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ORIGINAL ARTICLE

Efficacy of pemetrexed combined with erlotinib/gefitinib in advanced non-small cell lung cancer patients during tyrosine kinase inhibitor treatment*

Guanzhong Zhang[1], Zhaozhe Liu (Co-first author)[1], Tao Han[1], Xiaodong Xie[1] (✉), Shunchang Jiao[2] (✉)

[1] Department of Oncology, General Hospital of Shenyang Military Region, Shenyang 110016, China
[2] Department of Oncology, Chinese PLA General Hospital, Beijing 100853, China

Abstract

Objective We aimed to evaluate the efficacy and safety of pemetrexed combined with erlotinib/gefitinib in advanced non-small cell lung cancer (NSCLC) patients during tyrosine kinase inhibitor (TKI) treatment.

Methods Thirty-two patients with advanced NSCLC were divided into two groups. Patients in the control group received continuous daily epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment, and patients in the experimental group received continuous daily EGFR-TKI along with pemetrexed treatment, which was administered on day 1 at 500 mg/m^2. Erlotinib (150 mg) or gefitinib (250 mg) was administered daily from day 1 to day 21, with a cycle of every 21 days. Dexamethasone, folic acid, and vitamin B_{12} were also administered during the treatment. The endpoint of the primary study was the disease control rate.

Results The objective response rate was 21.9% (95% CI: 7.6% to 36.3%) in the control group, whereas the disease control rate was 84.4% (95% CI: 71.8% to 97.0%) in the experimental group. The median progression-free survival was 6.2 (95% CI: 2.4 to 10.0). Grades 3 or 4 adverse effects of leucopenia (15.6%), neutropenia (12.5%), anemia (3.1%), and nausea or vomiting (3.1%) were found in the experimental group.

Conclusion The administration of pemetrexed combined with erlotinib or gefitinib showed a higher efficacy in TKI-resistant NSCLC patients. Further, the adverse effects of this drug combination were well tolerated by the patients. Pemetrexed combined with TKI treatment might provide a satisfactory therapeutic strategy for advanced NSCLC patients after TKI treatment.

Key words: non-small cell lung cancer; pemetrexed; erlotinib; gefitinib; resistance

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Lung cancer is the most common cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer cases. At diagnosis, 65% to 75% of NSCLC are locally advanced or metastatic cases and are unresectable [1–3]. Combination chemotherapy is the standard treatment for advanced NSCLC. Platinum-based chemotherapy with pemetrexed or a third-generation agent, such as gemcitabine, docetaxel, paclitaxel, or vinorelbine, has significantly improved the median survival and quality of life in patients with advanced NSCLC. For epidermal growth factor receptor (EGFR)-mutation patients, treatment with EGFR tyrosine kinase inhibitors (TKIs), namely, erlotinib or gefitinib, results in a longer progression-free survival (PFS) and better overall survival (OS) than with chemotherapy [4–6]. Maintenance treatment with TKIs after chemotherapy can also prolong the PFS and OS of patients with unknown EGFR status [7]. However, disease progression is rapid for patients who develop resistance to TKIs, and no standard treatment option is available for TKI-resistant patients [8].

Two preclinical studies showed that combined administration of pemetrexed and erlotinib had synergistic effects on human NSCLC cells [9–10]. Our preclinical study

✉ Correspondence to: Xiaodong Xie. Email: doctor_xxd@163.com; Shunchang Jiao. Email: crzs281@tom.com
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also showed that combined administration of pemetrexed and gefitinib had synergistic effects on human colorectal cancer cells, and such effects were significant in gefitinib-resistant cells [11]. TKI-treated patients showing progressive disease are resistant to TKI. Therefore, pemetrexed combined with erlotinib or gefitinib may exhibit satisfactory efficacy in NSCLC patients who undergo TKI treatment. In this study, we collected patients' clinical data to evaluate the efficacy and safety of pemetrexed combined with erlotinib or gefitinib in advanced NSCLC patients.

Materials and methods

Patients

A total of 32 advanced NSCLC patients were divided into two groups in the study, which was conducted from June 2013 to March 2016; the patients met the following criteria: results of consecutive histological and pathological tests indicated disease progression during TKI treatment. Other inclusion criteria included age ≤ 75 years; life expectancy of greater than 8 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; adequate hematologic values (absolute neutrophil count ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin concentration ≥ 9 g/dL); normal hepatic function (total bilirubin concentration was less than 1-fold of the upper limit of the normal value, and alanine aminotransferase concentration was less than 1.5-fold of the upper limit of the normal value or elevated up to 3-fold of the upper limit of the normal value in patients with known hepatic metastases); and normal renal function (calculated creatinine clearance rate of > 45 mL/min).

