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Pemetrexed Monotherapy and Pemetrexed Plus Platinum Combination Therapy as Non-First-Line Treatments for Advanced Non-Small Cell Lung Cancer

Fang WANG[1,2]*
Gui-fang GUO[1,2]*
Hui-juan QIU[1,2]
Xu-xian CHEN[1,2]
Pi-li HU[1,2]
Fei-fei ZHOU[3]
Wen-zhuo HE[1,2]
Bei ZHANG[1,2]
Liang-ping XIA[1,2]

[1] State Key Laboratory of Oncology in South China, Guangzhou 510060, Guangdong Province, China
[2] VIP Region, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China
[3] Tumor Center, The Foshan First People's Hospital, Foshan 510060, Guangdong Province, China

*These authors contributed equally to this study and share the first authorship.

Correspondence to: Liang-ping XIA
Tel: 86-20-8734 3107
E-mail: xialiangping@163.com

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E-mail: editor@cocronline.org
Tel (Fax): 86-22-2352 2919

OBJECTIVE Data on the efficacy profiles of pemetrexed monotherapy and pemetrexed plus platinum combination therapy in the non-first-line setting for patients with advanced non-small cell lung cancer (NSCLC) are limited, and previous studies have reported contradictory results. This study investigated and compared the efficacy and toxicity profiles of these two regimens to provide a broader understanding of their dynamics.

METHODS Previously treated patients with advanced and/or recurrent NSCLC who received pemetrexed monotherapy or pemetrexed plus platinum combination therapy between January 1, 2006, and December 31, 2009, at Sun Yat-sen University Cancer Center were evaluated. The primary endpoint of this study was progression-free survival (PFS), whereas the secondary endpoints were overall response rate (ORR), disease control rate (DCR), overall survival (OS), and toxicity. Survival was analyzed using the Kaplan–Meier method. Univariate analysis was performed to identify the factors potentially influencing OS, and chi-square analysis was carried out to compare ORR and DCR.

RESULTS Forty-six patients with advanced and/or recurrent NSCLC were analyzed; of these patients, 25 were given pemetrexed monotherapy and 21 received pemetrexed plus platinum combination therapy. The following correspond to the rates recorded for the pemetrexed monotherapy group and the pemetrexed plus platinum group: median PFS, 1.97 and 2.3 months ($P=0.565$); median OS, 30.93 and 30.33 months ($P=0.877$); ORR, 8% (2/25) and 9.5% (2/21) ($P=0.857$); and DCR, 32% (8/25) and 57.1% (12/21) ($P=0.09$). Univariate analysis revealed that no factor was correlated with OS from NSCLC ($P>0.05$ for all). Gastrointestinal toxicity in the pemetrexed plus platinum group was modestly higher than that in the pemetrexed monotherapy group ($P=0.034$), but other adverse events were similar between the groups.

CONCLUSION Compared with pemetrexed monotherapy, pemetrexed plus platinum combination therapy causes more gastrointestinal toxicities and does not exhibit improved efficacy, in terms of ORR, DCR, PFS, and OS, in the non-first-line setting for NSCLC. However, further research with a higher patient population is necessary to validate this finding.

KEY WORDS: pemetrexed, non-small cell lung cancer, efficacy, safety, non-first-line setting.

Abbreviations: NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; PS, performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Introduction

Lung cancer is the leading cause of cancer death worldwide due to its high and increasing incidence and the low median overall survival (OS) rate associated with it (< 1 year)[1,2]. Research has shown the significance of epidermal growth factor receptor (EGFR) mutations in this disease[3]: the tyrosine kinase inhibitors (TKIs) of EGFR prolong the median OS to 18.6–30.5 months if the tumor harbored EGFR mutations[4–6]. Mok et al.[4] reported that only a few patients have had the opportunity to benefit from TKIs as only a limited number of patients are able to provide sufficient quantities of tumor tissue for gene testing (e.g., 35.9% of their patients) and due to the low rates of EGFR mutation in the entire non-small cell lung cancer (NSCLC) population[4]. Whether TKIs should be administered in the first-line or second-line setting remains unclear, as preliminarily data from Hong Kong and Japan have demonstrated that TKIs followed by chemotherapy and chemotherapy followed by TKIs are equally effective[4,5]. As such, cytotoxic chemotherapy still plays a key role in NSCLC treatment. The issue of finding superior patients who may benefit from different cytotoxic agents also needs to be addressed. Pemetrexed has been proven to be able to distinguish such patients based on pathological data. Patients with non-squamous cell carcinoma, especially adenocarcinoma, reportedly show greater sensitivity to pemetrexed compared with patients with squamous cell carcinoma[7–9].

