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Docetaxel-Based Doublet Versus Pemetrexed-Based Doublet as Second-Line Therapy

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Abstract

This research aims to investigate the comparative effectiveness and safety of docetaxel-based versus pemetrexed-based doublet as second-line therapy in EGFR TKI treated NSCLC patients with EGFR mutations. Sixty-nine patients without T790M mutation who failed EGFR TKI therapy received second-line cytotoxic 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

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Introduction

Non-Small-Cell Lung Cancer (NSCLC) accounts for 85% of lung cancer, and is often diagnosed at an advanced stage. With first-line platinum-based chemotherapy regimens, median survival is 7–10 months [1-2]. Targeted therapies are actively being developed to improve efficacy in activating EGFR mutation patients of NSCLC. EGFR-activating mutations in exon 19 (Del19) and exon 21 (L858R) correlated with a 70% TKI treatment response rate and a striking PFS prolongation for patients receiving gefitinib or erlotinib. However, no difference in OS could be detected [3-5]. EGFR mutation covers about 10% in the European patients, it is as high as 30-40% in East Asian patients, and the survival of patients with EGFR mutation is longer than EGFR wild type patients. Therefore, EGFR TKIs were proposed as the preferred first-line treatment for NSCLC patients with EGFR mutations.

Second-line treatments are indicated after disease progression, many trials have been conducted to evaluate the efficacy and safety of docetaxel-based or pemetrexed-based doublets therapies in previously treated with first-line platinum-doublet chemotherapy NSCLC. Meta-analyses results show that both doublet combination therapies significantly improved Progression Free Survival (PFS) and Overall Response Rate (ORR) compared with single agent chemotherapy, it does not translate into an Overall Survival (OS) advantage [6]. To date, no randomized prospective studies have 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 shows that second-line pemetrexed singlet therapy provides significantly prolonged PFS compared to second-line platinum-based doublet chemotherapy for NSCLC patients with EGFR mutations who failed first-line EGFR TKI [7]. We consider it particularly important to investigate the comparative effectiveness and safety of docetaxel-based versus pemetrexed-based doublet as second-line therapy in EGFR TKI treated NSCLC patients with EGFR mutations.

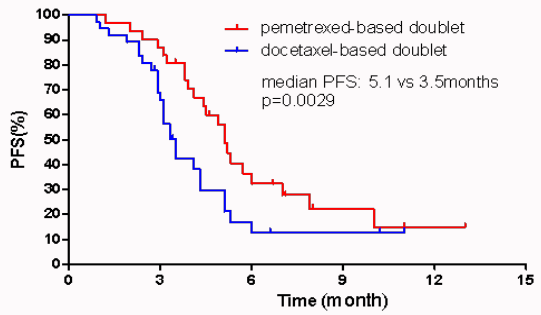

Figure 1: Kaplan–Meier curves showing progression-free survival, stratified by the use of second-line chemotherapy.

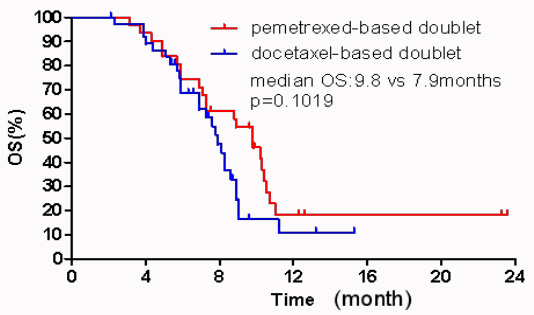

Figure 2: Kaplan–Meier curves showing overall survival, stratified by the use of second-line chemotherapy.

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 were eligible for inclusion in this study at the age of 18 or older, had confirmed advanced NSCLC (stage IV), activating EGFR mutations consisting of microdeletion in exon 19 or an L858R point mutation in exon 21, received first-line EGFR-TKIs treatment and at least 1 measurable tumor lesions as evaluated by imaging detection. Exclusion Criteria:

1. Any evidence of severe or uncontrolled systemic diseases (unstable respiratory, cardiac, hepatic, or renal disease or other serious internal diseases or uncontrolled infection).

