Management of Central Nervous System Metastases in Patients With Advanced Anaplastic Lymphoma Kinase-Rearranged Non–Small-Cell Lung Cancer During Crizotinib Treatment

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Abstract

The optimal treatment approach for central nervous system metastases in patients with anaplastic lymphoma kinase (*ALK*)-positive non–small-cell lung cancer on crizotinib has not been established. Those who receive a second *ALK* tyrosine kinase inhibitor (TKI), particularly brigatinib, showed superior clinical outcomes compared with other treatments. The newly approved TKIs showed promise in the control of brain metastases, even without radiotherapy.

Background: Central nervous system (CNS) progression is a common manifestation of acquired resistance to crizotinib in anaplastic lymphoma kinase (*ALK*)-rearranged non–small-cell lung cancer (NSCLC). However, an optimal tailored treatment approach has not been established in patients with CNS failure during crizotinib treatment. **Patients and Methods:** Patients with *ALK*-rearranged NSCLC with CNS progression during crizotinib treatment between January 2013 and December 2016 were included for analysis. Clinical data for different treatments after CNS failure during crizotinib treatment were retrospectively collected. **Results:** Among the 44 patients who had CNS progression during crizotinib treatment, 19, 15, 8, and 2 patients received crizotinib treatment beyond progressive disease (CBPD), a second *ALK* tyrosine kinase inhibitor (TKI), chemotherapy, and best supportive care, respectively. Post progression survival offered by treatment with a second *ALK* TKI was significantly more favorable than that of chemotherapy ($P < .001$) or CBPD ($P = .045$). In addition, patients who received sequential treatment with a second *ALK* TKI had significantly longer intracranial time to progression (IC-TTP) compared with those treated with chemotherapy ($P < .01$) or CBPD after radiotherapy ($P = .003$). In the 7 patients who received brigatinib, the median IC-TTP was 21.8 months (95% confidence interval, 11.7-32.0). The additional use of CNS radiotherapy in patients treated with a second *ALK* TKI showed no significance in terms of IC-TTP ($P = .54$). **Conclusion:** Although CBPD is an option in patients with isolated CNS progression during crizotinib treatment, sequential treatment with a second *ALK* TKI, particularly brigatinib, might be preferable. The newly approved TKI, brigatinib, showed promise in the control of brain metastases, even without radiotherapy.

Clinical Lung Cancer, Vol. 20, No. 6, e631-7 © 2019 Published by Elsevier Inc.
Keywords: Brain metastases, Brigatinib, Crizotinib, Next-generation *ALK* TKI, Progression

Introduction

The central nervous system (CNS) is one of the most common sites for metastases in lung cancer. Approximately 10% to 25% of patients with advanced non–small-cell lung cancer (NSCLC) present with brain metastases at diagnosis, with a progressive increase in incidence during the course of the disease.[1,2] Anaplastic lymphoma kinase (*ALK*) rearrangement is a common molecular alteration in NSCLC, occurring in approximately 5% of unselected cases and 13% of nonsmokers.[3-5] As previously reported, patients with

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Submitted: Mar 28, 2019; Revised: May 16, 2019; Accepted: Jun 7, 2019; Epub: Jun 18, 2019

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1525-7304/$ - see frontmatter © 2019 Published by Elsevier Inc.
https://doi.org/10.1016/j.cllc.2019.06.013

oncogene-addicted NSCLC have a higher likelihood of developing brain metastases; approximately 46.7% and 58.4% of epidermal growth factor receptor (*EGFR*)-mutant and *ALK*-rearranged patients, respectively, have brain metastases at 3 years.[6]