Pemetrexed combined with platinum has been proven effective as a traditional standard platinum-based doublet in the first-line setting for NSCLC[10–16]. Data support the rational combination of pemetrexed with other cytotoxic agents. However, docetaxel, pemetrexed, and erlotinib, the three agents recommended by the National Comprehensive Cancer Network in the second-line setting for NSCLC, are all monotherapies[17–19]. In fact, some patients with good performance status (PS) even after the failure of their first-line treatment may tolerate the combination of two cytotoxic agents in a single regimen. However, only two studies[20,21] have focused on whether pemetrexed should be given alone or in combination with other agents in the second-line setting, and their outcomes were inconsistent. Moreover, information about the use of pemetrexed beyond the second-line setting is currently unavailable. The present study compared NSCLC patients who received pemetrexed monotherapy with those given pemetrexed plus platinum combination therapy in the non-first-line setting to elucidate this issue.

Patients and Methods

Patients

Patients who met the following criteria were included in this study: (1) had histologically or cytologically proven NSCLC; (2) with recurrent disease or in advanced stages at the time of receiving a pemetrexed-containing regimen; (3) failed any prior chemotherapy without pemetrexed-containing regimens; (4) accepted either pemetrexed monotherapy or pemetrexed plus platinum combination therapy between January 1, 2006, and December 31, 2009, at Sun Yat-sen University Cancer Center; and (5) had adequate hematological function and adequate hepatic/renal function. Forty-six patients were enrolled in this study, of whom 25 accepted pemetrexed monotherapy and 21 received pemetrexed plus platinum combination therapy. The patients' basic characteristics are listed in Table 1.

Methods

Pemetrexed at a dose of 500 mg/m^2 was given to patients every 3 weeks. This dose was selected as it proved to be equally effective as doses of 900–1000 mg/m^2 [22,23]. Other cytotoxic agents were administrated under standard dosages and schedules. All patients were followed up, with the median follow-up time being 46.2 months (range, 24.0–84.3 months). The last patient follow-up via telephone interview was conducted on July 10, 2010. Treatment efficacy was evaluated consistently according to the RECIST response evaluation criteria[24], which included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). DCR was defined as the number of patients rated as having PR, CR, or SD divided by the total number of patients evaluated ($\times 100\%$).

Statistical analysis

All statistical analysis was conducted with SPSS 13.0. The primary endpoint of this study was progression-free survival (PFS), which was calculated as the interval between the date of pemetrexed administration and the date of disease progression or upon death without progression. The secondary endpoints were OS (from diagnosis to date of death or last date of follow-up), ORR, DCR, and toxicity. Treatment safety was evaluated as grade 0, I, II, III, or IV according to the National Cancer Institute Common Toxicity Criteria (version 3.0)[25]. The Kaplan–Meier method was used for survival analysis; chi-square analysis was employed to compare characteristics, ORR, DCR, and toxicity between groups; and univariate analysis was adopted to determine the influential factors of disease prognosis. $P<0.05$ was considered statistically significant.

Results

Efficacy

Of the 46 patients, 2 from the pemetrexed plus platinum group were lost to follow-up. Thirty-one patients (67.4%) died at the time of data analysis, including 16 patients from the pemetrexed monotherapy group and 15 from the pemetrexed plus platinum group. Analysis of

Table 1. Baseline characteristics of the study patients.

