

ORIGINAL ARTICLE

Crizotinib versus platinum-based double-agent chemotherapy as the first line treatment in advanced anaplastic lymphoma kinase-positive lung adenocarcinoma

Quan Zhang, Na Qin, Jinghui Wang, Jialin Lv, Xinjie Yang, Xi Li, Jingying Nong, Hui Zhang, Xinyong Zhang, Yuhua Wu & Shucui Zhang

Department of Medical Oncology, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, Capital Medical University, Beijing, China

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Correspondence

Shucui Zhang, Department of Medical Oncology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing 101149, China.

Tel: +86 10 89509324

Fax: +86 10 80507685

Email: szhang6304@163.com

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Abstract

Background: To explore the efficacy and safety of crizotinib versus platinum-based double agent chemotherapy as the first-line treatment in patients with advanced anaplastic lymphoma kinase (ALK)-positive lung adenocarcinoma.

Method: We retrospectively analyzed data from 19 patients with advanced ALK-positive lung adenocarcinoma who had received no previous systemic treatment for advanced disease. Seven patients received oral crizotinib at a dose of 250 mg twice daily; 12 patients were administered standard chemotherapy (pemetrexed, paclitaxel, vinorelbine or gemcitabine plus either cisplatin or carboplatin) every three weeks for up to six cycles. The primary endpoint was overall response rate (ORR), disease control rate (DCR), and safety.

Results: The ORR was significantly higher with crizotinib than with chemotherapy (83.3% in the crizotinib vs. 25.0% in the chemotherapy group, $P < 0.05$); the DCRs were 100% and 75%, respectively ($P < 0.05$). The common adverse events associated with crizotinib were visual abnormality and diarrhea, whereas those associated with chemotherapy were neutropenia and nausea. In the crizotinib group, liver aminotransferase elevation (adverse events grade 3 or 4) occurred in one patient (14.3%). In the chemotherapy group, the same grade neutropenia adverse event occurred in two patients (16.6%). The incidence of treatment-related grade 3 or 4 adverse events was similar in both groups. Compared with chemotherapy, crizotinib was associated with a greater reduction in lung cancer symptoms and a greater improvement in quality of life.

Conclusion: As a first-line treatment, crizotinib was superior to platinum-based double chemotherapy in patients with previously untreated advanced ALK-positive lung adenocarcinoma. Therefore, crizotinib is an optimal therapy as a first-line treatment in these patients.

Introduction

In 2007, Soda *et al.* first discovered the fusion gene of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) in non-small cell lung cancer (NSCLC).¹ They defined a distinct subgroup of NSCLC that typically occurs in younger patients who have never smoked or have a history of light smoking with adenocarcinoma histologic characteristics.^{2–4} EML4-ALK is a new fusion gene developed via the translocation of EML4 and ALK at the position of chromosome 2 short arms, which occupy the

preferential effects of promoting tumorigenesis, tumor proliferation, and metastasis, both *in vivo* and *in vitro*. In addition, ALK-targeted small molecule inhibitors can efficiently block these biological effects, indicating that EML4-ALK is one of the driver genes of lung cancer. Multiple clinical studies including PROFILE 1001, PROFILE 1007, and PROFILE 1029 revealed that crizotinib, as an ALK inhibitor, has achieved significant clinical efficacy in the treatment of ALK-positive NSCLC. In August 2011, the United States Food and Drug Administration (FDA) approved crizotinib for curing ALK-positive patients. In January 2013, crizotinib was

listed on the market and was approved in mainland China for ALK-positive NSCLC treatment. In December 2014, in a randomized phase 3 trial involving patients with advanced ALK-positive NSCLC who were previously untreated, crizotinib showed efficacy superior to that of platinum-based double-agent chemotherapy with either pemetrexed or docetaxel. Crizotinib significantly prolonged progression-free survival (PFS) in previously untreated patients with ALK-positive advanced NSCLC when compared to standard platinum-based chemotherapy regimens (median PFS 10.9 vs. 7.0 months; hazard ratio [HR]: 0.45; 95% confidence interval [CI]: 0.35–0.60; $P < 0.001$). Crizotinib also demonstrated a significantly higher overall response rate (ORR) when compared to standard platinum-based chemotherapy regimens (74% vs. 45%; $P < 0.001$).⁵

We retrospectively analyzed data from 19 patients with previously untreated ALK-positive advanced NSCLC to verify the efficacy and safety of two different therapeutic strategies: crizotinib versus platinum-based double chemotherapy as a first line treatment.

