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ORIGINAL ARTICLE

Study of Gefitinib and Pemetrexed as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer Harboring EGFR Mutation

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Abstract To evaluate the efficacy and safety of a combination regimen of gefitinib and pemetrexed as first-line chemotherapy in advanced EGFR-mutated non-small cell lung cancer (NSCLC) patients. Patients and methods Patients with advanced non-squamous NSCLC harboring asensitive EGFR mutation were included in this study and randomly divided into gefitinib + placebo group and gefitinib + pemetrexed group. Pemetrexed or placebo was administered on day 1 at a dose of 500 mg/m^2, and gefitinib was sequentially administered on days 2 ~ 16. This treatment regimen was repeated every 3 weeks until disease progression. All investigators and participants were masked to treatment allocation. The overall response rate (ORR) and disease control rate (DCR) of gefitinib + pemetrexed group were higher than that of gefitinib + placebo group but only the difference of DCR between two groups was statistically significant ($P < 0.05$). The median progression-free survival (PFS) of gefitinib + placebo group and gefitinib + pemetrexed group were 14.0 months vs. 18 months respectively and the difference was statistically significant ($P < 0.05$). The 2-year PFS rates of gefitinib + pemetrexed group (20.00 %) was higher than that of gefitinib + placebo group (8.89 %) and the difference was statistically significant ($P < 0.05$). The median overall survival (OS) of gefitinib + placebo group and gefitinib + pemetrexed group were 32.0 months vs. 34 months respectively and the difference was not statistically significant ($P > 0.05$). The 3-year OS rates of gefitinib + pemetrexed group (44.44 %) was higher than that of gefitinib + placebo group (35.56 %) but the difference was not statistically significant ($P > 0.05$). Major grade 3 or 4 hematological toxicities included neutropenia, leukopenia and anemia. The main grade 3 or 4 non-hematological toxicities were infection, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, fatigue, diarrhea and pneumonitis. The difference of toxicities between two groups was not statistically significant ($P > 0.05$). The combination regimen of gefitinib + pemetrexed used in this study showed a higher ORR and DCR, longer median PFS and acceptable toxicity.

Keywords Gefitinib · Pemetrexed · Advanced non-small cell lung cancer · EGFR mutation

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Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85 % of all lung cancer cases [1]. Although many patients with advanced NSCLC initially achieved clinical remission or disease control with first-line chemotherapy (e.g., docetaxel, paclitaxel, gemcitabine, vinorelbine and irinotecan), most subsequently experienced disease progression and death. Epidermal growth factor receptor

(*EGFR*) is a member of the ErbB receptor tyrosine kinase (TK) family and has an essential action in the development and progression of NSCLC [2–4]. It has been reported that the signaling pathways of *EGFR* could influence angiogenesis, activation and regulation of cellular proliferation, and the epithelial–mesenchymal transition [5–8]. The gene with the most frequent mutations in NSCLC is *EGFR*. The most common *EGFR* mutations reported are deletions in exon 19 and the p.L858R point mutation in exon 21 (85 % – 90 %) [9, 10]. Previous clinical trials have identified epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), as a first-line treatment option for patients with NSCLC harboring sensitive EGFR mutations. Gefitinib and erlotinib are oral EGFR-TKIs. These inhibitors have been found to induce marked radiographic and clinical improvement in patients with EGFR-mutated NSCLC [11, 12]. The extremely high response rate (RR) for EGFR-TKIs is associated with active EGFR mutations in tumor cells such as in-frame deletions in exon 19 or point mutations in exon 21 [13–15]. Despite the benefits of EGFR-TKIs in the treatment of NSCLC patients with an EGFR mutation, most patients ultimately develop resistance to these drugs after a median duration of 9 ~ 13 months [16, 17]. The optimum management strategies for patients with acquired resistance to first-line EGFR-TKIs are undefined [18].

