Original Article

Sequential therapy according to distinct disease progression patterns in advanced *ALK*-positive non-small-cell lung cancer after crizotinib treatment

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Abstract

Objective: Crizotinib is recommended as the first-line therapy for advanced anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer (NSCLC). Despite its initial efficacy, patients ultimately acquire resistance to crizotinib within 1 year. In such patients, the optimal sequential therapy after crizotinib treatment remains unknown. This study explored which sequential therapy option confers the greatest benefit.

Methods: A total of 138 patients with advanced *ALK*-positive NSCLC resistant to crizotinib were studied. Based on patterns of disease progression of metastases, patients were divided into 3 groups: brain progression, non-liver progression, and liver progression. Sequential therapies included crizotinib continuation plus local therapy, next-generation *ALK* inhibitors (ALKi's), and chemotherapy. The primary endpoint was overall survival (OS) from the time of crizotinib resistance to death or last follow-up.

Results: The 138 patients included 64 cases with progression in brain, 57 cases in non-liver sites and 17 cases in liver. A significant difference in OS was observed among the distinct progression pattern (median OS, 25.4 months in brain, 15.8 months in non-liver, and 10.8 months in liver, respectively, P=0.020). The difference in OS among sequential therapies was statistically significant in the non-liver progression group (median OS, 27.6 months with next-generation ALKi's, 13.3 months with crizotinib continuation, and 10.8 months with chemotherapy, respectively, P=0.019). However, crizotinib continuation plus local therapy seems to provide non-inferior median OS compared with next-generation ALKi's for patients with brain progression (median OS, 28.9 months *vs*. 32.8 months, P=0.204). And no significant differences in OS were found in patients with progression in liver (P=0.061).

Conclusions: Crizotinib continuation together with local therapy might be a feasible strategy for patients with progression in brain beyond crizotinib resistance, as well as next-generation ALKi's. Next-generation ALKi's tended to provide a survival benefit in patients with non-liver progression.

Keywords: ALK; crizotinib; non-small-cell lung cancer; resistance; sequential therapy

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of lung cancers, most of which are adenocarcinoma (1,2). In the past few years, the incidence of adenocarcinoma has dramatically increased, and it has become the predominant histological subtype of lung cancer in most countries (3). From 2002 to 2012, the

proportion of adenocarcinomas increased from 21.96% to 43.36% (4). Unfortunately, some patients with NSCLC present with advanced disease at diagnosis, and the median overall survival (OS) is less than 1 year (5).

Since the discovery of oncogenic driver mutations and the availability of molecular targeted therapy, the management paradigm for patients with NSCLC has drastically changed in the past decade. Genomic rearrangement in anaplastic lymphoma kinase (*ALK*) receptor tyrosine kinase, a specific molecular subtype of NSCLC, occurs in 5%–7% of patients with NSCLC (6-8). However, due to the large population of patients with NSCLC, the absolute number of *ALK*-positive NSCLC patients is astonishing, with an estimated 40,000 cases occurring worldwide each year (9). Interestingly, *ALK* rearrangement is observed predominantly in younger patients and never or light smokers with adenocarcinoma.

Currently, crizotinib is recommended as the first-line standard therapy for *ALK*-positive advanced or metastatic NSCLC by the National Comprehensive Cancer Network (NCCN) guideline due to its superior efficacy compared with a platinum/pemetrexed doublet therapy in a phase III clinical trial (PROFILE 1014) (10). However, despite its initial efficacy, patients ultimately acquire resistance to crizotinib within 1 year of treatment initiation which commonly manifests in the form of oligoprogressive metastases (11). Sequential therapy options beyond disease progression in patients with crizotinib resistance include continuation of crizotinib therapy together with local treatment, next-generation *ALK* inhibitors (ALKi's), and chemotherapy. However, the optimal sequential therapy options for specific progression patterns in patients with advanced *ALK*-positive NSCLC after the occurrence of crizotinib resistance have not yet been fully elucidated.

