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Original Article

Third-line or fourth-line chemotherapy in non-small-cell lung cancer patients with relatively good performance status

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Abstract

Background: Our aim here was to explore treatment efficacy of pemetrexed and docetaxel in non-small-cell lung cancer patients who had failed previous chemotherapy and epidermal growth factor receptor-tyrosine kinase inhibitor therapy.
Methods: We retrospectively reviewed clinical data of our non-small-cell lung cancer patients who received third- or fourth-line chemotherapy with pemetrexed or docetaxel in our institution from January 2006 to December 2009.
Results: One hundred and twenty-three patients received treatment, including 85 patients with pemetrexed treatment and 38 patients with docetaxel treatment. There was no difference in tumor response rate and toxicity profiles when using pemetrexed as third- or fourth-line treatment, neither was there difference in docetaxel treatment of third- versus fourth-line treatment. There was also no difference between docetaxel and pemetrexed in response rate and control rate when they were used as fourth-line treatment. However, docetaxel used in fourth-line treatment had higher incidence of neutropenia and more frequent need of granulocyte colony-stimulating factor support compared with pemetrexed in fourth-line treatment. Median progression-free survivals (PFSs) were 2.6 months and 3.8 months when using pemetrexed as third- and fourth-line treatment, respectively ($p = 0.417$). Median PFSs were 3.8 months and 4.8 months when using docetaxel as third- and fourth-line treatment, respectively ($p = 0.882$). There was also no difference in PFS between pemetrexed and docetaxel, both in third- and fourth-line treatment. Median survivals were 13.4, 12.2, 13.2, and 13 months for pemetrexed in third-line, fourth-line, and docetaxel in third-line and fourth-line treatment, respectively.
Conclusion: This retrospective study of pemetrexed and docetaxel showed relatively safe toxicity profile, reasonable response rate, and long survival when used as third- and fourth-line chemotherapy. Thus, it is reasonable to give good performance status patients third- and fourth-line chemotherapy. A phase III randomized trial is needed for better clarification of these issues.

Keywords: Adenocarcinoma; Chemotherapy; Docetaxel; Non-small-cell lung cancer; Pemetrexed

1. Introduction

Third-generation anti-cancer drugs and their combination with platinum have shown better response rates and survival than conventional regimens during the last two decades, and this kind of doublet treatment has been used as standard first-line treatment of treatment-naïve advanced non-small-cell lung cancer (NSCLC).[1–3] There have been three phase III randomized studies, including two studies of docetaxel that showed better survival of NSCLC patients who received docetaxel as second-line therapy compared with best supportive care or other chemotherapy,[4,5] and one study of pemetrexed that showed pemetrexed treatment had advantages in terms of tolerability and quality of life compared with

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docetaxel treatment.[6] After these studies, docetaxel and pemetrexed were recommended as standard second-line chemotherapy for patients with disease progression after first-line treatment.

Recently, with more frequent usage of epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI), because of their relative convenience of use and better toxicity profiles, as second-line treatment of NSCLC, drugs that were used previously as second-line chemotherapeutic agents, such as docetaxel and pemetrexed, have been reserved for third-line and even fourth-line treatment, after the patient has failed third-line treatment that used one of two effective second-line agents.[7–9] Because those three phase III randomized studies that showed better survival of NSCLC patients who received docetaxel as second-line therapy,[4,5] and pemetrexed had advantages of better tolerability and quality of life than docetaxel[6] were performed before the era of EGFR-TKI, whether or not docetaxel and pemetrexed still have similar efficacy in patients who have received two lines of treatment, including platinum-based chemotherapy and EGFR-TKI treatment, are unknown and need further investigation.[1]

In the present study, we retrospectively reviewed our patients' data to define clinical characteristics, analyze, and compare the feasibility of using docetaxel or pemetrexed as third-line or fourth-line chemotherapy after the patients had failed previous platinum-based doublets and EGFR-TKI therapies.