Subjects and methods

Patients

During November 2013 to September 2014, we enrolled 19 patients who had undergone continuous screening of Ventana immunohistochemistry (IHC) (Ventana Medical Systems, Inc., Tucson, Arizona, USA) and were positively diagnosed with advanced ALK-positive lung adenocarcinoma by histopathology. The patients were treated with either crizotinib or two platinum-containing drug combination regimens as first line chemotherapy at the Beijing Chest Hospital, Capital Medical University. The platinum-based double chemotherapy was administered for at least two cycles, and crizotinib was administered for at least one month. Prior to treatment, blood routine, liver, renal, and cardiac functions were determined and the results conformed to the therapeutic requirement. The tumor tissue samples of these 19 patients were also assessed for epidermal growth factor receptor (EGFR) mutation using liquid chip technology and DNA sequencing. Clinical information of patients included age, gender, smoking status, tumor node metastasis (TNM) staging, performance status (PS), and treatment condition. TNM staging was determined according to the standard of the American Joint Committee for Cancer, seventh edition.

Method

Pre-diluted Ventana anti-ALK (D5F3) rabbit monoclonal primary antibody (Cell Signal Technology, Danvers, MA, USA.) was applied on 4- μ m-thick formalin-fixed, paraffin-

embedded (FFPE) slides on a Benchmark XT stainer (Ventana Medical Systems, Inc.). Optiview DAB IHC detection and Optiview Amplification kits (Ventana Medical Systems, Inc.) were used according to the manufacturer's instructions. We defined the presence of strong granular cytoplasmic staining in the tumor cells (any percentage of positive tumor cells) as ALK positive, while the absence of strong granular cytoplasmic staining in the tumor cells was ALK negative.

Therapeutic regimens

Crizotinib therapeutic regimen: 250 mg crizotinib, twice a day, orally. Platinum-containing two-drug combination regimen: 175 mg/m² paclitaxel on day one or 25 mg/m²; vinorelbine on days one and eight; 1250 mg/m² gemcitabine on days one and eight; or 500 mg/m² pemetrexed on day one, combined with 75 mg/m² cisplatin on day one, or carboplatin area under the curve 5 on day one. In the combined regimens mentioned above, a period of 21 days was regarded as one therapeutic cycle. Prophylactic antiemetic and other pre-treatments were realized routinely during the process of treatment.

Evaluation criteria

Response Evaluation Criteria in Solid Tumors (version 1.1) was used for evaluation. The definition of curative efficacy included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The ORR consisted of CR and PR. The disease control rate (DCR) consisted of CR, PR, and SD. In the chemotherapy group, evaluation of curative efficacy was performed after every two cycles. In the crizotinib group, evaluation was conducted one month after initial treatment, and every two months subsequently. The optimal curative effects were selected as curative records within the duration of follow-up in both groups. Adverse events were classified and graded according to Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was adopted for data processing and statistical analysis. The Fisher's exact test was used to compare the efficacy and adverse reaction rates between the groups and $P < 0.05$ was considered statistically significant.