Outside clinical trials, treatment options include systemic chemotherapy alone or continuation of EGFR-TKIs in combination with chemotherapy at the time of disease progression [18]. The potential tumors heterogeneity suggests that continuation of EGFR-TKIs in combination with chemotherapy might be beneficial-a hypothesis supported by findings from a retrospective study [19]. Goldberg and colleagues reported that 48 % of patients with tumors resistant to EGFR-TKIs treatment who were subsequently treated with a combination of chemotherapy and erlotinib achieved a tumor response versus 18 % of patients treated with chemotherapy alone [19]. However, most previous clinical trials failed to show a benefit for combination of platinum-based doublet chemotherapy and EGFR-TKIs as first-line treatment for patients with NSCLC harboring sensitive EGFR mutations.

Gefitinib is known to suppress the expression of thymidylate synthase (TS) in NSCLC cell lines, regardless of the presence of EGFR mutations [20]. Low TS expression is a predictive factor for the treatment efficacy of pemetrexed in NSCLC patients [21]. Thus, the addition of pemetrexed may increase treatment efficacy in patients treated with gefitinib. The research was designed to evaluate the efficacy and safety of pemetrexed combined with gefitinib as first-line therapy in patients with advanced NSCLC harboring a sensitive EGFR mutation.

Patients and Methods

Patient Eligibility

Eligibility criteria included a diagnosis of histologically or cytologically proven non-squamous NSCLC with a common sensitive EGFR mutation, measurable lesions, stage IIIB (including only patients without indications for curative radiotherapy) or IV disease, an estimated life expectancy of at least 12 weeks, and adequate major organ function. Patients were excluded for any of the following reasons: myocardial infarction within the previous 3 months, uncontrolled angina pectoris or arrhythmia, brain metastasis, uncontrolled hypertension or diabetes, active infection, pulmonary fibrosis, pleural effusion or ascites requiring drainage, or cerebrovascular disease. The patients were divided into gefitinib + placebo group and gefitinib + pemetrexed group. All investigators and participants were masked to treatment allocation. Written informed consent was obtained from all the patients, and the study protocol was approved by the ethics committee.

Patient Evaluation

The pretreatment evaluation consisted of a complete blood cell count, routine chemistry measurements, chest radiography, chest and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI) or CT, and radionuclide bone imaging or 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (^{18}F-FDG PET)/CT.

During the trial and for 30 days after the last dose of gefitinib or pemetrexed, patients were evaluated by a complete blood cell count, routine chemistry measurements, chest radiography, and a toxicity evaluation once per cycle (3 weeks).

Procedures

Pemetrexed or placebo was administered at a dose of 500 mg/m^2 over 10 min by intravenous infusion on day 1. Gefitinib was sequentially administered at a dose of 250 mg/body on days 2 ~ 16. This combination treatment was repeated every 3 weeks until disease progression. All patients received prophylactic dexamethasone doses (4 mg orally, twice per day) on days 1 ~ 3. Moreover, they all receivedoral folic acid (500 μg) daily and a vitamin B12 injection (1000 μg) every 9 weeks, beginning 1 ~ 2 weeks before the first dose of the combination therapy and continuing until 3 weeks after the last dose. Pemetrexed was only administered if the patient had a leukocyte count of ≥3000/μl and a platelet count of ≥100,000/μl. If the leukocyte or platelet count had not returned to these levels on day 1 of the next cycle of chemotherapy, both drugs were withheld until complete recovery of the counts. Cycle delays of up to 22 days were permitted for

recovery from adverse events. Dose reductions of gefitinib were not allowed. Pemetrexed-related toxic effects and dose modifications were managed as per standard clinical practice.

Response and Toxicity Evaluation

The Revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 were used to evaluate anti-tumor activity [22]. Toxicity was graded according to the National Cancer Institute of Common Toxicity Criteria, version 4.0. The highest toxicity grade for each patient in all cycles of chemotherapy was considered in the toxicity analysis.

Statistical Analysis

Statistical analysis was performed using statistics package for social science 21.0 (SPSS 21.0). Statistical comparisons were performed using Chi-square test and differences at $P < 0.05$ were considered statistically significant.

The overall survival (OS) was calculated from enrolment to the date of the last follow-up or death from any cause, and progression-free survival (PFS) was calculated from enrolment to the date of disease progression, recurrence, or death from any cause. Survival curves were estimated using the Kaplan–Meier method.