Therefore, this real-world study explored which sequential therapy option confers the greatest benefit in patients with distinct disease progression patterns.

Materials and methods

Patients

This retrospective, single-center study enrolled 157 patients with locally advanced or metastatic *ALK*-positive NSCLC (stage IIIB–IV) who had acquired crizotinib resistance. The patients were treated between January 2013 and December 2017 at the National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Patients aged ≥18 years who met the following criteria were registered: histologically- or cytologically-confirmed advanced or metastatic NSCLC in whom the presence of *ALK* rearrangement was confirmed by fluorescence *in situ* hybridization or Ventana immunohistochemistry; progression beyond crizotinib treatment within only one site evaluated by imaging examination; measurable target lesions documented by computed tomography (CT) images of the chest and abdomen or magnetic resonance imaging (MRI) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and a documented Eastern Cooperative Oncology Group performance status (ECOG PS). Patients harboring untreated or treated brain metastases with crizotinib as first-line or second-line crizotinib therapy were eligible.

Patients were excluded if they had received any previous ALKi therapy other than crizotinib or had progression in multiple metastatic sites. Smokers were defined as current or former smokers while non-smokers were defined as individuals who had smoked <100 cigarettes in their lifetime. Non-liver progression defined as other metastatic sites excluding liver and brain metastases. Data were collected from electronic medical records including clinical and survival data. As an observational study, the present study was exempted from obtaining patients' informed consent but the study was approved by the institutional review board of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Treatment

Patients underwent initial treatment with crizotinib at a dosage of 250 mg twice daily. Continuation of crizotinib beyond disease progression was permitted if the patients' clinician had observed clinical benefit. Based on the site of progressive metastases after crizotinib resistance, patients were divided into 3 groups: brain metastases (n=64), non-liver metastases (n=57), and liver metastases (n=17). Sequential therapy mainly included continuation of crizotinib beyond disease progression together with local therapy, next-generation ALKi treatment (ceritinib, alectinib, or AP26113), and chemotherapy. Patients were permitted to cross over to other therapies if progression occurred during the course of treatment.

Outcomes

Disease was assessed at baseline after the first dose of study therapy and repeatedly until radiographic progressive disease (PD) was determined by imaging examination, including a CT scan of the chest and abdomen or MRI of the brain. Thereafter, scan intervals were about every 2 months. Evaluations of the response included complete response (CR), partial response (PR), stable disease (SD), and PD. Both the objective response rate (ORR), defined as patients showing CR and PR, and disease control rate (DCR), defined as patients showing CR, PR and SD, were calculated. Progression-free survival (PFS) was defined as the time from crizotinib treatment to progressive disease, death or last follow-up. The primary endpoint of the study was median OS from the time of crizotinib resistance to death or the date of the last follow-up (31 December, 2017).

Statistical analysis

SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Baseline characteristics were presented by applying descriptive statistics. The data for dichotomous variables were presented as the number of patients (n) and percentages (%) and continuous variables were presented as median and range values. The Chi-square test or Fisher's exact test was adopted for dichotomous data comparison among groups. The PFS and OS from the time of crizotinib resistance were analyzed using the Kaplan-Meier method. All statistical tests were two-tailed with $P<0.05$ considered statistically significant. Variables included age, sex, smoking history, clinical stage, pathological and histological type, ECOG PS scores, the crizotinib therapy line, the progression pattern, and subsequent treatments. GraphPad Prism 6.0 was used to present survival curves.

Results

Baseline characteristics

Of the 157 patients initially enrolled, 19 were excluded as they received no antitumor therapy after the development of crizotinib resistance, and 138 patients were evaluated in the final analysis. The baseline characteristics of the patients are shown in *Table 1*. Their median age was 50 (range: 20–83) years, 75 (54.3%) were women, 79 (57.2%) had a good ECOG PS of 0–1, and 98 (71.0%) were non-smokers with adenocarcinoma. Thirty patients (21.7%) developed with brain metastases before oral crizotinib treatment; 74 received crizotinib as the first-line treatment, and 64 were treated in a second-line setting or later.