Crizotinib (Xalkori, Pfizer, New York, NY) is an oral molecule targeting *ALK*, cellular mesenchymal-epithelial transition factor, and c-ros oncogene 1, receptor tyrosine kinase.[7-9] Several clinical trials have confirmed its superior efficacy compared with conventional chemotherapy in *ALK*-rearranged NSCLC. However, its efficacy in CNS metastases is limited.[8,10] A pooled retrospective analysis of the single-arm phase II and phase III trials, namely, PROFILE 1005 (ClinicalTrials.gov Identifier: NCT000932451) and PROFILE 1007 (ClinicalTrials.gov Identifier: NCT00932893), respectively, have shown that the respective intracranial time to progression (IC-TTP) for patients with previously untreated and irradiated brain metastases was 7.0 and 13.2 months. One-fifth of patients without evidence of brain involvement at baseline eventually develop brain metastases in a median duration of 29.9 weeks.[11] In the phase III PROFILE 1014 trial, crizotinib showed a significantly higher intracranial disease control rate (DCR) compared with chemotherapy in patients with treated brain metastases at baseline. There was no significant improvement in IC-TTP in patients with or without treated brain metastases. However, the data at the cutoff date were immature.[12] The unsatisfactory efficacy of crizotinib in CNS disease is related to its poor penetration of the blood brain barrier (BBB) and active efflux by the P-glycoprotein.[13] Consequently, the progression of preexisting disease, or the development of new brain metastases is a common manifestation of acquired resistance to crizotinib.[11]

The optimal treatment for CNS progression in crizotinib-refractory patients with *ALK*-rearranged NSCLC requires further investigation. Next-generation *ALK* tyrosine kinase inhibitors (TKIs), including ceritinib, alectinib, and brigatinib are superior to chemotherapy in patients in whom crizotinib treatment has failed.[14-16] Although clinical trials have shown that they can all cross the BBB efficiently with promising efficacy in CNS disease,[17-19] similar data from real-world clinical practice are lacking. Notably, some patients with isolated CNS metastases might still benefit from crizotinib after disease progression, with or without local therapy. Previous research has shown that crizotinib treatment beyond progressive disease (CBPD) might provide survival benefits in patients with advanced *ALK*-positive NSCLC.[20,21] However, whether a second *ALK* TKI provides equivalent or superior survival benefits compared with CBPD in patients with CNS progression, is unknown. Before the advent of next-generation *ALK* TKIs, surgery and radiotherapy had been the mainstay of treatment in these patients. Whole-brain radiotherapy (WBRT) has been the standard of care in patients with multiple brain metastases. Surgical resection or stereotactic radiosurgery (SRS) alone, or in combination, is usually offered for oligometastatic or solitary CNS progression. The phase-III ALEX (ClinicalTrials.gov Identifier: NCT02075840) study showed a slightly higher objective response rate (ORR) of CNS lesions in patients who had received alectinib after radiotherapy compared with those who had not.[18] In an analysis of CNS efficacy of brigatinib, the intracranial ORRs were similar between patients who had received previous treatment for brain metastases and those who had not.[19] However, details on the previous treatments for brain metastases, including the type of radiotherapy (WBRT or SRS) and timing, were limited. Data from large-scale prospective clinical trials are not available to confirm whether radiotherapy when used in addition to next-generation *ALK* TKIs might further extend intracranial progression-free survival; this is an area of unmet need. In this retrospective analysis we aimed to address these issues and to provide new insights into a tailored treatment approach for CNS metastases in crizotinib-pretreated patients with advanced *ALK*-positive NSCLC.

Patients and Methods

In patients with advanced *ALK*-rearranged NSCLC for whom crizotinib therapy had failed in our hospital between January 2013 and December 2016, those with intracranial progression were identified. Screening for *ALK* rearrangement was performed using immunohistochemistry using either an *ALK* antibody (D5F3 Ventana; Roche, Basel, Switzerland) or break-apart fluorescence in situ hybridization (FISH). Patients without complete medical records were excluded.

After CNS progression during crizotinib treatment, patients were treated using a variety of approaches including CBPD with or without brain radiotherapy (WBRT or SRS), sequential treatment with a second *ALK* TKI, chemotherapy, and best supportive care. To define CBPD, a period of 4 weeks of continuing crizotinib after progression was considered the cutoff, because in our hospital, most patients were evaluated every 4 weeks. This was the time frame within which doctors decided whether to continue CBPD.

