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Original Research Article

Comparative efficacy and safety of pemetrexed and crizotinib in Chinese patients with advanced lung cancer: A preliminary clinical trial

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Abstract

Purpose: *To carry out a pilot clinical trial to compare the effectiveness and safety of crizotinib and pemetrexed-based regimens in Chinese patients with advanced lung cancer (ALC).*
Method: *Patients with confirmed diagnosis of ALC were randomly grouped and treated intravenously with a mixture of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) plus BSC, or crizotinib (250 mg BD) + BSC in a 1:1 ratio. Efficacy parameters such as overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) were assessed after pemetrexed and crizotinib treatments. The safety of pemetrexed and crizotinib was determined. Survival time with respect to disease progression was also assessed.*
Results: *Pemetrexed-based regimens showed significantly higher OS and PFS than crizotinib (OS: median = 13.23 and 7.47 months, respectively; $p < 0.001$; PFS: median = 11.32 and 4.17 months, respectively). Objective response was also favorable in the patients treated with pemetrexed, when compared with those given crizotinib. Pemetrexed-based regimen was superior to crizotinib in improving OS, PFS and ORR, and it offered significantly greater clinical benefits than crizotinib in Chinese patients with ALC.*
Conclusion: *The results of clinical trial would help clinicians select appropriate therapeutic intervention for patients with ALC.*

Keywords: *Crizotinib, Pemetrexed, Efficacy, Safety, Advanced lung cancer*

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INTRODUCTION

Lung cancer (LC) is a leading cause of cancer-related mortality worldwide [1]. The disease is highly prevalent among Asian countries [1-4]. There are several approved treatment modalities in Asian countries. Currently, surgery is the typical treatment for LC patients. However, 20 to 30 % of subjects with ALC develop relapse in spite of surgical removal of cancerous cells [1-9]. Recently, nivolumab, oral multikinase inhibitor and newer agents such as nintedanib and ramucirumab have been identified as new therapeutic options for LC patients. Several lines

of clinical evidence from pivotal studies have suggested that pemetrexed should be used as the first line therapy, in addition to crizotinib for ALC [2-8].

Pemetrexed belongs to the anti-folate class of cytotoxic agents. It is effective and well tolerated in lung cancer patients after *EGFR*-TKI failure, and has been recommended as the 1st line treatment for ALC due to its favorable efficacy and safety profile [10,11]. Crizotinib has been approved in most of Asian countries. It inhibits tyrosine kinase; it exerts anti-proliferation effect on lung tissue, and shows favorable efficacy in several type of tumors, including LC [12,13]. Several lines of clinical evidence have demonstrated the superior efficacy profile of crizotinib, relative to chemotherapy (except pemetrexed) in lung cancer patients. In clinical trials, crizotinib produced 57 % response, and the probability of OS and PFS was 5.9 months [12,13]. However, some patients who benefited earlier on developed resistance to crizotinib later, due to some intrinsic resistance mechanism which is not yet elucidated.

There are no studies on direct comparison of pemetrexed and crizotinib in Chinese patients with ALC. Comparison of efficacy and safety of pemetrexed versus crizotinib in Chinese ALC patients has not been carried out till date. Thus, the present trial was designed to evaluate, for the first time, the effectiveness and safety of pemetrexed-based regimens relative to crizotinib in Chinese patients with ALC.

METHODS

Study design, patients and ethics

Patients with confirmed diagnosis of unresectable non-squamous LC, with ECOG PS in the range of 0 – 1, and who had metastases were recruited in this trial. The primary objective of this study was to compare the effectiveness and safety of crizotinib with that of pemetrexed in Chinese patients with ACL. Efficacy parameters such as OS, ORR, and PFS were assessed after pemetrexed and crizotinib treatments. The safety of pemetrexed and crizotinib treatments was also assessed, in addition to survival time with respect to disease progression. Written consent was obtained from each enrolled subject. The trial protocol and other essential trial-related documents were approved by the Institutional Review Board of Central South University (approval no. IRB/XSMHCH/12-CSU/268-2018). Each patient was instructed to provide information on demography, medical history and family history using a pre-designed form as per our screening protocol before enrollment in the screening program.