Results

Patient Characteristics

Between March 2010 and January 2013, 90 patients were enrolled and eligible in this study. All patients were treated and assessed for response, survival, and safety. The patients' baseline characteristics are shown in Table 1. The patients' median age was 65 years (range, 57 ~ 83 years), and all patients had a good performance status. A total of 50 men and 40 women participated in the study. The histological type of the patient's cancer was adenocarcinoma in all cases. Eighty patients had stage IV and ten patients had stage IIIB disease. Sixty patients were never smokers. EGFR mutations were detected in all patients, with 35 patients having a deletion in exon 19, and 55 patients, a L858R point mutation in exon 21.

Table 1 Patient characteristics

	gefitinib + placebo (N = 45)	gefitinib + pemetrexed (N = 45)
Characteristics		
Age	66.89 ± 12.46	65.72 ± 13.02
Sex		
Male	25	25
Female	20	20
Stage		
IIIB	6	4
IV	39	41
Histology		
Adenocarcinoma	45	45
Others	0	0
EGFR mutation status		
Exon 19 deletion	17	16
Leu858Arg	28	29
Smoking history		
Current or former	26	25
Never smoker	19	20
Metastases		
Brain	23	24
Lung	17	16
Bone	11	12
Pleura	8	9
Liver	5	5
Adrenal gland	6	7
Others	8	7

Treatment Efficacy and Survival

The objective tumor RR is described in Table 2. During the observation period, 33 met the criteria for partial response (PR), 6 exhibited stable disease (SD), and 6 exhibited progressive disease (PD) in the gefitinib + placebo group. The overall response rate (ORR) and disease control rate (DCR) of gefitinib + placebo group were 73.33 % and 86.67 %. 36 patients met the criteria for PR, 8 exhibited SD, and 1 exhibited PD in the gefitinib + pemetrexed group. The ORR and DCR of gefitinib + pemetrexed group were 80.00% and 97.83%. The ORR and DCR of gefitinib + pemetrexed group were higher than that of gefitinib + placebo group but only the difference of DCR between two groups was statistically significant ($P < 0.05$).

The median PFS of gefitinib + placebo group and gefitinib + pemetrexed group were 14.0 months (95 %

Table 2 Tumor response

	gefitinib + placebo Number(%)	gefitinib + pemetrexed Number(%)
CR	0(0.00 %)	0(0.00 %)
PR	33(73.33 %)	36(80.00 %)
SD	6(13.33 %)	8(17.78 %)
PD	6(13.33 %)	1(2.22 %)*
ORR = CR + PR	33(73.33 %)	36(80.00 %)
DCR = CR + PR + SD	39(86.67)	44(97.83 %)*

CI, 11.8 ~ 16.2) vs. 18 months (95 % CI, 15.7 ~ 16.2) respectively and the difference was statistically significant ($P < 0.05$). The 2-year PFS rates of gefitinib + pemetrexed group (20.00 %) was higher than that of gefitinib + placebo group (8.89 %) and the difference was statistically significant ($P < 0.05$) (Fig. 1a). The median OS of gefitinib + placebo group and gefitinib + pemetrexed group were 32.0 months (95 % CI, 26.7 ~ 37.2) vs. 34 months (95 % CI, 28.7.7 ~ 39.2) respectively and the difference was not statistically significant ($P > 0.05$). The 3-year OS rates of gefitinib + pemetrexed group (44.44 %) was higher than that of gefitinib + placebo group (35.56 %) but the difference was not statistically significant ($P > 0.05$) (Fig. 1b).

Adverse Events

Table 3 lists the incidence of hematological and non-hematological toxicities in two groups. Neutropenia was the most common grade 3/4 adverse event in two groups and occurred in 20.00 % vs. 22.22 %. No cases of febrile neutropenia were observed. Other grade 3/4 hematological toxicities in two groups included leukopenia (8.89 % vs. 11.11 %) and anemia (2.22 % vs. 4.44 %). No grade 4 non-hematological toxicities were found in two groups. Grade 3/4 non-hematological toxicities in two groups included increased alanine aminotransferase (ALT) (11.11 % vs. 13.33 %) and aspartate aminotransferase (AST) (8.88% vs. 11.11 %) levels, infection (11.11 % vs. 13.33 %), fatigue (4.44 % vs. 4.44 %), diarrhea (2.22 % vs. 4.44 %), and pneumonitis (2.22 % vs. 4.44 %). No treatment-related deaths occurred. The difference of adverse events between two groups was not statistically significant ($P > 0.05$).