Crizotinib (Xalkori; Pfizer, New York, NY) was either administered as first-line treatment or after treatment failure with platinum-based chemotherapy at 250 mg twice daily. In our study, next-generation TKIs used subsequent to crizotinib including ceritinib (Zykadia; Novartis, Basel, Switzerland), alectinib (Alecensa; Roche, Basel, Switzerland), brigatinib (Alunbrig; ARIAD, Cambridge, MA), and PLB1003 (ClinicalTrials.gov Identifier: NCT03130881) were orally taken at doses of 750 mg once daily fasted, 600 mg twice daily, 180 mg once daily with a 7-day lead-in at 90 mg, and 100 mg once daily, respectively. WBRT was delivered in a course of 30 Gy in 10 fractions. Stereotactic surgery (SRS) was delivered with a Gamma Knife Perfexion (Elekta AB, Stockholm, Sweden) unit in doses ranging from 15 to 25 Gy, depending on the tumor size. Magnetic resonance imaging (MRI) was routinely used for the diagnosis and surveillance of brain metastases. Patients with contraindications for MRI underwent computed tomography imaging with contrast. All patients underwent imaging of the CNS along with the other systems at diagnosis, and were followed-up every 4-12 weeks, or as clinically indicated. Response was evaluated according to the Response Criteria in Solid Tumors guideline, version 1.1 (RECIST).

The primary end point of this study was overall survival (OS), which was measured from the time of CNS progression during crizotinib treatment until death or last follow-up in patients who received second *ALK* TKIs, other systemic treatment, or CBPD. The secondary end point included the IC-TTP, DCR, and ORR.

The baseline characteristics were compared between treatment groups using the χ^2 and Fisher exact tests, for categorical and continuous variables, respectively. Intracranial time to progression was calculated from the date of intracranial progression during

crizotinib treatment to the date of CNS failure during subsequent treatment or in the absence of subsequent progression, the last date of evaluation. OS was defined as the date from progression during crizotinib treatment to death from any cause, or last follow-up (within December 31, 2018). Survival curves were generated using the Kaplan–Meier method for comparing IC-TTP and OS; these were further compared using the log rank test. A P value of $< .05$ was considered statistically significant. Metastatic lesions with sizes exceeding 1 cm were considered measurable. All of the analyses were performed using the Statistical Package for Social Science (IBM Corp) version 22.0 for Windows software.

Results

Patients

A total of 176 patients with *ALK*-positive NSCLC who received crizotinib in our hospital between January 2013 and December 2016 were identified. A total of 138 patients had sufficient clinical data to allow assessment of the first site of progression. Among them, 34 patients had brain metastases before crizotinib therapy. At the cutoff date, progression during crizotinib treatment was noted in 68% (23/34) patients who had brain metastases during initiation of crizotinib treatment; among them, 61% (14/23) had intracranial progression. For patients without evidence of brain metastases at baseline, the development of new lesions occurred in 29% (30/104) patients. Finally, a total of 44 patients with intracranial progression were included in the analysis.

In these 44 patients, 19 received CBPD at the discretion of the treating physician because they would potentially benefit from crizotinib treatment. Among these 19 patients, 13 with isolated CNS progression received CNS radiotherapy followed by continued crizotinib treatment, and 6 patients received CBPD only. At the point of data cutoff, only 2 patients were still receiving treatment, and the median duration of CBPD was 29.3 weeks (range, 5.2-79.6 weeks).

In the remaining patients, 15 were offered a second *ALK* TKI, including either ceritinib (20%; 3/15), alectinib (13%; 2/15), brigatinib (47%; 7/15), or PLB1003 (20%; 3/15), which was administered through a clinical trial (NCT03130881); 8 patients received other systemic treatments including docetaxel (50%; 4/8), a carboplatin-pemetrexed doublet (37.5%; 3/8), and temozolomide (12.5%; 1/8). Best supportive care was offered to 2 patients.

