pemetrexed-based doublet, respectively. More patients in the docetaxel-based doublet (10, 26.3%) had progressive disease (PD) compared with pemetrexed-based doublet (6, 19.3%). However, the difference is not statistically significant (P = 0.720) (**Table 2**).

Pemetrexed group showed an improvement in PFS compared with docetaxel group

Median PFS was 3.5 months in the docetaxel-based doublet group and 5.1 months in the pemetrexed-based group, respectively (HR 1.457; 95% CI: 0.8904 to 2.7204; P = 0.0029; **Figure 1**). The results suggested that pemetrexed-based treatment result in significantly longer PFS than docetaxel-based therapy. In addition, the median OS was 7.9 months for the docetaxel-based doublet group and 9.8 months for pemetrexed-based doublet group (HR 0.6101; 95% CI: 0.3375 to 1.103; P = 0.1019; **Figure 2**).

Leucopenia was more pronounced in docetaxel group than pemetrexed group

All the 69 patients were evaluated for hematotoxicitya. The grade 3 or greater hematotoxicity observed during treatment are summarized in **Table 3**. In this study, 28 (73.7%) patients experienced grade 3 or 4 hematotoxicity in the docetaxel-based group and 10 (32.2%) in the pemetrexed-based group. No significant differences were observed between the two arms in terms of hematological toxicity, with the exception of leucopenia which was more pronounced in the docetaxel-based doublet group (P = 0.007). No significant differences were observed between the two arms in terms of other adverse effect such as nausea/vomiting, diarrhea, fatigue, rash.

Discussion

Platinum-based chemotherapy is the standard first-line treatment for patients with NSCLC, and the response rate is approximately 30%, usually lasting only 4 to 5 months [8]. Phase III trials suggest that no major efficacy differences exist between approved platinum-based treatments [9]. However, the efficacy of second-line treatment for patients with relapsing or progressing disease are generally poor, with response rate of less than 10% and OS of 7-8

Table 3. Hematotoxicity observed in patients treated with different regimens

Factors	Subgroups	Docetaxel-based doublet (%)	Pemetrexed-based doublet (%)	*P* value
Leucopenia	Grade 3	9 (23.7%)	2 (12.9%)	0.0045
	Grade 4	6 (15.7%)	1 (3.2%)	0.119
	Grade 3 or Grade 4	15 (39.4%)	3 (9.6%)	0.007
Thrombocytopenia	Grade 3	3 (7.9%)	1 (3.2%)	0.622
	Grade 4	1 (2.6%)	0	1.000
	Grade 3 or Grade 4	4 (10.5%)	1 (3.2%)	0.366
Neutropenia	Grade 3	6 (15.7%)	1 (3.2%)	0.119
	Grade 4	1 (2.6%)	1 (3.2%)	1.000
	Grade 3 or Grade 4	7 (18.4%)	2 (12.9%)	0.171
Anemia	Grade 3	2 (5.2%)	4 (12.9%)	0.397
	Grade 4	0	0	-
	Grade 3 or Grade 4	2 (5.2%)	4 (12.9%)	0.397

months [10-14]. A standard regimen of docetaxel or pemetrexed has been established based on results of randomized phase III studies of patients with previously treated advanced NSCLC [15, 16]. Although the role of platinum-based combination chemotherapy in the first-line treatment of advanced NSCLC is clearly defined, it is still a matter of debate in second-line treatment. The results of GOIRC 02-2006 provide convincing evidence that carboplatin does not add any significant benefit in terms of RR, PFS, or OS compared with pemetrexed alone, in the second-line treatment of patients with advanced NSCLC pretreated with platinum-based first-line chemotherapy [17]. However, the Dutch NVALT7 study demonstrated a statistically significant improvement in terms of PFS (from 2.8 to 4.2 months; HR, 0.67; 95% CI, 0.51 to 0.89; P < 0.005) in favor of carboplatin plus pemetrexed compared with pemetrexed alone [18]. Considering the greater toxicity of doublet therapy, singlet chemotherapy might be considered as one of the standard options for second-line treatment of advanced/metastatic NSCLC patients with poor PS and advanced age [19, 20]. Current guidelines recommend using platinum-based doublet therapy for NSCLC patients with EGFR mutations who fail first-line TKI therapy. However, no randomized studies have been reported to provide evidence to support the recommendations. On the other hand, a large phase III study showed that response and clinical benefit (CR/PR/SD) were similar to the second-line treatment of advanced NSCLC patients receiving either pemetrexed or docetaxel [15]. To date, studies comparing effectiveness and safety of docetaxel-based versus pemetrexed-based doublet as second-line therapy in EGFR TKI treated NSCLC patients with EGFR mutations are still lacking. Only a retrospective study found that second-line singlet pemetrexed for NSCLC patients with EGFR mutations who failed first-line EGFR TKI treatment showed longer PFS compared with patients receiving a platinum-based doublet. In addition, subpopulation analysis showed that the HR decreased in patients with good ECOG PS (0, 1) and in female patients [10]. Our results showed that the PFS of patients receiving pemetrexed-based doublet was significantly longer than that of patients receiving a docetaxel-based therapy. Median progression-free survival was 5.1 months in the pemetrexed-based group which was accorded with previous studies [18, 21]. The median progression-free survival of the docetaxel-based doublet are also in agreement with a large randomized phase III comparing the activity and toxicity of docetaxel/carboplatin (DC) doublet vs single agent docetaxel as second-line treatment in patients with advanced NSCLC [22]. There was no statistically significant difference in the OS between the patients treated with pemetrexed-based doublet and docetaxel-based doublet. The median OS was reported to be 9.8 months with pemetrexed-based doublet treatment and also longer than that of single pemetrexed (8.3 months) in Hanna's study [12].

In our study, the most frequent hematological toxicities were leucopenia and neutropenia. No significant differences were observed between the two arms in terms of hematological toxicity, with the exception of leucopenia which was

more pronounced in the docetaxel-based doublet (P = 0.007). In this study, no patient died of chemotherapy.

In this research, some limitations certainly exist. First, this study is a retrospective clinical study. Although the clinical characteristics of patients were balanced between the two treatment groups, the number of cases in each group is small, the bias is inevitable. So, it is necessary to conduct large sample, randomized and prospective clinical trials. Second, EGFR 19-del mutation is more frequent than L858R mutation in exon 21 in this study. Previous study found that, tumors with 19-del mutation is more sensitive to EGFR-TKIs treatment compare to those bearing L858R mutation [22, 23]. Therefore, composed different cases may impact the results.

In conclusion, the PFS of patients with EGFR mutations who failed first-line EGFR TKI treatment and then received pemetrexed-based doublet is significantly longer than those receiving a docetaxel-based therapy. Further prospective randomized clinical trials will confirm whether pemetrexed-based doublet is superior to docetaxel-based doublet for NSCLC patients with EGFR mutations who failed first-line EGFR TKI treatment.

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Disclosure of conflict of interest

None.

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