Study medication

Patients in the control group received continuous daily EGFR-TKI treatment, and patients in the experimental group received continuous daily EGFR-TKI along with pemetrexed treatment. Pemetrexed at 500 mg/m^2 was intravenously administered for 10 min on day 1, then erlotinib (150 mg) or gefitinib (250 mg) was orally administered from day 1 to day 21, and the cycle was repeated every 21 days. Erlotinib/gefitinib was administered even after patients exhibited disease progression during erlotinib treatment. Folic acid at 400 μg per day was orally administered starting from 1 week prior to the first dose of pemetrexed to 3 weeks after the end of therapy. Vitamin B12 (1,000 μg) was intramuscularly injected a week before day 1 of cycle 1, and the injection was repeated every 9 weeks until the end of the study. Dexamethasone (4 mg) was orally administered twice daily on the day before and after each dose of pemetrexed. If intolerable adverse effects occurred, treatments were delayed for up to 42 d to allow the patient to recover from toxicity. Therapy was resumed using only 75% of the previous dose when the adversely affected patients exhibited 3 or 4 grade on the Common Toxicity Criteria (CTC). A patient was excluded from the study if he or she required more than 42 d of recovery time or more than two reductions in dose because of toxicity. If radiotherapy was required by the patient, treatment was discontinued until 2 weeks after the completion of radiotherapy.

Assessments and statistical methods

Baseline tumor measurements were obtained at or less than 1 week before the start of treatment. Measurements were performed using the Response Evaluation Criteria in Solid Tumors version 1.1; tumor response was assessed using the same imaging technique that was used to obtain the baseline measurements [12]. The best response was recorded at the end of the treatment period. Safety measures, such as adverse effect monitoring, physical examinations, and clinical laboratory tests (hematology, blood biochemistry, and hepatic and renal function) were performed weekly. Toxicity was graded using version 2.0 of the National Cancer Institute CTC.

Statistical analysis was performed using the Statistical Package for Social Science v. 17.0. A statistical summary of patient characteristics and efficiency and safety variables was obtained [13]. Frequencies were reported as numbers and percentages. The objective response to chemotherapy was defined by the overall best response during treatment. PFS time was defined as the duration from enrollment in the study to disease progression or death. The OS time was defined as the duration from enrollment in the study to the time of death from any cause. PFS and OS times were analyzed using the Kaplan-Meier method.

Ethics statement

All patients were from China and received treatment at the PLA General Hospital. All clinical investigations were approved by the PLA General Hospital Ethical Committee. All patients submitted signed consent forms prior to treatment.

Results

Between June 2013 and March 2016, a total of 32 patients (16 men and 16 women) participated in the study. The baseline patient characteristics are listed in Table 1. The median age of the patients was 56 years (range: 30 to 75 years). All patients had good performance status, with 24 patients having an ECOG performance status of 0, whereas 8 patients had an ECOG performance status of 1. Four patients had stage IIIB tumors and 28 patients had stage IV tumors. Thirty-one patients had

Table 1 Characteristics of patients (n = 32)

Characteristics of patients	n (%)
Age (years, range)	56 (30–75)
Sex	
Male	16 (50.0)
Female	16 (50.0)
Weight (kg, mean ± s)	63 ± 8.9
Stage	
IIIB	4 (12.5)
IV	28 (87.5)
ECOG Performance status	
0	24 (75.0)
1	8 (25.0)

adenocarcinoma, and 1 patient had large cell carcinoma. Twenty-six patients had mutated *EGFR* and 6 patients had unknown *EGFR* status, i.e., the *EGFR* gene status was not detected before TKI treatment because of personal reasons.

Fifteen patients received erlotinib treatment, and 17 patients received gefitinib treatment. Seven patients were treated with TKI as first-line treatment, 13 patients were treated with TKI as second- or third-line treatment, and 12 patients were given TKI as maintenance treatment after first-line chemotherapy. Among 32 patients receiving EGFR-TKI treatment, 5 patients achieved a partial response (PR) and 24 had stable disease (SD) with an objective response rate (ORR) of 15.6% and a disease control rate (DCR) of 90.6%. The median PFS was 10.2 months (95% CI: 1.1 to 16.9). All patients who showed disease progression during erlotinib or gefitinib treatment were administered pemetrexed along with daily EGFR-TKI treatment.

Two patients completed only one cycle of treatment because of a decline in general physical condition, whereas the other 30 patients received at least two cycles of pemetrexed in addition to TKI treatment. The total number of treatment cycles was 186, and the median number of treatment cycles was six (in the range of 1 to 24). Three patients (9.4%) underwent dose modification, and treatment was delayed for 8 patients because of adverse effects. No mortality was recorded among the patients at the end of the follow-up period in August 2013. All patients were evaluated for treatment efficacy and adverse reaction. At follow-up, no disease progression was observed in 13 patients, 6 patients were still in treatment, and 30 patients were still alive.