Table 1 includes the characteristics of the patients who received CBPD, second *ALK* TKIs, and chemotherapy, respectively. Among them, 9, 8, and 5 patients received CBPD, second *ALK* TKI, and chemotherapy, respectively, had the largest brain metastases measuring >1 cm. Additionally, 11, 9, and 6 patients from these 3 cohorts had multiple brain metastases. A total of 13, 7, and 4 patients in the CBPD, second *ALK* TKI, and chemotherapy cohorts, respectively, received radiotherapy (WBRT or SRS). No significant difference was found between the 3 groups with respect to baseline characteristics.

Overall Survival From the Time of Intracranial Progression

At the cutoff date, 53% (10/19), 27% (4/15), and 88% (7/8) of patients in the CBPD, second *ALK* TKI, and chemotherapy cohorts, respectively, had died; the median OS from the time of CNS progression on crizotinib was 39.8 (95% confidence interval [CI], 24.5-55.1), 19.6 (95% CI, 13.6-25.7), and 13.8 (95% CI, 0-29.4) months, respectively (Figure 1). The OS from the time of CNS failure significantly favored sequential treatment with a second *ALK* TKI compared with chemotherapy (hazard ratio [HR], 0.17; 95% CI, 0.04-0.69; $P < .001$), and CBPD (HR, 0.33; 95% CI, 0.12-0.95; $P = .045$).

Intracranial Time to Progression

The IC-TTP was defined from the date of intracranial progression during crizotinib treatment to the date of CNS failure during subsequent treatment, or in the absence of subsequent progression, the last date of evaluation. Patients who continued crizotinib treatment experienced intracranial progression-free survival after radiotherapy. Therefore, the 13 patients who continued crizotinib treatment after CNS radiotherapy were included in the analysis. For CNS progression during subsequent treatment, assessed according to RECIST—progressive disease (PD) occurred in 85% (11/13), 47% (9/15), and 100% (8/8) of patients receiving CBPD, second *ALK* TKI, and chemotherapy, respectively. The IC-TTP in these cohorts was 7.6 (95% CI, 5.6-9.6), 18.6 (95% CI, 9.8-27.5), and 3.3 (95% CI, 0.03-5.1) months, respectively (Figure 2A). Patients who received sequential treatment with a second *ALK* TKI had a significantly longer IC-TTP compared with those treated with CBPD (HR, 0.31; 95% CI, 0.12-0.83; $P = .003$) and chemotherapy (HR, 0.18; 95% CI, 0.03-0.65; $P < .01$).

Among those treated with a second *ALK* TKI at the time of intracranial progression during crizotinib treatment, 7 and 8 patients received and did not receive CNS radiotherapy, respectively. The subgroups did not significantly differ with respect to IC-TTP (HR, 1.45; 95% CI, 0.37-5.70; $P = .54$; Figure 2B).

Brigatinib for the Treatment of Brain Metastases

In our study, 7 patients received brigatinib after failure of crizotinib treatment, of whom 4 received local radiotherapy at progression; the DCR in these patients was 100% (7/7). A total of 3 patients had evaluable brain metastases. Among them, 2 and 1 had partial response and stable disease, respectively, resulting in an ORR of 66.7% (2/3). The IC-TTP in these patients was 21.8 months (95% CI, 11.7-32.0).

Discussion

Brain metastases, which are particularly common in *ALK*-rearranged NSCLC, mark the final stage of advanced disease. Crizotinib is a small-molecule TKI with multiple targets, including *ALK* rearrangements. Previous research has shown that because of the poor CNS penetration of crizotinib, brain metastases are a common manifestation of acquired resistance the drug.[11,12] In this study, we retrospectively investigated the various treatments for CNS failure during crizotinib treatment, with the aim to identify the optimal management strategy.