Trial drug administration

The enrolled ALC patients were randomly assigned to two groups containing equal number of patients. One group received 250 mg crizotinib plus BSC, while the other group was given pemetrexel at a dose of 500 mg/m^2 plus BSC. The subjects in the crizotinib group were given crizotinib (250 mg BD + BSC mixed in a 1:1 ratio with cisplatin (75 mg/m^2). Both treatments were given intravenously.

Efficacy assessment

Using RECIST Criteria, OS and PFS were recorded for each patient using CT scan and/or MRI. The number of patients with PR, CR, SD or PD were recorded. Moreover, OS and PFS were recorded for each patient. The survival time of patients was assessed from date of diagnosis of lung cancer to date of death due to lung cancer, or date lost to follow up. The primary trial endpoints were comparison of OS, ORR and PFS after pemetrexed and crizotinib treatments, to determine which treatment was more effective in improving these parameters. The secondary trial endpoint was comparison of safety of pemetrexed and crizotinib.

Safety assessment

The incidence and severity of drug-induced liver injury in subjects with and without liver metastasis were evaluated based on laboratory criteria. Treatment-related TEAEs or SAEs referred to any event considered to be causally related to the trial drug according to the physician's subjective judgment. No re-escalation was done for the patients who needed dose reductions. In addition, patients who were serially and repeatedly subjected to treatment were monitored for evidence of cumulative toxicity. Serious adverse events were followed up until recovery, death, or loss to follow-up, if a causal relation with the investigational drug could not be ruled out.

Statistical analysis

Since the present investigation was designed as a preliminary study, a formal calculation of sample size was not carried out. Analyses of population was applied to those who received at least one dose of either pemetrexed or crizotinib. Patients who received at least one dose of either pemetrexed or crizotinib were included in safety analysis. Comparison of PFS and OS and

response was made between both treatment groups using a log-rank test. Data analysis was conducted using Sigma Plot (ver 11.0).

RESULTS

Baseline characteristics of subjects and drug exposure

A total of 120 patients were enrolled in this study from Jan 2017 to Dec 2018. They were randomly allocated to pemetrexed plus BSC (n = 60) or crizotinib plus BSC (n = 60). Both treatment groups had similar demography and baseline characteristics. The demography and clinical features of all recruited patients are shown in Table 1.

Table 1: Characteristics of the included patients

Characteristic	Crizotinib (n=60)	Pemetrexed-based regimen (n=60)
Age (years), mean (SD)	42 (4.7)	44 (4.6)
Gender		
Male	26	24
Female	34	36
KS status		
=<50%	49	46
>50%	11	14
Previous use of anti-VEGF agents		
Yes	43	42
No	17	18
Previous use of anti-EGFR agents		
Yes	52	51
No	8	9

*(*K-*ras* = mutations in the Kirsten *ras*; n = number of patients; VEGF = vascular endothelial growth factor; EGFR = epidermal growth factor receptor)

Treatment efficacy

Pemetrexed-based regimens showed significantly higher OS and PFS than crizotinib (OS: median = 13.23 and 7.47 months, respectively; $p < 0.001$; PFS: median = 11.32 and 4.17 months, respectively). Objective response was considerably greater in patients treated with pemetrexed than in those that received crizotinib. These results are shown in Table 2.

Safety and tolerability

In the crizotinib group, the most common treatment-related AE of all grades (in >30 % of patients) were increased blood pressure, palmar-plantar erythrodysaesthesia syndrome (HFSR), and increased urinary protein content (Table 3). Hepatic laboratory abnormalities such as increased levels of bilirubin, ALT and AST were higher in the crizotinib group than in the pemetrexed group. Majority of the hepatotoxicity events in patients treated with crizotinib were of grade 1 or 2.