Characteristics	Pemetrexed monotherapy, *n* (%)	Pemetrexed plus platinum, *n* (%)	*P*
Gender			
Male	17 (68)	16 (76.2)	0.539
Female	8 (32)	5 (23.8)	
Age, years			
<60	19 (78)	14 (66.7)	0.484
⩾60	6 (22)	7 (33.3)	
Surgery history			0.617
Yes	5 (20)	4 (19)	
No	20 (80)	17 (81)	
Radiotherapy history			0.514
Yes	7 (28)	4 (19)	
No	18 (72)	17 (81)	
Pathological type			0.077
Adenocarcinoma	20 (80)	14 (66.7)	
Squamous cell carcinoma	5 (20)	3 (14.3)	
NSCLC	0 (0)	4 (19)	
Initial clinical stage			0.315
I	0	2 (9.5)	
II	1 (4)	0	
III	7 (28)	4 (19)	
IV	17 (68)	15 (71.5)	
First-line chemotherapy regimens			0.101
Docetaxel + platinum	4 (16)	5 (23.8)	
Vinorelbine + platinum	0	5 (23.8)	
Vinorelbine+ Gemcitabine	3 (12)	2 (9.5)	
TKI	5 (20)	3 (14.3)	
Docetaxel or Platinum	4 (16)	0	
Paclitaxel+ platinum +TKI	2 (8)	0	
Gemcitabine+ platinum	2 (8)	3 (14.3)	
Paclitaxel+ Carboplatin	5 (20)	3 (14.3)	
The lines of pemetrexed application			0.052
The Second-line	5 (20)	4 (19.1)	
The third-line	13 (52)	3 (14.3)	
The fourth line	4 (16)	3 (14.3)	
The fifth line	3 (12)	5 (23.8)	
The Sixth line	0	2 (9.5)	
The seventh line	0	2 (9.5)	
The Eighth line	0	2 (9.5)	
Sequence of TKIs applied			0.066
Ahead of pemetrexed treatment	17	19	
After pemetrexed treatment	8	2	
The 1 cycle application of pemetrexed	4	8	1

n indicates number of patients.

treatment efficacy was conducted on all 46 patients. The following correspond to the rates recorded for the pemetrexed monotherapy group and the pemetrexed plus platinum group: median PFS, 1.97 and 2.3 months ($P=0.565$) (Fig.1); median OS, 30.93 and 30.33 months ($P=0.877$) (Fig.2); ORR, 8% (2/25) and 9.5% (2/21) ($P=0.857$); and DCR, 32% (8/25) and 57.1% (12/21) ($P=0.09$). The pemetrexed monotherapy group included 2 patients with PR, 6 with SD, and 17 with PD; none demonstrated CR. On the other hand, the pemetrexed plus platinum group was composed of 2 patients with PR, 10 with SD, and 9 with PD; none exhibited CR either.

Univariate analysis

The common potential prognostic factors identified are listed in Table 2. The factors included gender (male *vs.* female), age (<60 *vs.* ⩾60 years), radiotherapy history, surgery history, initial clinical stage, pathological types, response to first-line regimens, application of pemetrexed, and application of TKIs. None of the factors significantly affected OS ($P>0.05$ for all).

Toxicity

The side effects of pemetrexed observed are listed in Table 3. Significant differences in toxicity, except for gastrointestinal toxicity, were not observed between the groups. Gastrointestinal toxicity was modestly higher in the pemetrexed plus platinum group (38%) compared with the pemetrexed monotherapy group (12%) ($P=0.034$); however, all such occurrences did not exceed grade II.

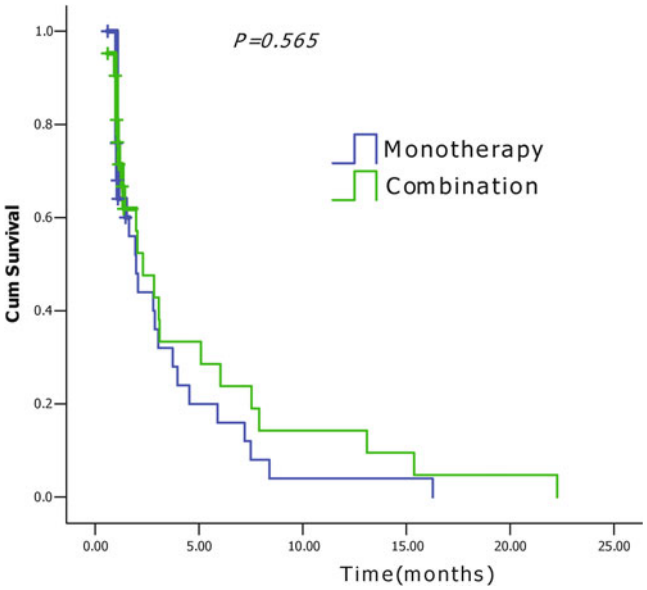

Fig.1. PFS rate curves of the study groups. The median PFS rates of the pemetrexed monotherapy and pemetrexed plus platinum groups were 1.97 and 2.3 months, respectively. The difference was not statistically significant at $P=0.565$.