In this analysis, 19 of 44 patients continued crizotinib treatment after intracranial progression. The median treatment duration beyond progression was 29.3 weeks (ranging from 5.2 to 79.6 weeks), which was slightly longer than that of previous reports. In the PROFILE 1014 trial, the median post-PD treatment duration in 22 patients with CNS progression was 20.4 weeks (ranging from

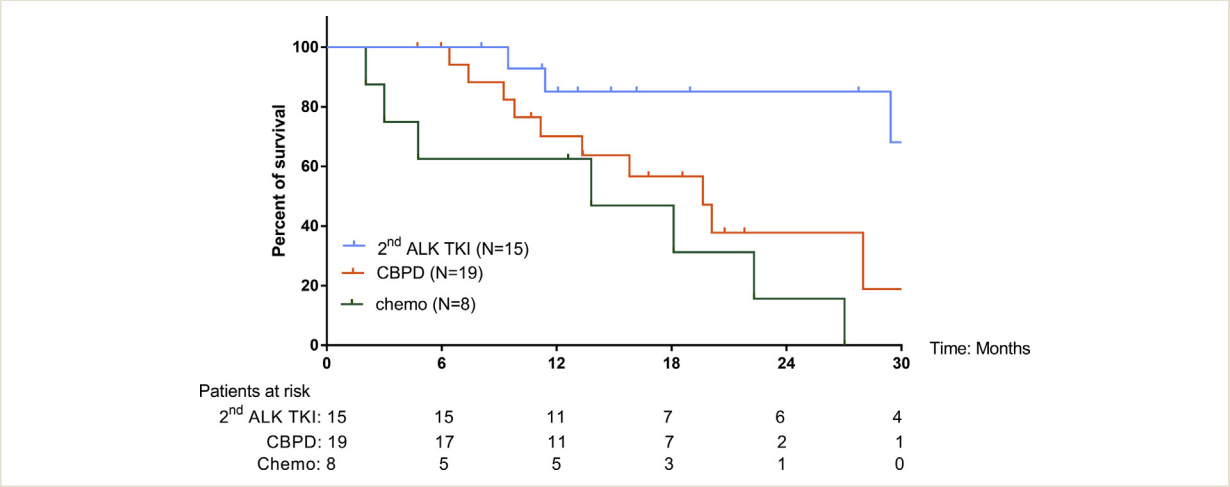
Table 1 Characteristics of the Patients Who Had CNS Progression During Crizotinib Treatment According to the Type of Postprogression Treatment Received

Characteristics	CBPD (n = 19)	Second *ALK* TKIs (n = 15)	Chemotherapy (n = 8)	*P*
Sex, n (%)				.38
Male	6 (32)	8 (53)	2 (25)	
Female	13 (68)	7 (47)	6 (75)	
Median Age (Range), Years	60 (33-82)	55 (27-76)	56 (35-68)	.13
Smoking, n (%)				.85
No	17 (89)	12 (80)	7 (88)	
Yes	2 (11)	3 (20)	1 (12)	
PS at Intracranial Progression, n (%)				.18
0-1	16 (84)	14 (93)	5 (63)	
2-3	3 (16)	1 (7)	3 (37)	
Symptomatic BM at Intracranial Progression, n (%)				.92
Yes	11 (58)	10 (67)	5 (63)	
No	8 (42)	5 (33)	3 (37)	
BM at Intracranial Progression, n (%)				.84
1-3	8 (42)	6 (40)	2 (25)	
>3	11 (58)	9 (60)	6 (75)	
Failed Lines of Systemic Therapy Before Crizotinib, n (%)				.64
0-1	17 (89)	12 (80)	6 (75)	
≥2	2 (11)	3 (20)	2 (25)	
Size of the Largest BM, n (%)				.85
≤1 cm	10 (53)	7 (47)	3 (38)	
>1 cm	9 (47)	8 (53)	5 (62)	
Radiotherapy at Intracranial Progression, n (%)				.36
Yes	13 (68)	7 (47)	4 (50)	
WBRT	7 (37)	4 (27)	3 (38)	
SRS	6 (31)	3 (20)	1 (12)	
No	6 (32)	8 (53)	4 (50)	
Next-Generation *ALK* TKIs, n (%)				
Ceritinib	–	3 (20)	–	
Alectinib	–	2 (13)	–	
Brigatinib	–	7 (47)	–	
PLB1003	–	3 (20)	–	
Extracranial Organs With Metastases at Intracranial Progression, n (%)				.78
0	2 (11)	1 (7)	2 (25)	
1	7 (37)	5 (33)	3 (38)	
≥2	10 (53)	9 (60)	3 (38)	

Abbreviations: *ALK* = anaplastic lymphoma kinase; BM = brain metastases; CBPD = crizotinib beyond progressive disease; PS = performance status; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole-brain radiotherapy.