2. Any pregnant or lactating woman.

3. 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

3Among the 198 patients, 69 NSCLC patients with EGFR mutations who failed first-line TKI were enrolled. Thirty-eight patients 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). 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 endpoint was progression-free survival after second-line chemotherapy. PFS was defined as the lapse of time between the start of docetaxel-based or pemetrexed-based doublet therapy and progressive disease under the targeted therapy or death. The secondary endpoint was Overall Survival (OS) in such patients. OS was defined as the lapse of time between the start of docetaxel-based or pemetrexed-based doublet therapy and 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 and December 2014. PFS and OS were assessed using the Kaplan-Meier method and compared between risk groups using the chi-square test. P values less than 0.05 were considered to be 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 χ^2 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 participated in this retrospective study. The majority of patients were male (60.8%), had PS scores of 0-1 (85.5%), and had histological diagnoses of adenocarcinoma (97.1%). All patients were positive for EGFR mutation at the central laboratory in each treatment group. Among the 69 patients, 36 patients with bone metastases, 18 patients with brain metastases, 5 patients with adrenal metastases, 2 patients with liver metastases. 38 patients treated with a docetaxel-based doublet (docetaxel/cisplatin, n=17; docetaxel/carboplatin, n=21) and 31patients treated with a pemetrexed-based doublet (pemetrexed/carboplatin, n=30; pemetrexed /cisplatin, n=1). Baseline clinical and pathological characteristics are presented in Table 1.

Responses to the second line therapy

Overall response rate was closing in 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, while six (15.79%) and seven (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 had progressive disease (PD) compared with pemetrexed-based doublet; PD was observed in 10 (26.3%) and 6(19.3%) patients, respectively (p = 0.495) (Table 2).

Survival after second-line therapy

Median progression-free survival was 3.5 months in the docetaxel-based doublet group and 5.1 months in the pemetrexed-based group (HR 1.457; 95% CI: 0.8904 to 2.7204; p=0.0029; Figure 1). The results suggested that pemetrexed-based treatment resulted in significantly

Table 1: Baseline characteristics of the study population.

Patient characteristics	Docetaxel-based doublet(38)	Pemetrexed-based doublet(31)
Age-(year)		
Mean	61.6	59.2
Rang	38-85	36-81
Sex		
Male	19(50%)	20(64.5%)
Female	19(50%)	23(74.1%)
Histologic feature of tumor		
Adenocarcinoma	36(94.7%)	31(100%)
Squamas cell	2(5.2%)	0
EGFR statue		
L858R	16(50%)	13(41.9%)
19DEL	22(57.8%)	18(58.0%)
Disease stage		
IV	38(100%)	31(100%)
Site of metastasis		
Brain	10(26.3%)	8(25.8%)
Liver	1(2.6%)	1(3.3%)
Bone	14(36.8%)	22(70.9%)
Suprarenal gland	2(5.2%)	3(9.6%)
WHO performance status		
0-1	34(89.4%)	25(80.6%)
2-3	4(10.5%)	6(19.3%)
WC<3.5 X 109	2(5.2%)	2(6.4%)
Neutrophils<2 X 109	1(2.6%)	1(3.2%)
Platelets<100X109	3(7.8%)	3(9.6%)
Haemoglobin<11.5 g/dl(woman),13g/dl(man)	14(36.8%)	13(41.9%)
ALP	4(10.5%)	15(48.3%)

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(19.3%)	0.473
SD	4(7.8%)	5(16.1%)	0.492
PD	10(26.3%)	6(19.3%)	0.72
ORR	10(26.3%)	12(38.7%)	0.308

longer progression-free survival 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 (HR0.6101; 95% CI: 0.3375 to 1.103; p=0.1019; Figure 2).

Adverse reactions

All the 69 patients were evaluated for hematotoxicitya. The grade 3 or greater hematotoxicity and observed during treatment are summarized in Table 3. In this retrospective study, 28 (73.5%) and 10 (32.2%) patients experienced grade 3 or 4 hematotoxicity in the docetaxel-based and the pemetrexed-based group respectively. 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).

Discussion

Platinum-based chemotherapy is the standard first-line treatment, and it has a response rate of approximately 30%, the response usually lasts only 4 to 5 months [8]. Phase III trials suggest that no major efficacy differences exist between approved platinum-based treatments [9]. However, results 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 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

Table 3: Hematotoxicity observed in patients treated with different regimens.

Factors	Subgroups	Docetaxel-based doublet (%)	Pemetrexed-based doublet (%)	p
Leucopenia	Grade 3	9(23.7%)	2(12.9%)	0.005
	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
	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
	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

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 should 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 use of 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. Although, a large phase III study showed that response and clinical benefit rates (CR/PR/SD) were similar to the second-line treatment of advanced NSCLC patients receiving either pemetrexed or docetaxel [15]. Series 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 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 for 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 non-small cell lung cancer [22] .There was no statistically significant difference in the OS of our patients treated using pemetrexed-based doublet versus docetaxel-based doublet. The median OS time was 9.8 months, which was 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 cases number is more than L858R mutation in exon 21 in this study. Previous study found that, 19-del mutation is more sensitive to EGFR-TKIs compare to L858R mutation [22,23]. Therefore, composed different cases may have impact to 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 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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