Results

General information

A total of 19 patients were confirmed with ALK-positive lung adenocarcinoma and conformed to the inclusion criteria of

Table 1 Baseline clinical characteristics of 19 patients with advanced lung adenocarcinoma

	Crizotinib group (n = 7)	Chemotherapy group (n = 12)
Age		
Median age	53	52
Range of age	35–62	41–65
Gender		
Male	4 (57.1%)	6 (50.0%)
Female	3 (42.9%)	6 (50.0%)
Smoking		
No smoking	6 (85.7%)	8 (66.7%)
Smoking	1 (14.3%)	4 (33.3%)
PS Scoring		
0	1 (14.3%)	1 (8.3%)
1	6 (85.7%)	11 (91.7%)
2	0	0

PS, performance status.

this study through Ventana IHC continuous screening and clinical pathological examination. Seven cases received crizotinib orally and 12 cases received systemic chemotherapy, in which three cases received a paclitaxel plus platinum-based regimen, three received a pemetrexed plus platinum-based regimen, two received a vinorelbine plus platinum-based regimen, two received a gemcitabine plus platinum-based regimen, and two cases received a docetaxel plus platinum-based regimen. (Table 1).

Assessment of efficacy

As of 28 February 2015, the final date of follow-up, the data for efficiency evaluation in six of the seven cases in the crizotinib group were available. One case was assessed as SD, while the other five cases achieved PR based on the best efficacy during the follow-up period. Another case in this group was found during surgery to have multiple tumor pleura and diaphragm metastasis; therefore palliative resection of the primary lesion in the lung was performed (because of a lack of measurable lesion data, this case was not included in efficacy evaluation). The patients received crizotinib treatment after surgery.

In the chemotherapy group, the data were eligible for evaluation in all 12 cases. Three cases were assessed as PR after six cycles of chemotherapy: two cases received vinorelbine, and one received pemetrexed. However, in three cases of PD, the disease progressed after two cycles of chemotherapy, with one case receiving gemcitabine, one paclitaxel, and one docetaxel treatment.

After statistical analysis of the data of the 18 available cases for efficacy evaluation, the ORR of crizotinib as the first line treatment was significantly increased compared with the chemotherapy group (83.3% vs. 25.0%, $P = 0.043$) (Table 2).

Table 2 Efficacy of first line treatment in 19 patients with stage IV lung adenocarcinoma

	Group crizotinib (n = 7)	Group chemotherapy (n = 12)
Case available for evaluation		
CR	0	0
PR	5 (83.3%)	3 (25.0%)
SD	1 (16.7%)	6 (50.0%)
PD	0	3 (25.0%)
ORR	5/6 (83.3%)	3/12 (25.0%)
DCR	6/6 (100.0%)	9/12 (75.0%)
Case unavailable for evaluation.		
	1	0

CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety and adverse events

Common adverse events associated with crizotinib were visual abnormalities and diarrhea and all were at grade 1 or 2. Adverse events higher than grade 3 included an elevated level of liver aminotransferase, with an overall incidence of 14.3%. In the chemotherapy group, the most common adverse events were neutropenia and nausea; most of these were in grade 1 or 2. Neutropenia at grade 3 occurred in two cases with a total incidence of 16.6%. The incidence of adverse events higher than grade 3 was similar in the two groups ($P > 0.05$), as shown in Table 3.

One patient in the crizotinib group showed an elevated level of liver aminotransferase; however, it returned to normal after drug discontinuation and liver protection management. We reduced the dosage of crizotinib to 200 mg, twice a day, for this patient. Unfortunately, the patient took 250 mg once a day himself without the consent of his doctor. In subsequent days, his aminotransferase elevated to the level of grade 1. One patient experienced nausea and vomiting, and although it was not more severe than grade 3, the patient complained of a decreased quality of life and was unable to tolerate the treatment further. We reduced the dosage of crizotinib to 200 mg, twice a day. The patient showed good tolerance in the subsequent medication period. Two patients in the crizotinib group had an elevated myocardial enzyme without an ischemic change detected via electrocardiogram. In the chemotherapy group, neutropenia at grade 3 or above occurred in two cases. One of these cases was neutropenia at grade 4 in combination with a secondary infection. The drug dosage was reduced in subsequent chemotherapy.