3.3 to 84.4 weeks); 9 of the 22 patients in the study were still receiving treatment on the cutoff date.[8] The median OS from the date of CNS failure for patients treated with CBPD in our study was 19.6 months (95% CI, 13.6-25.7), which was consistent with the OS reported in previous studies. In an analysis of the benefits of continuing *ALK* inhibition with crizotinib beyond intracranial or extracranial progression using data pooled from 2 phase I and II trials (PROFILE 1001 and 1005, respectively), 120 patients who received CBPD achieved a median post-PD OS of 16.4 months (95% CI, 14.5 to not reached), which was significantly longer than that of patients who did not receive CBPD.[21] Cumulative evidence has shown that patients with disease progression might still experience prolonged progression-free survival when the same targeted therapy is continued after local ablative therapy.[20,22,23] Weickhardt et al showed that in *EGFR*/*ALK*-addicted NSCLC, the second median progression-free survival from the time of first progression

Figure 1 Overall Survival From the Time of Central Nervous System Progression During Crizotinib Treatment According to the Type of Post-PD Treatment Received



Abbreviations: *ALK* = anaplastic lymphoma kinase; CBPD = crizotinib beyond progressive disease; chemo = chemotherapy; TKI = tyrosine kinase inhibitor.

was 6.2 months after local therapy.[20] Takeda et al reported that continued administration of crizotinib with local radiotherapy for isolated CNS progression might achieve local control for at least another 4 months.[23] In our study, the median IC-TTP for those who continued crizotinib treatment with local radiotherapy was 7.6 months (95% CI, 5.6-9.6). This suggests that this is a potential treatment option in patients with CNS progression.

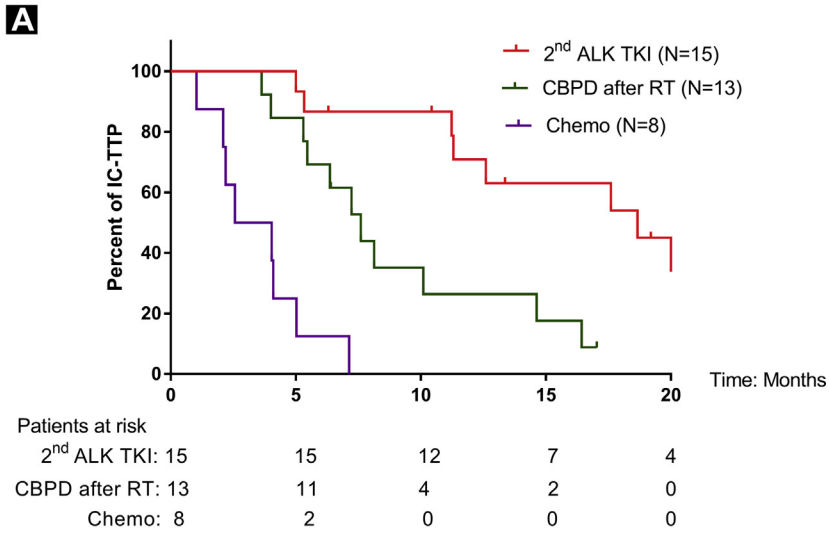
Notably, in this cohort, 15 patients whose disease progressed during crizotinib treatment received a second *ALK* TKI. In agreement with results of previous trials, we found that these *ALK* TKIs might sustain prolonged CNS control with a median IC-TTP of 18.6 months (95% CI, 9.8-27.5) from the date of intracranial progression during crizotinib treatment. A total of 7 of the 15 patients in our study received brigatinib as the subsequent *ALK* TKI. The overall DCR was 100% (7/7); the ORR in the evaluable patients was 66.7% (2/3), which was within the reported range of 46% to 67% for patients who received brigatinib for crizotinib-treated, *ALK*-rearranged NSCLC in clinical trials.[19] The IC-TTP was 21.8 months (95% CI, 11.7-32.0), which was slightly longer than that of the earlier trials for brigatinib (14.6-18.4 months). This could be partly attributed to the fact that in our study, the starting point for time-to-event analyses was the date of CNS progression during crizotinib treatment, whereas in the clinical trials, this point was the date of initiation of brigatinib treatment.