Disease progression patterns after crizotinib resistance

In terms of the site of disease progression with crizotinib treatment, the brain was the most common site, accounting for 46.4% of patients. Thirty patients had brain metastases before crizotinib treatment, and 34 patients experienced brain metastatic progression during the course of crizotinib treatment. Other progressions were observed in lung and pleura (26.8% of patients), liver (12.3% of patients), and other metastatic sites (14.5% of patients) (*Figure 1*).

Survival analysis in patients with distinct progression patterns after crizotinib treatment

Among the 138 patients with advanced *ALK*-positive NSCLC, the median OS from the time of metastases diagnosis in all patients was 43.4 (95% CI: 32.9–53.8) months, and 16.8 (95% CI: 12.4–21.1) months from the beginning of crizotinib resistance. Among the distinct metastatic sites, no significant differences in the PFS with crizotinib therapy were observed (P=0.646) (*Figure 2A*). The PFS with crizotinib therapy was 11.8 months in patients with brain metastases (n=64), 9.6 months in those with non-liver metastases (n=57), and 7.9 months in those with liver metastases (n=17). However, after crizotinib resistance, analyses of OS showed a significant difference among the distinct progression sites (P=0.020). The median OS was 25.4 months in patients with brain metastases, 15.8 months in those with non-liver metastases, and 10.8 months in those with liver metastases (*Figure 2B*).

Sequential therapy options according to patients' distinct progression patterns

The 138 patients were separated into 3 groups according to the sequential therapy administered: 22 patients received chemotherapy, 62 received crizotinib continuation together with local therapy, and 54 received next-generation ALKi's. We further analyzed the OS of different sequential therapy options according to the patients' distinct progression patterns after crizotinib resistance.

Patients with brain metastases

In this group (n=64), chemotherapy was administered to 5

Table 1 Baseline characteristics in patients with advanced *ALK*-positive NSCLC after occurrence of crizotinib resistance among distinct metastatic sites

Characteristics	All (n=138)	Metastatic sites			P
		Brain (n=64)	Non-liver (n=57)	Liver (n=17)	
Age (year)					1.000
≥60	31 (22.5)	14 (21.9)	13 (22.8)	4 (23.5)	
<60	107 (77.5)	50 (78.1)	44 (77.2)	13 (76.5)	
Sex					0.939
Male	63 (45.7)	30 (46.9)	25 (43.9)	8 (47.1)	
Female	75 (54.3)	34 (53.1)	32 (56.1)	9 (52.9)	
Smoker history					0.829
Yes	40 (29.0)	18 (28.1)	16 (28.1)	6 (35.3)	
No	98 (71.0)	46 (71.9)	41 (71.9)	11 (64.7)	
Pathologic and histological types					0.157
ADC	131 (94.9)	63 (98.4)	52 (91.2)	16 (94.1)	
Non-ADC	7 (5.1)	1 (1.6)	5 (8.8)	1 (5.9)	
Clinical stage					0.790
IIIB	9 (6.5)	5 (7.8)	4 (7.0)	0 (0)	
IV	129 (93.5)	59 (92.2)	53 (93.0)	17 (100)	
ECOG PS scores					0.575
0–1	79 (57.2)	39 (60.9)	32 (56.1)	8 (47.1)	
≥2	59 (42.8)	25 (39.1)	25 (43.9)	9 (52.9)	
Crizotinib therapy					0.146
1 line	74 (53.6)	39 (60.9)	29 (50.9)	6 (35.3)	
≥2 line	64 (46.4)	25 (39.1)	28 (49.1)	11 (64.7)	

ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; ADC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

patients, crizotinib continuation treatment with local therapy (which included whole brain radiotherapy or stereotactic radiotherapy) was administered to 36 patients, and next-generation ALKi's were administered to 23 patients. No significant difference in OS was observed among the sequential therapies (P=0.204). The median OS was 32.8 months in patients who received next-generation ALKi therapy, 28.9 months in patients who received crizotinib continuation plus local therapy, and 15.5 months in those who received chemotherapy (*Figure 3A*).