Table 2: Efficacy of crizotinib and pemetrexed in patients with lung cancer

Variable	Crizotinib (n=60)	Pemetrexed-based regimens (n=60)
OS		
Median (months)	7.47	13.23
HR (95% CI) Probability value	0.48 (0.4-0.6) $P < 0.001$	
Progression-free survival		
Median (months)	4.17	11.32
HR (95% CI), Probability value	0.59 (0.5-0.7) $P < 0.001$	
ORR		
CR	3	4
PR	7	6
SD	36	37
PD	14	13

Table 3: Treatment-related adverse events in lung cancer patients treated crizotinib and and those treated with pemetrexed

Preferred term	Crizotinib (n=60)	Pemetrexed-based regimen (n=60)
Hypertension	23	6
HFSR	31	5
Rash	13	4
Proteinuria	19	8
Occult blood positive	14	8
Epistaxis	19	7
Hematuria	12	2
Blood urine present	12	1
Hypothyroidism	19	3

(AEs = adverse events; n = number of patients in each category)

DISCUSSION

The current investigation is the first trial carried out to compare the efficacy and safety of pemetrexed and crizotinib in Chinese patients with ALC. No direct comparison of pemetrexed and crizotinib was performed. Moreover, there has been no comparison of effectiveness and safety profiles of pemetrexed and crizotinib in

Chinese patients till date. Thus, the present trial was designed to compare the effectiveness and safety of pemetrexed-based regimens with crizotinib in Chinese patients with ALC. Pemetrexed-based regimens showed significantly greater OS and PFS than the crizotinib-based treatment. The objective response was also favorable among the patients treated with pemetrexed, when compared with crizotinib-treated cases.

The present trial results showed that pemetrexed-based regimens were superior to crizotinib in improving OS, PFS and ORR, and it offered significantly greater clinical benefits for ALC patients than Crizotinib. The results of the present trial may help clinicians to select appropriate treatment modalities for ACL. These results are consistent with previous reports [10-13]. In general, pemetrexed and crizotinib were well-tolerated in the ALC patients.

The finding pertaining to pemetrexed is consistent with previous reports which showed that it is efficacious and of acceptable safety profile in patients with LC. Indeed, pemetrexed has been recommended as first line therapy for ALC. Due to its good efficacy and safety profile, the present trial also showed that pemetrexed was efficacious in the treatment of patients with ACL. Moreover, earlier reports showed that crizotinib produced 57 % response, with OS and PFS of 5.9 months. However, a few patients who benefited later developed resistance to crizotinib due to some yet-to-be elucidated intrinsic resistance mechanisms. In the present trial, crizotinib showed 76 % response, which was slightly less than that of pemetrexed (77 %), and it resulted in longer survival time (7.47 months) than was seen in previous reports [10-13].

However, crizotinib treatment produced slightly lower PFS in the present report (4.17 months) than in earlier reports. Overall, in both studies, pemetrexed yielded greater clinical benefits than crizotinib, with respect to OS and PFS among the Chinese ACL patients. Pemetrexed treatment resulted in significantly longer survival time, OS and PFS, than crizotinib. The overall response (DCR and ORR) in patients treated with pemetrexed was superior to that due to crizotinib.

The most common treatment-related AE of all grades (occurring in > 30 % of patients) were increased blood pressure, palmar-plantar erythrodysaesthesia syndrome (HFSR), and increased urinary protein content. Hepatic laboratory abnormalities such as increased levels of bilirubin, ALT and AST were higher in the crizotinib group than in the pemetrexed-treated patients. Most of the hepatotoxicity events in patients treated with crizotinib were of grade 1 or 2. The safety results are consistent with previous reports.

Limitations of the study

Since the present trial was conducted at a single hospital in China, the findings cannot to be generalized to the Chinese population. Moreover, the sample size used was small. Thus, a wider, multi-center clinical trial with larger sample size is needed to confirm the present findings.

CONCLUSION

The present trial results show that pemetrexed-based regimens are superior to crizotinib in improving OS, PFS and ORR. Moreover, pemetrexed offers significantly greater clinical benefits than crizotinib in Chinese ACL patients. These results may help clinicians in the selection of appropriate treatment modalities for patients with ACL.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. This manuscript was written by Bolin Chen. Lin Wu and Min Yang collected data and did statistical analysis. Jia Li and Li Xu gave suggestions in designing of this study. The whole work was supervised by Kang Li.

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