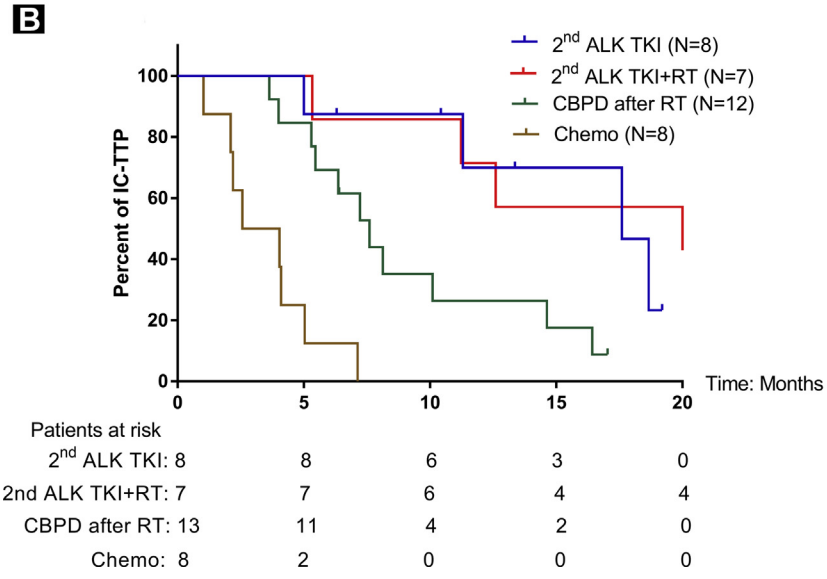
Although numerous clinical trials have shown that next-generation *ALK* TKIs have substantially superior systemic and CNS efficacy compared with chemotherapy in crizotinib-pretreated *ALK*-positive NSCLC patients, studies that have compared the efficacy of continued CBPD and next-generation *ALK* TKIs in these patients are limited. Chiari et al reported no significant difference in terms of post-PD OS between patients treated with a second *ALK* TKI, mainly ceritinib, and patients who received CBPD after isolated CNS progression or oligo- PD.[24] However, in our study, patients who received a second *ALK* TKI, particularly brigatinib, had a significantly longer IC-TTP and post-PD OS compared with those who received chemotherapy and CBPD; this suggests that next-generation *ALK* TKIs are the optimal treatment option after intracranial progression during crizotinib treatment, including isolated CNS progression.

We found an impressive median OS of 39.8 months from the date of progression during crizotinib treatment in patients treated sequentially with a second *ALK* TKI; this was better than the reported median survival of 18.1 months in crizotinib-refractory patients treated with ceritinib.[14] However, there are few mature data available on the survival of crizotinib-pretreated patients who receive alectinib and brigatinib. The satisfactory survival rate in this cohort shows that the Food and Drug Administration (FDA) newly-approved *ALK* TKIs might effectively control brain metastases with long-term benefits.