Discussion

Small-molecule TKIs that target the EGFR, including the reversible inhibitors afatinib, gefitinib and erlotinib, were the first targeted drugs to enter clinical use for the treatment of

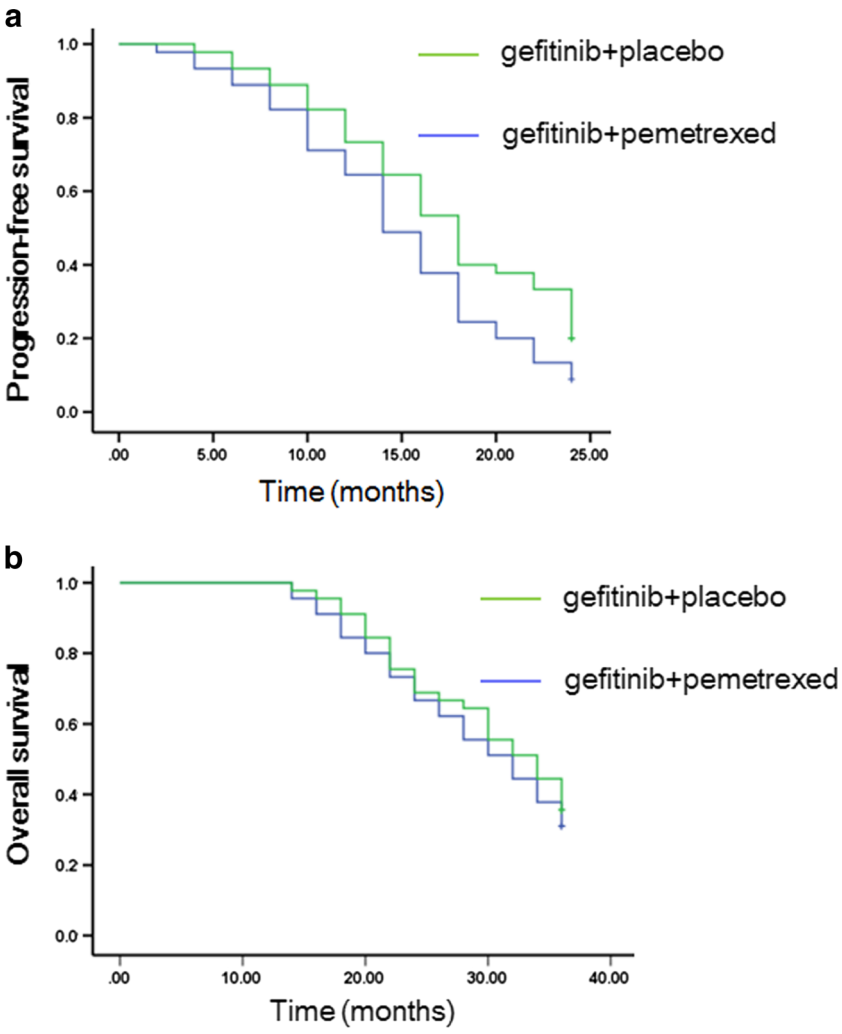

Fig. 1 **a** Kaplan–Meier estimate of the progression-free survival (PFS) in all patients. The median PFS of gefitinib + placebo group and gefitinib + pemetrexed group were 14.0 months (95 % CI, 11.8 ~ 16.2) vs. 18 months (95 % CI, 15.7 ~ 16.2) respectively and the difference was statistically significant ($P < 0.05$). **b** Kaplan–Meier estimate of the overall survival (OS) in all patients. The median OS of gefitinib + placebo group and gefitinib + pemetrexed group were 32.0 months (95 % CI, 26.7 ~ 37.2) vs. 34 months (95 % CI, 28.7.7 ~ 39.2) respectively and the difference was not statistically significant ($P > 0.05$)