Patients with non-liver metastases

In this group (n=57), chemotherapy was administered to 11 patients, crizotinib continuation with local therapy to 26 patients, and next-generation ALKi's to 20 patients. A statistically significant difference in OS was observed among the various sequential therapies (median OS, 27.6 months with next-generation ALKi's, 13.3 months with crizotinib continuation with local therapy, and 10.8 months with chemotherapy, respectively, P=0.019). Considering crizotinib continuation together with local therapy as a standard treatment, patients who received next-generation ALKi's after crizotinib resistance achieved a longer OS from the time beyond crizotinib resistance (27.6 months *vs*. 13.3 months, respectively; P=0.033), but no significant difference was found between chemotherapy and crizotinib continuation with local therapy (10.8 months *vs*. 13.3 months, respectively; P=0.789) (*Figure 3B*).

Patients with liver metastases

In this group (n=17), chemotherapy was administered to 6 patients, crizotinib continuation with local therapy to 5 patients, and next-generation ALKi's to 6 patients. Unlike patients with non-liver metastases, no significant differences in OS were found among the sequential therapies (P=0.061), and those patients receiving next-generation ALKi's tended to achieve superior survival, with median OS not reached. The median OS was 10.8 months

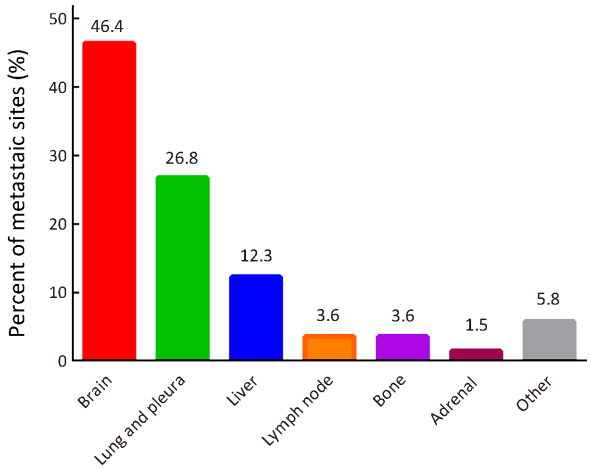

Figure 1 Distribution of disease progression patterns after crizonitib resistance.

with crizotinib continuation and 7.0 months with chemotherapy (*Figure 3C*).

Discussion

In this study, we performed a retrospective analysis of PFS with crizotinib and a robust OS estimation of sequential therapies in patients with advanced *ALK*-positive NSCLC who experienced crizotinib resistance. The median PFS of 10.4 months with crizotinib therapy was shorter than that reported in previous studies (11,12). A possible explanation was that 64 (46.4%) patients received chemotherapy before crizotinib treatment, and the benefit of chemotherapy is less than that of crizotinib. We found that the median OS from the time of crizotinib resistance in patients with advanced *ALK*-positive NSCLC was 16.8 months, which was shorter than that reported in other studies (13,14). The reason for the shorter OS in our study was that we calculated OS from the time of crizotinib resistance rather than from the time of the initial diagnosis. In this regard, our study confirmed the results of the PROFILE 1007 (15) and PROFILE 1014 (10) research which concluded that crizotinib confers a long PFS in patients both previously treated and untreated with *ALK*-positive adenocarcinoma.

