Treatment Optimization for Brain Metastasis from Anaplastic Lymphoma Kinase Rearrangement Non-Small-Cell Lung Cancer

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Keywords

Non-small-cell lung cancer · Brain metastasis · Anaplastic lymphoma kinase · Tyrosine kinase inhibitor · Radiation therapy

Abstract

Background: Brain metastasis is common in non-small-cell lung cancer (NSCLC) with driver gene mutations. Anaplastic lymphoma kinase (*ALK*) gene rearrangement is one of the common driver mutations in NSCLC. Tyrosine kinase inhibitor (TKI) has been the research hotspot at present. However, there are relatively few studies specified on the treatment of brain metastasis from *ALK* gene rearrangement NSCLC. The prognosis of these patients, the role of *ALK*-TKI, and the proper combination model of *ALK*-TKI with radiotherapy are worth further exploring. This review focuses on new data on the prognosis of *ALK*-TKI and the proper combination model of *ALK*-TKI with radiotherapy. **Summary:** According to some retrospective trials, for *ALK*-naïve *ALK* rearrangement NSCLC patients with brain metastasis, crizotinib together with radiotherapy seem to improve intracranial control rate, progression-free survival, and very likely improve overall survival; next-generation *ALK*-TKIs are now replacing crizotinib as first-line treatment. For patients with central nervous system progression during crizotinib application, combining radiotherapy could improve the local control rate while continuing crizotinib to control systemic disease. Second-/third-generation *ALK* inhibitors had higher intracranial ORR and

DCR even after crizotinib-refractory situations, and they alone had a strong efficacy against intracranial tumors, in which situation radiotherapy might be omitted. Stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) were both local treatment options for brain metastasis, and the preferred choice was hard to make. *ALK* resistance is complicated with a wide range of molecular changes, and future studies are needed to solve these problems. Anyway, further and larger prospective studies are worth exploring to offer a confirmed preferred choice of drugs and radiation. **Key Messages:** Next-generation *ALK*-TKIs are now replacing crizotinib as first-line treatment in *ALK*-naïve *ALK* rearrangement NSCLC patients with brain metastasis, and they alone might have a strong efficacy against intracranial tumors in crizotinib-refractory situations in which occasion radiotherapy might be omitted. SRS and WBRT are both local treatment options for brain metastasis.

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Introduction

There are varieties of genomic changes in non-small-cell lung cancer (NSCLC). About 2–7% of the NSCLC patients show anaplastic lymphoma kinase (*ALK*) gene rearrangement [1]. Compared with NSCLC without *ALK* rearrangement, *ALK*-positive NSCLC features more advanced-stage and more metastasis lesions of which the brain is the most common site of metastasis and tumor

progression [2, 3]. Treatment of brain metastasis (BM) from *ALK* rearrangement NSCLC mainly includes the following two aspects: one is systemic therapy, such as target therapy and chemotherapy; the other is local treatment, such as whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection. However, there is no defined recommendations for therapeutic options of *ALK* rearrangement NSCLC with BM nowadays. Moreover, the selection, combination, and sequence of the different treatment options always depend on the timing, severity of BM, and economic factors. Till now, there are no large-scaled researches on the impact of the different treatment modes on disease control and overall survival (OS).

General Introduction of BM and *ALK*-Tyrosine Kinase Inhibitor in *ALK* Rearrangement NSCLC

Incidence and Prognosis of BM from ALK Rearrangement NSCLC

The incidence of BM ranges from 20 to 30% in newly diagnosed NSCLC patients with *ALK* rearrangement, which is similar to unselected advanced-staged patients [1]. With the application of *ALK*-tyrosine kinase inhibitor (*ALK*-TKI, *ALK*i) in clinical practice, OS of *ALK*-positive NSCLC patients is significantly prolonged [2]. Consequently, the incidence of BM significantly increased over time in patients with *ALK* rearrangement. A retrospective study indicated that the cumulative BM rate in *ALK*-positive NSCLC patients was 45.5% at 2 years, and 58.4% at 3 years [3]. Another study found that 40% of the *ALK*-positive NSCLC patients showed evidence of progressive BM when they died [4]. The most common clinical manifestations of BM were fatigue (39%), shortness of breath (38%), nausea and vomiting (33.3%), and headache (23.9%) [5]. In addition, the rate of nervous system-related symptoms was as high as 36–82% [6, 7].