Efficacy

We failed to observe a complete response (CR) in all patients treated with pemetrexed plus erlotinib or gefitinib. Seven patients (21.9%) achieved a PR, 20 patients (62.5%) achieved SD, and 5 patients (15.6%) showed progressive disease. The ORR [(CR + PR)/n] was 21.9% (in 7 of 32 patients, 95% CI: 7.6% to 36.3%). The DCR [(CR + PR + SD)/n] was 84.4% (in 27 of 32 patients, 95% CI: 71.8% to 97.0%). The tumor response is summarized in Table 2. The median PFS was 6.2 months (95% CI: 2.4 to 10.0). The Kaplan-Meier plot for PFS is displayed in Fig. 1. The 6-month and 1-year PFS rates were 53.3% and 32.1%, respectively.

Table 2 Response for patients with NSCLC treated with pemetrexed plus erlotinib or gefitinib (n = 32)

Response	n (%)
CR	0 (0.0)
PR	7 (21.9)
SD	20 (62.5)
PD	5 (15.6)
ORR	7 (21.9)
DCR	27 (84.4)

Safety

Toxicity was evaluated in all patients and in all cycles. Twenty-one patients (65.6%) reported at least one adverse effect during the study. Five and two patients (15.6% and 6.3%, respectively) experienced grades 3 and 4 adverse effects, respectively. The common adverse effects were leucopenia (in 21 of 32 patients, 65.6%), neutropenia (in 19 of 32 patients, 59.4%), nausea or vomiting (in 18 of 32 patients, 56.3%), rash (in 17 of 32 patients, 53.1%), and diarrhea (in 10 of 32 patients, 31.3%). Grades 3 or 4 adverse effects included leucopenia (in 5 of 32 patients, 15.6%), neutropenia (in 4 of 32 patients, 12.5%), anemia (in 1 of 32 patients, 3.1%), and nausea/vomiting (in 1 of 32 patients, 3.1%). By the end of the study, 2 patients had died because of disease progression. No mortality cases were caused by treatment.

Discussion

Several randomized phase III clinical trials showed that gemcitabine or paclitaxel plus platinum combined with continuous daily administration of erlotinib or gefitinib as first-line therapy failed to improve the survival of patients with advanced NSCLC [14–17]. Thus, chemotherapy combined with EGFR-TKI was not a satisfactory approach for treating NSCLC, and few researchers were interested in using this strategy. However, another randomized phase III study showed that PFS and OS were longer in advanced pancreatic cancer patients who received continuous daily erlotinib treatment in addition to gemcitabine compared with patients who received gemcitabine alone [18].

In the current study, we observed the efficacy and safety of pemetrexed combined with continuous daily administration of erlotinib or gefitinib (from day 1 to 21) in advanced NSCLC patients undergoing TKI treatment.

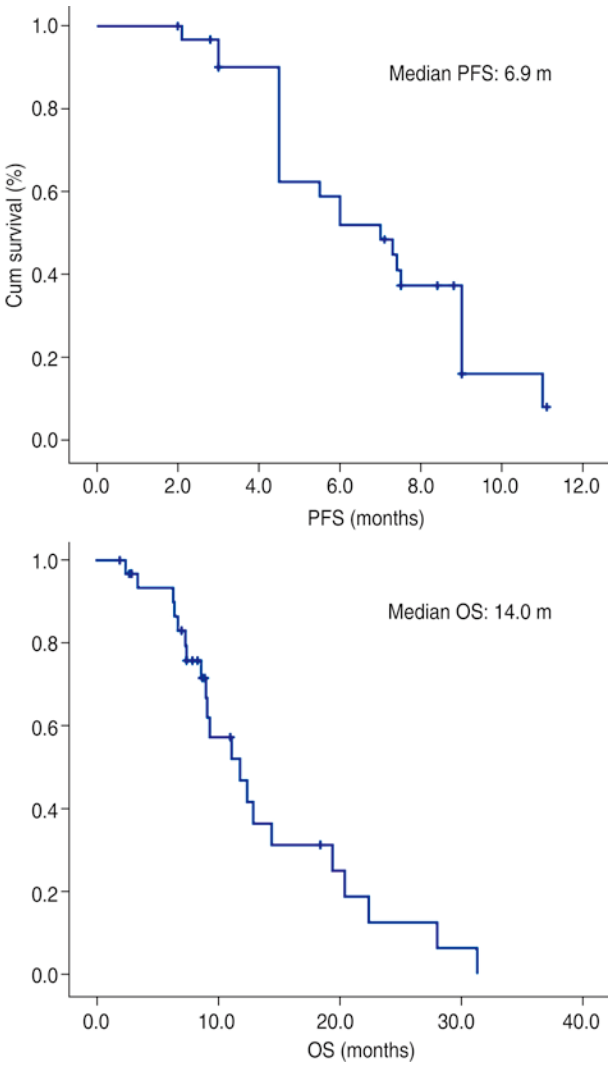

Fig. 1 PFS and OS (n = 32)

The treatment modality was effective and safe. Among 32 patients, 7 patients achieved a PR and 20 patients achieved SD. The DCR and ORR were 84.4% and 21.9%, respectively. The median PFS was 6.2 months. The grade 3 or 4 adverse effects were as follows: leukopenia, 15.6%; neutropenia, 12.5%; anemia, 3.1%; and nausea or vomiting, 3.1%.