Discussion

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase is one of the most important driver genes of lung adenocarcinoma. As EGFR mutation is

Table 3 Adverse events after first line treatment in 19 patients with stage IV lung adenocarcinoma

	Crizotinib group (n = 7)		Chemotherapy group (n = 12)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Visual abnormalities	5 (71.4%)	0	0	0
Diarrhea	5 (71.4%)	0	0	0
Nausea	4 (57.2%)	0	7 (58.3%)	0
Vomiting	2 (28.6%)	0	0	0
Abnormal liver function	1 (14.3%)	1 (14.3%)	1 (8.3%)	0
Neutropenia	1 (14.3%)	0	7 (58.3%)	2 (16.6%)
Anemia	1 (14.3%)	0	1 (8.3%)	0
Thrombocytopenia	0	0	1 (8.3%)	0
Dysgeusia	1 (14.3%)	0	0	0
Rash	0	0	1 (8.3%)	0
Secondary infection	0	0	1 (8.3%)	0
Ototoxicity	0	0	1 (8.3%)	0
Fatigue	0	0	2 (16.6%)	0
Elevated myocardial enzyme	2 (28.6%)	0	0	0

related to clinical and pathological characteristics including Asian, female, non-smoking and adenocarcinoma, ALK-positive is commonly found in young, non-smoking individuals and the solid, adenocarcinoma subtype of signet-ring cell carcinoma.^{4–8} In this study, the median age of patients was 52 years with 77.4% non-smokers, with a comparable gender ratio to previous studies. However, the diagnosis of each patient in this study was ultimately confirmed by the examination of bronchoscopy, lung biopsy or embedded sediment of pleural effusion. Because of the small sample size or lack of tissue structure, we were not able to further differentiate the histologic subtypes of adenocarcinoma.

Currently, there are three methods for the detection of EML4-ALK: fluorescence in situ hybridization (FISH), IHC, and reverse transcriptase polymerase chain reaction (RT-PCR). Each of them has their own advantages and disadvantages.⁹ The US FDA approved FISH as a companion diagnostic method because it was used in clinical trials involving the treatment of ALK-positive patients with crizotinib. As a new diagnostic technique, Ventana IHC (D5F3) is of an obvious advantage compared with conventional IHC. Criteria are defined as either negative or positive only, compared to the multi-level criteria of IHC staining intensity (0–3+), thereby reducing the risk of subjective error by the operator. The process is completed in an automatic IHC stainer with high repeatability and a negative control, avoiding the instability of manual operation. The sensitivity and specificity between Ventana IHC and FISH were compared through two studies, and both were >98%. Ventana IHC was approved by the European Union as a technique to identify NSCLC patients eligible for crizotinib treatment.^{10,11} In our hospital, Wang *et al.* analyzed 430 lung adenocarcinoma cases using FISH, IHC, and RT-PCR simultaneously.⁷ The results indicated that the sensitivity of Ventana IHC was

100% and the specificity was 98.2%, showing 98.4% consistency with the FISH test. Ventana IHC is also recommended as a test for detecting ALK gene rearrangement in the Chinese Guidelines on Diagnosis and Treatment of ALK Gene-positive Non-small Cell Lung Cancer (2014 edition).¹²

In a crizotinib-related stage I clinical trial, PROFILE 1001, crizotinib demonstrated ideal safety and efficacy.¹³ The ORR of 143 evaluable patients was 60.8%, of which over 80% of patients received the treatment in more than one regimen. The PROFILE 1007 study evaluated the efficacy of crizotinib-based second-line treatment in patients with ALK-positive NSCLC, compared with pemetrexed or docetaxel monotherapy.¹⁴ The results showed an ORR in the crizotinib group of 65.3%, significantly higher than that in the chemotherapy group (19.5%). Further analysis of subgroups disclosed that the ORR in the chemotherapy group with a pemetrexed regimen was 29%, while with the docetaxel regimen it was only 7%. Subgroup analysis also demonstrated that the response rate in the Asian population was consistent with that of the whole population. In 2014, the American Society of Clinical Oncology reported the primary results of the PROFILE 1014 study.¹⁵ The ORR of crizotinib as a first-line treatment was 74% versus 45% in patients treated with pemetrexed combined with platinum-based drugs as a control. Results from the PROFILE 1014 study published on 4 December 2014 in the *New England Journal of Medicine*, demonstrated that 250 mg of crizotinib twice daily significantly prolonged PFS in previously untreated patients with ALK-positive advanced NSCLC when compared to standard platinum-based chemotherapy regimens (median PFS 10.9 vs. 7.0 months; HR: 0.45; 95% CI: 0.35–0.60; $P < 0.001$).⁵