2. Methods

This retrospective review was approved by the institutional review board of Taipei Veterans General Hospital (VGHIRB No. 98-03-10A). We retrospectively reviewed chart records and case report forms of patients with advanced NSCLC of the lungs who had progressed after receiving two lines of treatment, including one line of platinum-based doublet and one line of EGFR-TKI, and received third-line or fourth-line chemotherapy with docetaxel (60 mg/m^2 Day 1 every 3 weeks for a maximum of 6 cycles; more cycles were allowed in those patients who responded to the treatment) or pemetrexed (500 mg/m^2 Day 1 every 3 weeks for a maximum of 6 cycles; more cycles were allowed in those patients who responded to the treatment) in our department from January 2006 to December 2009. In this retrospective study, EGFR-TKI was used as second-line treatment after the patients progressed from first-line platinum-based chemotherapy. Furthermore, only single-agent pemetrexed or docetaxel was allowed as third-line treatment in all patients. All patients received standard pre-medications for their chemotherapy. All patients were Stage IV when they received present docetaxel or pemetrexed salvage therapy. All patients had a World Health Organization performance status of 0–2 when starting third- or fourth-line treatment.

The clinical characteristics, response rate, toxicity profiles, progression-free survival (PFS), and overall survival time were recorded and analyzed. Treatment-related toxicities were recorded, based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0). Types of response were assessed with the use of the Response Evaluation Criteria in Solid Tumors.[9] Response rate, PFS, and overall survival time were analyzed with an intention-to-treat principle. PFS time and overall survival time were analyzed using the Kaplan-Meier estimation method and log-rank test. PFS was calculated from the date of initiation of treatment to the date of disease progression or death from any cause. If disease progression had not occurred by the time of this analysis, PFS was considered to have been censored at the time of the last follow-up visit. Survival time was measured from the date of the initiation of treatment to the date of death. Survival time was considered to have been censored at the last follow-up time if death had not occurred. The comparisons of clinical characteristics, response rates, and severity of treatment-related toxicity were performed using the χ^2 analysis. The SPSS (SPSS Inc., Chicago, IL, USA) statistical program was used.

3. Results

One hundred and twenty-three patients with Stage IV NSCLC who had progressive disease from previous one line of platinum-based chemotherapy treatment and one line of EGFR-TKI treatment were treated during this period. The clinical characteristics of these patients are listed in Table 1. Except for 11 patients, all had adenocarcinoma of histologic type. There was no difference in clinical characteristics between patients who received pemetrexed as third- or fourth-line treatment, docetaxel as third- or fourth-line treatment, or between pemetrexed and docetaxel, in terms of age, sex, performance status, histology, first-line chemotherapeutic agent and their response, and type of EGFR-TKI and their response or not.

Median treatment cycles numbered 4 in third- and fourth-line pemetrexed treatment, and also in docetaxel treatment. Treatment-related toxicities were few and mild in degree when pemetrexed was used as third- or fourth-line treatment. Grade 3 or 4 toxicities included 2 leukopenia and 4 neutropenia when pemetrexed was used as third-line treatment ($n = 42$), and 1 anemia, 4 leukopenia, 8 neutropenia, 2 thrombocytopenia, 1 fatigue when pemetrexed was used as fourth-line treatment ($n = 43$). There was no statistically significant difference in toxicity profiles (both hematological and non-hematological) between third-line or fourth-line pemetrexed treatments. Two patients in third-line treatment needed packed red blood cell blood transfusion during their treatment period, whereas 7 patients in fourth-line treatment needed packed red blood cell blood transfusion ($p = 0.424$). One patient in fourth-line treatment needed granulocyte colony-stimulating factor (G-CSF) support. There was also no statistically significant difference in toxicity profiles (both hematological and non-hematological) between third- ($n = 21$) or fourth-line ($n = 17$) docetaxel treatment. When considering pemetrexed or docetaxel used as fourth-line treatment, more neutropenia ($p = 0.04$), alopecia ($p = 0.004$), and G-CSF support ($p = 0.032$) was noted in the docetaxel arm. No toxic death occurred in these 123 patients.