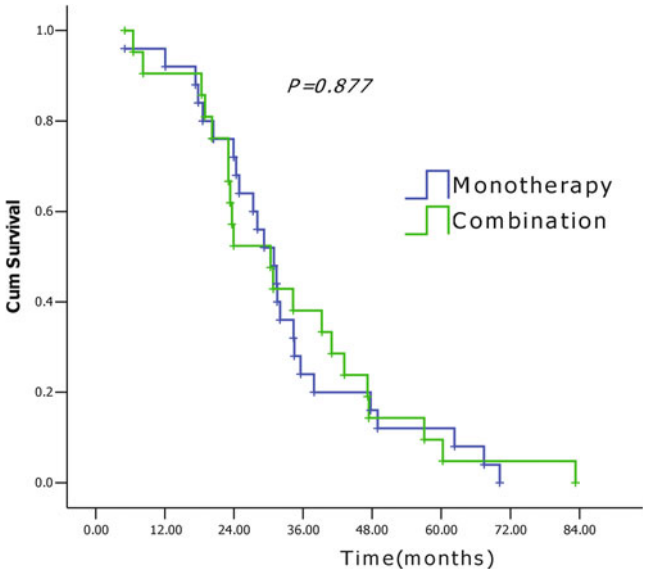

Fig.2. OS rate curves of the study groups. The median OS rates of the pemetrexed monotherapy and pemetrexed plus platinum groups were 30.93 and 30.33 months, respectively. The difference was not statistically significant at $P=0.877$.

Table 2. Univariate analysis of potential factors influencing OS.

Characteristics	No.of patients	Median OS (momths)	95%CI (momths)	*P*
Gender				
Male	33	28.07	24.12–34.87	0.067
Female	13	47.4	30.28–53.34	
Age, years				
<60	33	31.37	27.33–40.67	0.548
$\geqslant 60$	13	27.33	23.21–37.52	
Radiotherapy history				
Yes	11	35.57	27.63–54.61	0.092
No	35	28.06	25.1–35.73	
Surgery history				
Yes	9	23.03	18.1–58.79	0.890
No	37	30.8	26.93–36.36	
Initial clinical stage				0.495
I	2	33.1	0–161.0	
II	1			
III	11	34.33	21.89–48.33	
IV	32	27.7	25.70–37.77	
Pathological types				
Adenocarcinoma	34	31.21	29.91–41.96	0.167
Squamous cell carcinoma	8	22.18	34.75–23.40	
NSCLC	4	26.68	0–53.63	
Response to first-line regimens				
PR	12	26.11	23.29–40.14	0.154
SD	16	31.75	29.64–46.52	
PD	18	23.48	19.36–39.19	
Application of Pemetrexed				
Pemetrexed monotherapy	25	30.93	25.86–39.23	0.877
Pemetrexed plus platinum	21	30.33	25.07–41.90	
Application of TKIs				
Yes	39	30.33	26.06–34.06	0.359
No	7	20.03	11.57–34.50	

CI indicates confident interval.

Table 3. Summary of toxicities.

Toxicities	Grade	Pemetrexed monotherapy, n (%)	Pemetrexed plus platinum, n (%)	*P*
Hematology toxicity	0	19 (76)	15 (71.5)	0.586
	I	2 (8)	1 (4.8)	
	II	4 (16)	3 (14.2)	
	III	0 (0)	0 (0)	
	IV	0 (0)	2 (9.5)	
Elevated ALT and AST	0	17 (68)	19 (90.5)	0.054
	I	5 (20)	2 (9.5)	
	II	2 (8)	0 (0)	
	III	1 (4)	0 (0)	
Alopecia	0	24 (96)	16 (76.2)	0.055
	I	0 (0)	3 (14.2)	
	II	1 (4)	1 (4.8)	
	III	0 (0)	1 (4.8)	
Gastrointestinal toxicity	0	22 (88)	13 (61.9)	0.034
	I	3 (12)	6 (28.6)	
	II	0 (0)	2 (9.5)	
Febrile neutropenia	0	25 (100)	20 (95.2)	0.275
	III	0 (0)	1 (4.8)	

ALT indicates glutamic–pyruvic transaminase; AST, glutamic–oxalacetic transaminease.