In the era of targeted therapies, the role of radiotherapy is much debated, particularly in *ALK*-positive NSCLC patients who might achieve substantially long intracranial progression-free survival with next-generation *ALK* TKIs. It is known that radiotherapy (particularly WBRT) can cause cognitive decline.[25] Therefore, the timing of brain radiotherapy should be optimized. Large-scale data on the combined use of radiotherapy with next-generation *ALK* TKIs for the treatment of brain metastases are not available. We found that the additional use of radiotherapy with next-generation *ALK* TKIs after CNS progression during crizotinib treatment had no significant effect in terms of IC-TTP (HR, 1.45; 95% CI, 0.37-5.70; $P = .54$). However, because of the low number of patients in the 2 subgroups, the value of additional radiotherapy with next-generation *ALK* TKIs could not be conclusively evaluated. Despite this limitation, our study suggests that because of their prolonged survival, the avoidance of WBRT, which might cause long-term neurotoxicity, is an added benefit of *ALK* TKIs in these patients. Additional studies are therefore required to evaluate the

Figure 2 Kaplan–Meier Curves for (A) Intracranial Time to Progression (IC-TTP) of Patients Treated With a Second Anaplastic Lymphoma Kinase (*ALK*) Tyrosine Kinase Inhibitor (TKI), Crizotinib Beyond Progressive Disease (CBPD) After Radiotherapy (RT), and Chemotherapy (Chemo); and (B) IC-TTP of Patients Treated With a Second *ALK* TKI Alone, a Second *ALK* TKI Used in Combination With RT, CBPD After RT, and Chemo





efficacy of CNS radiotherapy in patients with *ALK*-rearranged NSCLC with CNS failure during crizotinib treatment.

The scope of our results are limited because of the retrospective nature of the analysis and the inclusion of patients from a single institute. Because missing data are common in retrospective studies, selection bias was inevitable. In addition, the *ALK* rearrangement was analyzed using 2 different methods, namely immunohistochemistry and FISH. However, reports suggest that these methods provide consistent results.[26] Additionally, the sample size in our study was relatively small and did not reliably represent the entire spectrum of crizotinib-pretreated *ALK*-rearranged NSCLC patients with CNS progression. Further prospective multi-institutional large-scale studies are required to investigate the tailoring of therapy in these patients.

Conclusion

In our study next-generation *ALK* TKIs showed superior efficacy in the control of CNS metastases and provided significantly longer survival compared with chemotherapy or CBPD in patients with *ALK*-rearranged NSCLC with progression during crizotinib treatment. In addition, the *ALK* TKI recently approved by the FDA, brigatinib, showed favorable and long-term control of brain metastases with a median IC-TTP of 21.8 months (95% CI, 11.7-32.0) in crizotinib-pretreated patients. Therefore, next-generation

ALK TKIs, particularly brigatinib, might be the preferred treatment approach in CNS failure on crizotinib. However, in areas in which the newest *ALK* TKIs such as alectinib and brigatinib have not yet been approved, or are too expensive to afford, CBPD remains an option in patients with isolated CNS failure. Finally, our findings suggest that *ALK* TKIs newly-approved by the FDA are effective in controlling brain metastases even without radiotherapy; consequently, WBRT might be delayed. Further studies are needed to investigate whether radiotherapy, particularly SRS, might further improve outcomes when used in combination with TKIs with high CNS activity.

Clinical Practice Points

- In this study we aimed at investigating the optimal treatment approach in patients with *ALK*-rearranged NSCLC with CNS failure during crizotinib treatment.
- Next-generation *ALK* TKIs have shown superior efficacy in crizotinib-pretreated *ALK*-positive patients compared with chemotherapy, with proven meaningful efficacy in the management of CNS lesions.
- As indicated by previous research, CBPD is also a potential treatment option in patients with isolated CNS progression, with proven survival benefits.
- However, in this setting, the preferred agent of choice between next-generation *ALK* TKIs and CBPD is unknown.
- In addition, reports on the efficacy of brigatinib in CNS metastases are scarce. Moreover, it remains to be known whether the additional use of radiotherapy with a second-line *ALK* TKI might provide more favorable outcomes.
- This retrospective analysis aimed to address these questions and to provide new insights into a tailored treatment approach for CNS metastases in crizotinib-pretreated patients with advanced *ALK*-positive NSCLC.

Acknowledgments

The authors thank all of the patients and their families for their contributions to this study.

Disclosure

The authors have stated that they have no conflicts of interest.

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