Nineteen of 123 patients had partial response to the treatment, with an overall objective response rate of 15.4%,

Table 1
Patient characteristics of 123 non-small-cell lung cancer patients who received pemetrexed or docetaxel as third- or fourth-line treatment

Patient number		Pemetrexed ($n = 85$)		Docetaxel ($n = 38$)		p[a]		
		Third line	Fourth line	Third line	Fourth line	$P_{\text{third versus fourth}}$	$D_{\text{third versus fourth}}$	P_{fourth} versus D_{fourth}
Age	Mean	60	63	66	61	0.36	0.203	0.183
Sex	Male/female	25/17	24/19	13/8	9/8	0.729	0.578	1
WHO performance status	0	1	1	2	0	0.998	0.418	0.799
	1	30	31	14	13			
	2	11	11	5	4			
Histology	Adenocarcinoma	36	38	21	17	0.553	1	0.34
	Squamous cell carcinoma	3	1	0	0			
	Type not specified	3	4	0	0			
First-line regimen	Vinorelbine	15	23	9	5	0.053	0.803	0.342
	Taxane	22	11	9	8			
	Gemcitabine	5	9	3	4			
Response to first-line chemo	Yes	8	15	2	3	0.1	0.461	0.228
	No	34	28	19	14			
EGFR-TKI	Gefitinib	26	34	12	10	0.082	0.917	0.193
	Erlotinib	16	9	9	7			
Response to EGFR-TKI	Yes	12	10	3	3	0.576	0.778	0.74
	No	30	33	18	14			

[a] Pearson two-sided χ^2 test.
EGFR-TKI = epidermal growth factor receptor–tyrosine kinase inhibitor; WHO = World Health Organization.

including 10 patients (23.8%) in third-line pemetrexed, 5 patients in fourth-line pemetrexed (11.6%), 2 patients in third-line docetaxel (9.5%), and 2 patients in fourth-line docetaxel (11.8%). There was no statistically significant difference in response rate between third- and fourth-line pemetrexed, third- and fourth-line docetaxel, or when pemetrexed or docetaxel was used as fourth-line treatment (Table 2). The disease control rates were 57.1%, 58.1%, 57.1%, and 70.6%, respectively, in third-line pemetrexed, fourth-line pemetrexed, third-line docetaxel, and fourth-line docetaxel.

The median PFSs in 85 patients who received pemetrexed therapy were 2.6 months [95% confidence interval (CI) 0–5.4 months] and 3.8 months (95% CI 1.2–6.5 months), respectively, for third- and fourth-line pemetrexed treatment ($p = 0.4168$, Fig. 1). The median survivals were 13.4 months (95% CI 8.5–18.4 months) and 12.2 months (95% CI 8.8–15.5 months), respectively ($p = 0.8507$, Fig. 2). The 1-year survival rates were 53.9% and 50.1%, respectively. There was also no difference in PFS and overall survival time in patients who received docetaxel as third- or fourth-line treatment (Table 2). Median PFSs of 60 patients who received pemetrexed ($n = 43$) or docetaxel ($n = 17$) as fourth-line therapy was 3.8 months (95% CI 1.2–6.5 months) in pemetrexed and 4.8 months (95% CI 1.7–8 months), respectively ($p = 0.6973$, Fig. 3). The median survivals were 12.2 months (95% CI 8.8–15.5 months) in fourth-line pemetrexed and 13 months (95% CI 8.6–17.4), respectively ($p = 0.7833$, Fig. 4).