Naruo *et al* conducted a phase II clinical study involving the administration of pemetrexed combined intermittently with gefitinib or erlotinib (from day 2 to day 16) after relapse to gefitinib or erlotinib treatment in advanced NSCLC patients [19]. In the study of Naruo *et al*, the DCR and ORR were 77.8% and 25.9%, respectively, and the median PFS was 7 months. The adverse effects were also well tolerated by the patients.

In a multicenter, international, and randomized phase III trial reported by Hanna *et al*, the effects of single-agent pemetrexed were compared with those of docetaxel for previously treated NSCLC patients. The ORR for pemetrexed and docetaxel were 9.1% and 8.8%, respectively. The DCR was 45.8% for pemetrexed and 46.8% for docetaxel [20]. Results of an international, randomized clinical trial showed that erlotinib had a similar efficacy, but lower toxicity, compared with docetaxel in 731 EGFR-unselected patients [21–23].

The above-mentioned studies determined whether pemetrexed and erlotinib could become standard second-line treatments for NSCLC. Compared with the current standard second-line treatment of NSCLC, our findings and those of Naruo *et al* showed higher ORR and DCR, and the adverse effects were well tolerated. Thus, pemetrexed combined with erlotinib or gefitinib may be more effective than the conventional second-line treatments (pemetrexed, docetaxel, and EGFR TKIs) for NSCLC.

Some preclinical studies discussed the mechanism underlying the synergistic effects of pemetrexed and TKIs. TKIs affect the expression and activity of thymidylate synthase enzyme in tumor cells, and such enzymes increase the effectiveness of pemetrexed against tumor cells [10–11]. Pemetrexed increases the activity of the EGFR signal transduction pathway, which in turn increases the independence of the cell from the pathway. The magnitude of the increase in activity is significantly reduced by TKIs [9, 11]. Previous research results explained the mechanism underlying the efficacy of pemetrexed in combination with TKI in NSCLC patients.

Li *et al* reported an antagonistic interaction between pemetrexed and erlotinib in NSCLC cells when erlotinib administration preceded that of pemetrexed. Erlotinib arrested the cell cycle at the G_1 phase and consequently reduced the effect of pemetrexed on tumor cells. In contrast, a synergistic or additive interaction was observed when pemetrexed administration preceded that of erlotinib or when pemetrexed and erlotinib were simultaneously used [9]. Naruo *et al* administered pemetrexed to patients on day 1 and TKIs on days 2 to 16 within a 21-day cycle, i.e., pemetrexed was combined with TKIs intermittently. Li *et al* suggested that the antagonistic interaction was much less in TKI-resistant cells than in TKI-sensitive cells [9]. NSCLC patients who show disease progression during TKI treatment are resistant to TKI. Thus, the antagonistic effect is expected to be low when pemetrexed is administered in combination with continuous TKI treatment.

Continuous TKI treatment may show strong synergistic effects with pemetrexed because of the long duration of tumor exposure to the drug. Moore *et al* showed that gemcitabine combined with continued daily oral erlotinib treatment showed satisfactory effects for advanced pancreatic cancer patients [18]. In Moore's study, 90% of the patients had KRAS gene mutations and

showed TKI resistance [23–24]. The same TKI treatment modality used in Moore's research was applied in the current study. No significant difference was found between the efficacy of our continuous TKI treatment and Naruo *et al*'s intermittent TKI treatment, possibly because the sample sizes were small in both trials. Further studies are required to determine whether pemetrexed combined with continuous TKI treatment can have better efficacy than pemetrexed combined with intermittent TKI treatment.

In this study, all patients who underwent TKI treatment showed progressive disease, thereby indicating their resistance to TKIs. The synergistic effect was stronger in resistant cells than in sensitive cells, consistent with our preclinical study [11]. Thus, NSCLC patients who showed progressive disease during TKI treatment responded well to the administration of pemetrexed combined with TKIs.

In conclusion, compared with conventional treatment, pemetrexed combined with continuous TKI treatment showed high efficacy and the adverse effects were well tolerated by patients with advanced NSCLC. We believe that pemetrexed combined with TKI treatment might provide a satisfactory therapeutic strategy for advanced NSCLC patients after TKI treatment. However, further studies are required to validate the effects of this combined therapeutic strategy.

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