Our study involved a retrospective analysis of the first-line treatment regimen in 19 cases with ALK-positive stage IV lung adenocarcinoma, including 18 cases eligible for curative

efficient evaluation. The results showed that the ORR of the crizotinib group was 83.3%, which was significantly higher than the 25.0% of the chemotherapy group as a control, and was slightly higher than reported in previous studies. This may be a result of the small sample size of this study. The ORR of the first-line chemotherapy in our study was slightly lower than in previous first-line chemotherapy studies, and was slightly higher than previous second-line chemotherapy studies, results that could possibly be attributed to the scattered therapeutic regimens and small patient sample size. Two PR patients received a vinorelbine regimen, while the remaining patients received a pemetrexed regimen. Multiple studies have shown that ALK-positive NSCLC patients treated with a pemetrexed regimen can achieve better efficacy. The PROFILE 1007 and PROFILE 1014 studies revealed that the ORRs of pemetrexed-based second-line treatment and first-line treatment for ALK-positive NSCLC patients were 29% and 45%, respectively. Li *et al.* suggested that the low level of thymidylate synthase ribonucleic acid might be the molecular basis of better efficacy in ALK-positive patients treated with a pemetrexed regimen.¹⁶ Vinorelbine as a regimen for ALK-positive NSCLC patients has rarely been reported. One retrospective report from Germany indicated that ALK-positive NSCLC patients who received either pemetrexed, vinorelbine or cetuximab regimens had a prolonged PFS, suggesting that a vinorelbine regimen may have advantages for treating ALK-positive NSCLC patients compared with other non-pemetrexed regimens.¹⁷ However, the findings require further exploration by prospective clinical trials. By the end of the follow-up period in our study, all cases in the crizotinib group continuously received crizotinib; only one patient exhibited disease progression, with PFS of five months. The longest medication period was 16 months. In the chemotherapy group, 83.3% of patients (10/12) were clinically identified as experiencing disease progression, with a median PFS of 7.6 months. Follow-up continues, therefore we will deliver a subsequent report on the PFS difference between the two groups.

Adverse events experienced in both the crizotinib and chemotherapy groups were of grade 1 or 2. In the chemotherapy group, the most common adverse events were neutropenia and nausea; while in the crizotinib group, the common adverse events were visual disorder and diarrhea. No severe fatal adverse events were observed in the two groups. The drug dose was reduced for one patient in the chemotherapy group because of grade 4 neutropenia, and one case in the crizotinib group because of grade 3 elevated aminotransferase. One patient did not follow medical advice and reduced their dose without consultation; despite acting contrary to medical advice, the patient experienced improved tolerance. As our study only included a small number of cases, our experience of crizotinib must be accumulated in order to recommend crizotinib as a clinical medication.

In summary, the ORR of crizotinib as a first-line treatment for patients with advanced ALK-positive adenocarcinoma was significantly superior to those who received systemic chemotherapy. Patients showed less severe adverse events and tolerated crizotinib treatment well. Crizotinib is an effective option as a first-line treatment for these patients. Because of the relatively lower positive rate of ALK rearrangement, shorter market time, higher medical cost, scattered chemotherapy regimens, and lack of information available in China, large-scale, prospective, multi-center clinical trials are required for further exploration of the best first-line treatment regime for ALK-positive patients.

Conclusion

Our study further confirmed that crizotinib increased the curative response rate in patients with advanced ALK-positive adenocarcinoma compared with chemotherapy. Therefore, crizotinib is an effective option as a first-line treatment for these patients.

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Disclosure

No authors report any conflict of interest.

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