4. Discussion

Docetaxel and pemetrexed had been recommended as standard second-line chemotherapy when patients had disease progression after first-line chemotherapy. With more frequent use of EGFR-TKI, such as erlotinib and gefitinib, as second-line

Table 2
Efficacy of pemetrexed and docetaxel in third- and fourth-line chemotherapy

Patient number		Pemetrexed ($n = 85$)		Docetaxel ($n = 38$)		p[a]		
		Third line ($n = 42$)	Fourth line ($n = 43$)	Third line ($n = 21$)	Fourth line ($n = 17$)	$P_{\text{third versus fourth}}$	$D_{\text{third versus fourth}}$	P_{fourth} versus D_{fourth}
Type of response, number	PR	10	5	2	2	0.257	0.694	0.65
	SD	14	20	10	10			
	PD	18	18	9	5			
Median progression-free survival (mo)		2.6	3.8	3.8	4.8	0.4168	0.8815	0.6973
Median survival (mo)		13.4	12.2	13.2	13	0.8507	0.9645	0.7833

[a] Pearson two-sided χ^2 test for comparison of type of response, log-rank test for comparison of progression-free survival.
PD = progressive disease; PR = partial response; SD = stable disease.

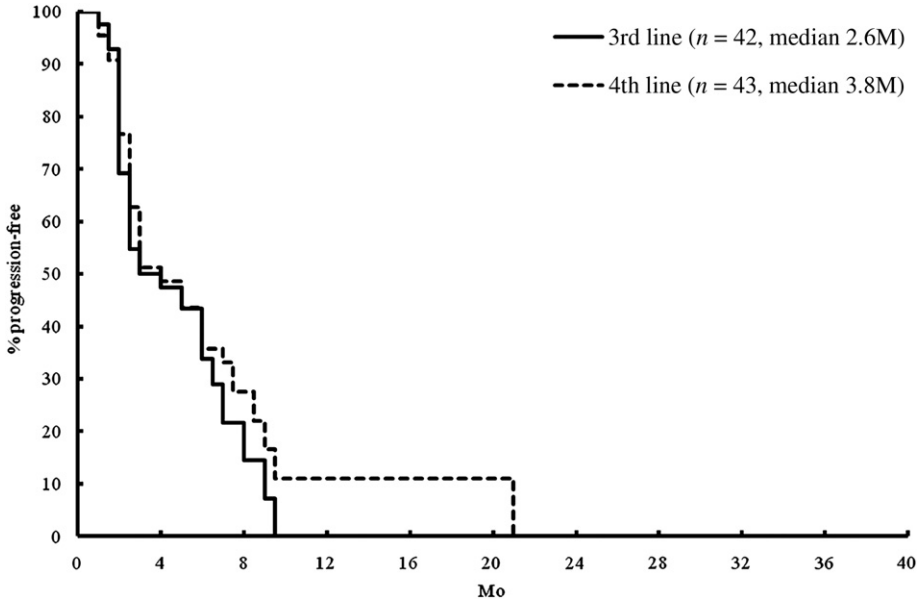

Fig. 1. Progression-free survival (PFS) of 85 Stage IV non-small-cell lung cancer patients who received pemetrexed as third-line ($n = 42$, Censor 12) or fourth-line therapy ($n = 43$, Censor 6). The median PFSs were 2.6 months (95% confidence interval 0–5.4) and 3.8 months (95% confidence interval 1.2–6.5), respectively ($p = 0.4168$).

or even first-line treatment, use of docetaxel and pemetrexed is now reserved for third-line, or even fourth-line treatment, if the patient has not used pemetrexed or docetaxel as first- or second-line treatment.

The available data in the last decade are not sufficient to make a recommendation for or against using a cytotoxic drug as third-line therapy, not to mention fourth-line treatment. The American Society of Clinical Oncology suggests that those patients who have progressive disease after two lines of systemic treatment should consider clinical trials, experimental treatment, or receive best supportive care.[1] In this retrospective review, a response rate around 15% and control rate around 60% for third- and fourth-line treatment with pemetrexed or docetaxel against NSCLC is very good and similar to the efficacy of pemetrexed or docetaxel used in the second-line setting. Thus, it is worthwhile to treat previously platinum-treated and EGFR-TKI treated NSCLC patients with one of these two agents, if they have never been exposed to pemetrexed or docetaxel. Furthermore, the toxicity profiles showed that these agents are still relatively safe when used in third- or fourth-line treatment.