Another important finding of our study was that it provided a real-world OS estimation of subsequent therapy options in patients with *ALK*-positive NSCLC who develop crizotinib resistance according to distinct progression patterns. We showed that the progression patterns with crizotinib resistance in patients with advanced *ALK*-positive NSCLC varied, and mostly took the form of slowly oligoprogressive metastases. Brain metastases were the most common site following resistance to crizotinib, accounting for 46.4% of our patients. Patients with brain progression in advanced *ALK*-positive NSCLC still had a longer OS from the time of crizotinib resistance (median 25.4 months) than those with other progression patterns. One reason for the long OS in patients with brain metastases is that the proportion of the study population

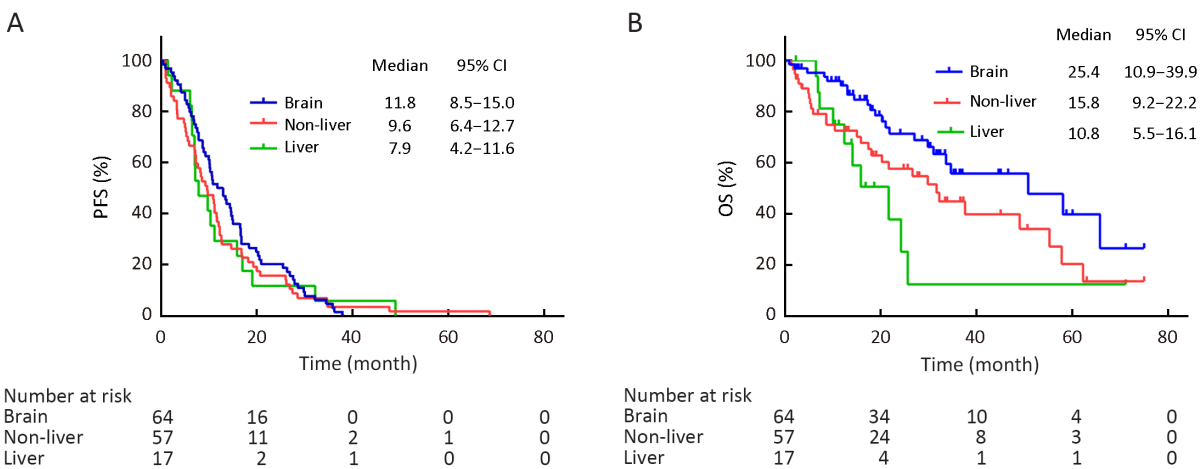

Figure 2 Kaplan-Meier survival analysis from time of crizotinib resistance in advanced anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer (NSCLC) patients, according to distinct progression sites. (A) No significant difference in progression-free survival (PFS) was found with crizotinib therapy among distinct progression sites, including brain, non-liver, and liver (P=0.646); (B) Difference in overall survival (OS) from the time of crizotinib resistance was statistically significant among distinct progression sites, including brain, non-liver, and liver (P=0.020). 95% CI, 95% confidence interval.