Discussion

All endpoints, including ORR, DCR, PFS, and OS, did not significantly differ between the pemetrexed monotherapy group and the pemetrexed plus platinum group. The results are credible as several factors were considered during analysis: First, the primary mechanism of action of pemetrexed is to inhibit the enzyme thymidylate synthase[26], which results in decreased levels of thymidine, a pyrimidine necessary for DNA synthesis, as well as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase, a folate-dependent enzyme involved in purine synthesis[17,27,28]. Research has shown that highly expressed thymidylate synthase in adenocarcinoma yields good outcomes for pemetrexed in NSCLC patients with non-squamous cell carcinoma[7–9,29,30]; however, as this relationship between pemetrexed and non-squamous cell carcinoma was recognized only after 2008, the present study administered pemetrexed treatment to eight patients with squamous cell carcinoma and four others without definitive adenocarcinoma. Significant differences in the proportions of pathological types between the groups were not detected ($P=0.077$).

Second, the PFS curves of the two groups did not significantly deviate from each other (Fig.1), with the PFS rates for the pemetrexed monotherapy and pemetrexed plus platinum groups being 1.97 and 2.3 months ($P=0.565$), respectively, which are somewhat smaller than previously reported rates from clinical trials in the second-line treatment setting[17–19,31]. This finding may be attributed to the fact that 80.43% of our study patients (40/49) received their pemetrexed-containing regimen post-second-line therapy. It may also be explained by the fact that 26.9% of the patients (12/46) accepted only one cycle of their pemetrexed therapy due to tumor progression, poor PS, or their refusal to undergo further treatments, although the number of patients who received only one treatment cycle balanced well in the two groups ($P=1.00$).

Third, the pemetrexed monotherapy and pemetrexed plus platinum groups showed high median OS rates at 30.93 and 30.33 months, respectively, with no conspicuous separation of curves (Fig.2). TKIs (gefitinib or erlotinib) were given to 84.8% of the patients, and they all achieved 6 months of PFS, which may account for their prolonged OS. The application of TKIs in the two groups was balanced ($P=0.359$), and the results are congruent with previously reported OS rates[6]. Moreover, the prolonged OS may be associated with the Asian patients' higher sensitivity to chemotherapy, as mentioned in a Japanese Phase III clinical study and a retrospective study about pemetrexed monotherapy versus pemetrexed plus platinum combination therapy as second-line treatment for advanced NSCLC[20,30].

Fourth, more patients in our study accepted the combination therapy after the third-line setting and the monotherapy in the second- or third-line setting because pemetrexed was recommended as a single agent in the second-line setting and its combination with platinum was found ideal for the first-line setting. In our practice, physicians select treatments depending on their experience as guidelines for post-third-line treatment are not available; combination therapy is typically considered for patients with good PS.

Finally, the pemetrexed monotherapy and pemetrexed plus platinum combination therapy did not significantly affect OS when they were evaluated along with other potential prognostic factors via univariate analysis. Pemetrexed in combination with targeted medicine is another trend. Up to now, research has shown that the efficacy of pemetrexed combined with cetuximab[32], enzastaurin[7], vandetanib[33], and bevacizumab[34] in the second-line therapy of NSCLC did not improve, although their toxicities were well tolerated.

Studies have reported significant toxicities for pemetrexed, including myelosuppression, skin rash, mucositis, and fatigue[17,35]. Toxicity profiles were not completely recorded in the present study due to its retrospective

nature, as well as the fact that the patients typically stayed in the hospital for 1 day only as pemetrexed simply triggered minor side effects. Gastrointestinal toxicity in the pemetrexed plus platinum group was modestly higher than that in the pemetrexed monotherapy group, whereas other adverse events were similar between the groups. All toxicities were lower than grade IV and could be well tolerated, in agreement with findings from other clinical trials about pemetrexed[17], confirming that pemetrexed could be well tolerated even in the post-second-line setting.

In conclusion, this study found that ORR, DCR, PFS, and OS did not significantly differ between patients with advanced NSCLC who received pemetrexed monotherapy and those who accepted pemetrexed plus platinum combination therapy in or after the second-line setting. Both treatments demonstrated similar toxicity profiles, except for the modestly higher gastrointestinal toxicity in the pemetrexed plus platinum group. Despite these valuable findings, the limitations of this study, such as the small number of patients evaluated and the diversity in their treatment history, should not be ignored.

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Conflict of Interest Statement

No potential conflicts of interest were disclosed.

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