Based on this retrospective data, there were no statistical differences in toxicity profiles, disease response rate and control rate, and survival data (including PFS and overall

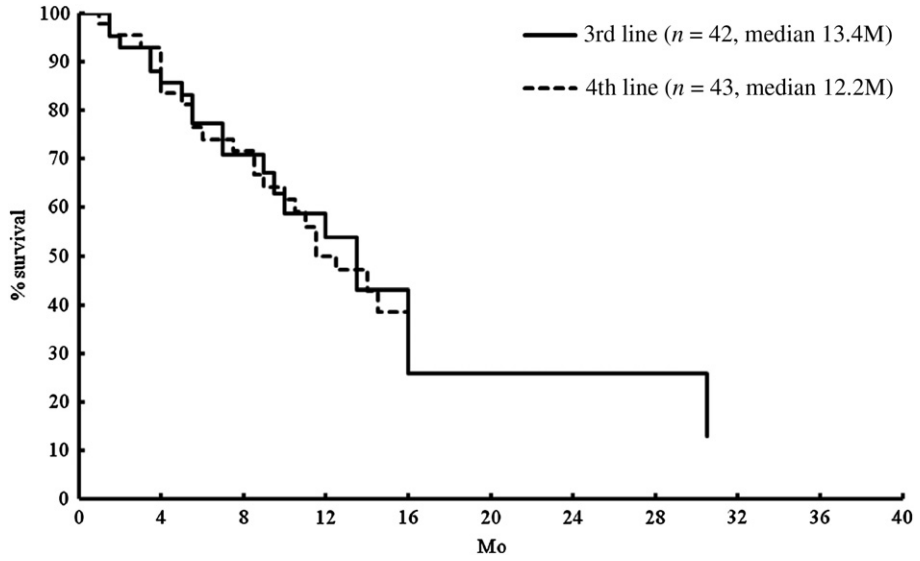

Fig. 2. Survival curve of 85 Stage IV non-small-cell lung cancer patients who received pemetrexed as third-line ($n = 42$, Censor 22) or fourth-line therapy ($n = 43$, Censor 19). The median survivals were 13.4 months (95% confidence interval 8.5–18.4) and 12.2 months (95% confidence interval 8.8–15.5), respectively ($p = 0.8507$). The 1-year survival rates were 53.9% and 50.1%, respectively.

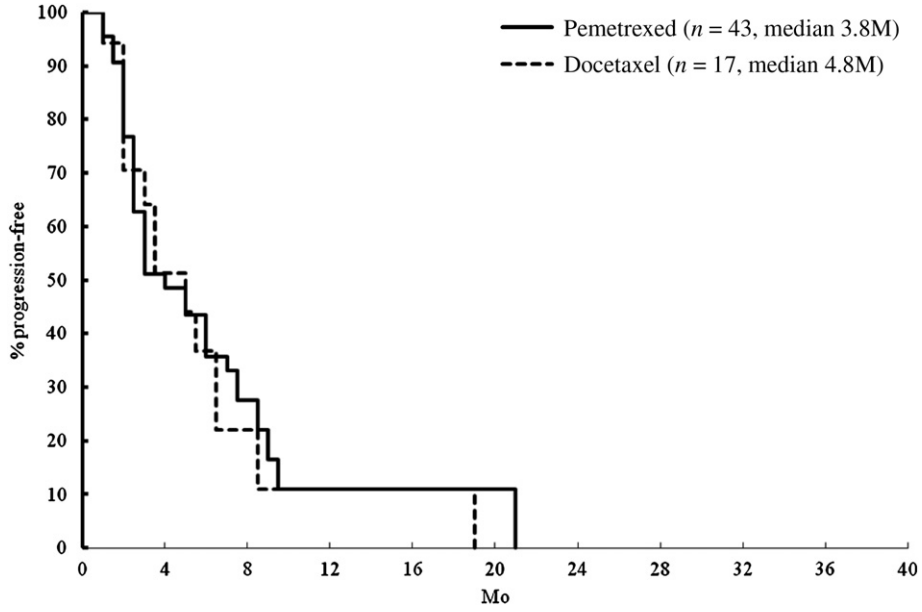

Fig. 3. Progression-free survival (PFS) of 60 Stage IV non-small-cell lung cancer patients who received pemetrexed ($n = 43$) or docetaxel ($n = 17$) as fourth-line therapy. The median PFSs were 3.8 months (Censor 6, 95% confidence interval 1.2–6.5) in pemetrexed and 4.8 months (Censor 3, 95% confidence interval 1.7–8), respectively ($p = 0.6973$).