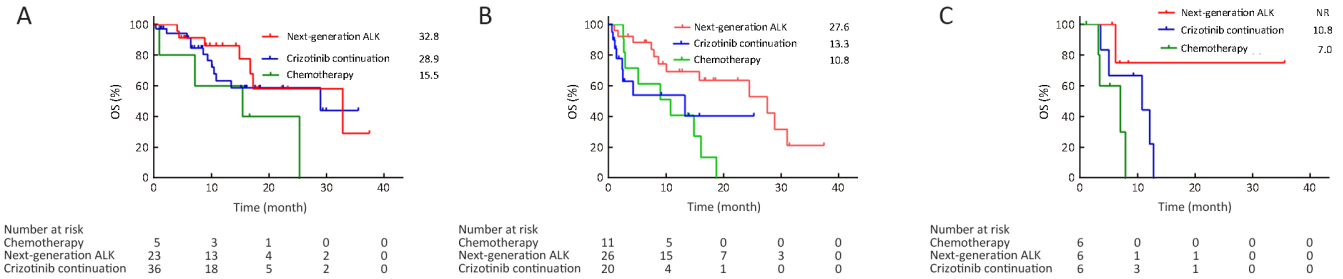

Figure 3 Kaplan-Meier survival analysis for overall survival (OS) from time of crizotinib resistance among different sequential therapy administration after crizotinib treatment in advanced anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer (NSCLC) patients according to distinct metastatic sites (n=138). (A) In patients with brain progression, no statistically significant difference in OS was observed among different sequential therapies (P=0.204); (B) In patients with non-liver progression, the difference in OS was statistically significant among different sequential therapies (P=0.019); (C) In patients with liver progression, no significant difference in OS was found among different sequential therapies (P=0.061).

who received next-generation ALKi's and crizotinib continuation beyond progressive disease was high (92.2%). Another reason is that the mechanism of brain progression may differ from that of other progression sites. This may be related to the low cerebrospinal fluid (CSF)-to-plasma ratio of crizotinib (16) and its low drug penetration into the central nervous system (CNS) in patients whose disease might been sensitive to crizotinib therapy if adequate drug concentrations had been delivered into the CNS (17). Therefore, patients who experience isolated CNS progression should not be considered as having acquired systemic resistance to crizotinib. In this regard, we found that crizotinib continuation together with local therapy had a non-inferior OS to that of next-generation ALKi treatment. The longer OS from the time of crizotinib resistance in the former group of patients may therefore have been due to their disease being particularly amenable local therapy, including whole brain radiotherapy and stereotactic radiotherapy. Autopsy reports have shown that CNS metastases may remain free of mutations which are associated with secondary resistance (18). Gainor *et al*. (19) demonstrated that only a minority of *ALK*-positive patients (about 20%) developed *ALK*-resistant mutations on crizotinib treatment. Therefore, crizotinib continuation with local therapy might be a feasible strategy after disease progression in patients with brain metastases, as well as next-generation ALKi's.

This study also demonstrated statistically significant differences in OS among different sequential therapy options in patients with non-liver metastases (P=0.019). Patients receiving next-generation ALKi's exhibited a long OS beyond crizotinib resistance (median OS, 27.6 months). However, in patients with liver metastases, the median OS with next-generation ALKi's was not reached. Although no significant difference in OS was found among the sequential therapy options due to the small sample size, patients with liver metastases receiving next-generation ALKi tended to achieve a long survival. Unlike brain metastases, patients with other progressions might not develop progression due to pharmacokinetic factors. Friboulet *et al*. (20) reported that the cell line from a liver biopsy which developed in a patient with crizotinib resistance retained sensitivity to crizotinib, but crizotinib failed to achieve antitumor adequate concentrations to completely inhibit *ALK* and the tumor cell could survive by activation of bypass tracks. This study indicated that next-generation ALKi's might have high activity in patients with crizotinib resistance with or without an *ALK* resistance mutation. Therefore, next-generation ALKi's might be preferred in patients with non-liver progression due to their ability to overcome crizotinib resistance.

Several limitations of our study must be acknowledged. Firstly, this is a single-center retrospective study with a relatively small sample size, especially for liver metastases subgroup, patients receiving next-generation ALKi's tended to achieve a long survival, more cases are needed to confirm our current results. Secondly, patients received local treatment at different time points during the course of crizotinib therapy or before oral crizotinib treatment. Thirdly, we performed neither re-biopsy after the development of resistance nor genomic analysis of progression sites, notably when progressive metastatic lesions occurred in the brain. In the future, a large-scale, prospective, multicenter evaluation is warranted.

Conclusions

The findings of this study indicate that crizotinib continuation together with local therapy might be a feasible treatment in patients with *ALK*-positive advanced NSCLC who develop brain progression after the occurrence of crizotinib resistance, as well as next-generation ALKi's. In patients with non-liver progression, next-generation ALKi's might be the preferred treatment option. Additional research looking into the molecular basis of drug resistance will hopefully lead to the development of more effective therapeutic strategies to overcome ALKi resistance.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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