Table 3 Adverse events

	Number of grade 3/4 (%)	
	gefitinib + placebo	gefitinib + pemetrexed
Leukopenia	4(8.89 %)	5(11.11 %)
Neutropenia	9(20 %)	10(22.22 %)
Anemia	1(2.22 %)	2(4.44 %)
Thrombocytopenia	0(0.00 %)	0(0.00 %)
Anorexia	0(0.00 %)	0(0.00 %)
Nausea	0(0.00 %)	0(0.00 %)
Vomiting	0(0.00 %)	0(0.00 %)
Diarrhea	1(2.22%)	2(4.44 %)
Constipation	0(0.00 %)	0(0.00 %)
Fatigue	2(4.44 %)	2(4.44 %)
Fever	0(0.00 %)	0(0.00 %)
Infection	5(11.11%)	6(13.33 %)
Febrile neutropenia	0(0.00 %)	0(0.00 %)
Pneumonitis	1(2.22%)	2(4.44 %)
Alopecia	0(0.00 %)	0(0.00 %)
Rash	2(4.44 %)	2(4.44 %)
Mucositis oral	0(0.00 %)	0(0.00 %)
Neuropathy	0(0.00 %)	0(0.00 %)
Edema	0(0.00 %)	0(0.00 %)
AST	4(8.88%)	5(11.11%)
ALT	5(11.11 %)	6(13.33 %)
Total bilirubin	0(0.00 %)	0(0.00 %)
Creatinine	0(0.00 %)	0(0.00 %)

unselected patients with NSCLC. EGFR-TKIs inhibit tumor cell growth and blocks synthesis of angiogenic proteins by tumor cells. Somatic mutations in the EGFR gene are associated with the therapeutic response to EGFR-TKIs in individuals with advanced NSCLC [23, 24]. Indeed, randomized phaseIII studies revealed that first-line EGFR-TKI treatment resulted in an improved progression-free survival compared with standard chemotherapy in patients with advanced NSCLC who were selected on the basis of the presence of EGFR mutations [12, 25–27].

The potential tumour heterogeneity suggests that continuation of EGFR-TKIs in combination with chemotherapy might be beneficial-a hypothesis supported by findings from a retrospective study [19]. However, most previous clinical trials failed to show a benefit for combination of platinum-based doublet chemotherapy and EGFR-TKIs as first-line treatment for patients with NSCLC harboring sensitive EGFR mutations. It is still unanswered whether combination strategy of TKI and chemotherapy is really beneficial, or which administrating schedule will produce the best efficacy. Gefitinib is known to suppress the expression of thymidylate synthase (TS) in NSCLC cell lines, regardless of the presence of EGFR mutations [20]. Low TS expression is a predictive factor for the treatment efficacy of pemetrexed in NSCLC patients [21]. Thus, the addition of pemetrexed may increase treatment efficacy in patients treated with gefitinib. The research was designed to evaluate the efficacy and safety of pemetrexed combined with gefitinib as first-line therapy in patients with advanced NSCLC harboring a sensitive EGFR mutation.

A phase I trial of dose- and schedule-determining studies of the erlotinib and pemetrexed combination therapy performed in patients with refractory advanced NSCLC and solid tumors showed that this combination regimen was well tolerated by the patients, and that the administration of pemetrexed on day 1 and erlotinib on days 2 ~ 16 was feasible [28]. In the FASTACT-2 study, the patients receive six cycles of gemcitabine plus platinum with intercalated erlotinib (150 mg/day on days 15 ~ 28, orally) or placebo orally every 4 weeks, showed a benefit in the EGFR-mutant subgroup with regard to PFS and OS [29]. Based on these studies, we chose intercalating schedule in this study. We also determined the dosage of gefitinib and pemetrexed in reference to the results of a phase I study of combination of erlotinib and pemetrexed and two phase III trials of combination of gefitinib and platinum doublet chemotherapy in advanced NSCLC [29–31]. We evaluated the response to treatment in all patients. Our data revealed that the combination regimen of gefitinib + pemetrexed showed a higher ORR and DCR, longer median PFS and acceptable toxicity.

In conclusion, we show that gefitinib and pemetrexed combination therapy as first-line treatment was effective and well tolerated by patients with advanced NSCLC harboring a sensitive EGFR mutation.

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