survival) when pemetrexed or docetaxel was used as third- or fourth-line treatment. Thus, the decision of which agent to be used first will depend on previously exposed chemotherapeutic agents (not to use again if already used as first- or second-line treatment), and histology (pemetrexed is preferred for non-squamous cell NSCLC, whereas docetaxel is suggested for squamous cell NSCLC).[10,11] However, docetaxel used in fourth-line treatment had a higher incidence of severe neutropenia and more frequent need of G-CSF support compared with pemetrexed in fourth-line treatment. Thus, patients should be carefully followed up if docetaxel is given as fourth-line chemotherapy. Because most patients who can receive third- or fourth-line treatment have adenocarcinoma, such as 112 of 123 (91.1%) in the present study who had adenocarcinoma, pemetrexed will be the preferred choice for third-line treatment in most patients if they have not received pemetrexed as first-line treatment. In such an instance, docetaxel will be delayed to fourth-line treatment and should be given carefully.

With advances in modern medicine and supportive care, lung cancer patients' general condition frequently remains robust even after they have had disease progression after two lines of treatment. In view of reasonable response rate and control rate, PFS was not inferior or similar to those agents used in second-line treatment, and relatively long median

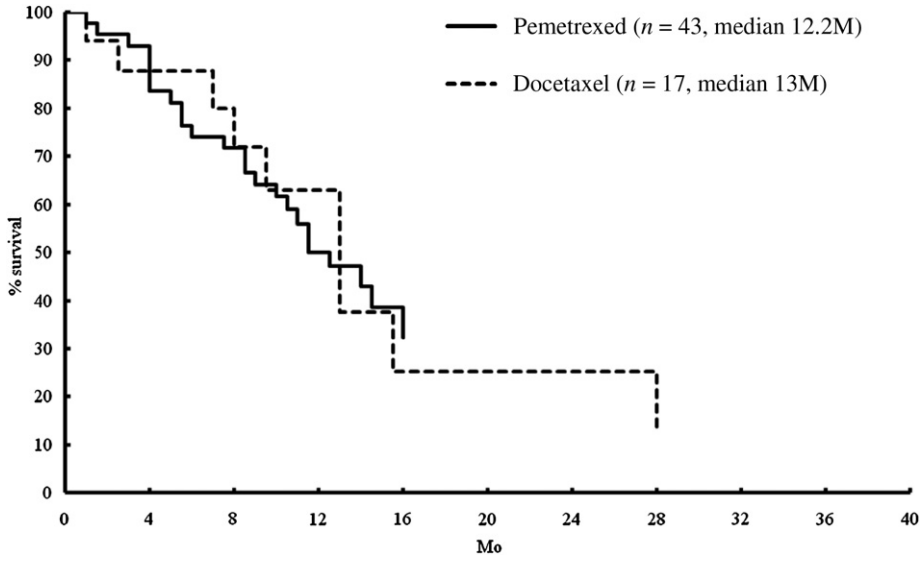

Fig. 4. Survival curve of 60 Stage IV non-small-cell lung cancer patients who received pemetrexed ($n = 43$) or docetaxel ($n = 17$) as fourth-line therapy. The median survivals were 12.2 months (Censor 19, 95% confidence interval 8.8–15.5) in pemetrexed and 13 months (Censor 8, 95% confidence interval 8.6–17.4), respectively ($p = 0.7833$).

survival time, use of pemetrexed or docetaxel in the third-line or fourth-line setting is encouraged if the patient's performance status is still good, between 0 and 2 and with adequate systemic organ functions. A prospective study is needed to better clarify the roles of pemetrexed or docetaxel in third-line or fourth-line treatment.

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