The natural course of lung cancer patients with brain metastases is only 3 months. Due to poor penetration of chemotherapeutic drugs, approximately one-third of the patients with advanced *ALK* rearrangement NSCLC after failure of at least one prior systemic therapy have brain metastases [8], and its prognosis is still worse. The GPA scoring system, established on the basis of the patient's age, KPS score, extracranial metastasis, and number of brain lesions, was proposed by Sperduto et al. [9, 10] to predict prognosis of NSCLC patients with BM, and results show an estimated 14.8 months of OS for patients with a high GPA score. Targeted therapy has become an important treatment option for patients with *ALK*-positive arrangement. *ALK* inhibitors are small molecular drugs, which can treat brain metastases through the

blood-brain barrier. Therefore, targeted therapy has a good therapeutic effect on brain metastases. The study by Johung et al. [4] concluded that the median OS of *ALK*-positive NSCLC patients with BM was 49.5 months on condition of *ALK*i-targeted therapy and radiotherapy. Later, Sperduto et al. [2] put epidermal growth factor receptor (EGFR) and *ALK* gene changes into the GPA scoring system and established a new Lung-mol GPA scoring system. The median OS of high-score patients in the new Lung-mol GPA scoring system could reach up to 46.8 months. Anyway, drug resistance will eventually occur, and treatment options are hard to make. Till now, there is not much evidence of prospective randomized controlled clinical trials on how to choose targeted drugs and radiotherapy for *ALK*-positive brain metastases. In this review, we summarize some retrospective studies and extract related information in some prospective randomized controlled clinical trials to conclude a better choice of treatment.

Introduction on ALK-TKI's Efficacy on BM in ALK Rearrangement NSCLC

Crizotinib, inhibiting *ALK*, *Met*, and *Ros1*, was the first generation *ALK*-TKI approved by Food and Drug Administration (FDA) and European Medicine Agency (EMA) and was recommended as the first-line treatment for stage IV lung cancer with *ALK* rearrangement or *Ros1* mutation [11, 12]. A pooled analysis of the PROFILE 1005 and 1007 trials showed that [8] among 109 BM patients with administration of crizotinib, the intracranial (IC)-objective response rate (ORR; complete response [CR]+partial response [PR]) reached 18%, the disease control rate (DCR; CR+PR+SD) at 12 weeks reached 56%, and the duration of response (DOR) was 26.4 weeks.

Second-generation *ALK*-TKI (including ceritinib, alectinib, and brigatinib) and the third-generation *ALK*-TKI (lorlatinib) are now showing great efficacy in BM treatment. Ceritinib, targeting *ALK*, *ROS1*, and IGF1 (insulin-like growth factor 1 receptor kinases), was evaluated in the "ASCEND" clinical trial programs, in which it demonstrated IC-ORR of 35–73%, IC-DCR of 61–86%, and IC-DOR of 8–11 months in either *ALK*-TKI-naïve and *ALK*-TKI-pretreated patients [13–16]. Alectinib, targeting *ALK*, *RET*, and *ROS1*, showing an IC-ORR of 54–81%, IC-DCR of 78–90%, and IC-DOR of 10.8 to NR (not reached) months in series of randomized trials [17–20]. Brigatinib, targeting *ALK* and *ROS1*, in the ALAT trial also showed an interesting activity in the CNS, with an IC-ORR of 42–73% and an IC-DCR of 83–93% [21]. Lorlatinib, an extremely selective *ALK*-TKI with activity also against *ROS1* kinase, has demonstrated high CNS penetrance in preclinical models and an IC-ORR of 39%.

Therapy for ALKi-Naïve Patients with BM

First-Generation ALK Inhibitor (Crizotinib)

Many studies have shown that *ALK* inhibitors have therapeutic effects on *ALK*-positive NSCLC patients [22–24]. The PROFILE series confirmed a strong anti-tumor efficacy of crizotinib in stage IV *ALK*-positive NSCLC patients, with an ORR of 59.8–74% and a median progression-free survival (PFS) of 7.7–10.9 months [25, 26]. Compared with chemotherapy, crizotinib significantly improved ORR, quality of life, and prolonged PFS in patients with or without BM at baseline [26].

However, the efficacy of crizotinib in IC lesions was worse than in extracranial lesions. The central nervous system (CNS) was detected as the first site of tumor progression in up to 50% of the patients treated with crizotinib [27]. A retrospective analysis of the PROFILE 1005 and 1007 trials showed that [8], with use of crizotinib, ORR (18 vs. 53%), DOR (26.4 vs. 47.9 weeks), and median time-to-tumor progression (7.0 vs. 12.5 months) were all lower in IC lesions than in extracranial lesions. Moreover, the eventual brain progression rate was far lower (20 vs. 72%) in patients without BM than patients showing BM at the initiation of medication. A similar conclusion was drawn in a study enrolling 59 NSCLC patients with *ALK* rearrangement by Yoshida et al. [28]. The ORR of crizotinib was 66% for systemic control and only 20% for the IC lesions. The rate of brain lesion progression was lower (58 vs. 31%) in patients without BM than in patients with BM at baseline. In conclusion, the anti-BM effect of crizotinib on *ALK*-positive NSCLC was far from satisfaction. Other local treatment options might need to be combined to improve therapeutic activities.

Combination of Crizotinib and Radiotherapy

Radiotherapy was considered to be the main local treatment option for NSCLC with BM. However, the efficacy of WBRT was not encouraging. In a study of patients with *ALK* rearrangement, the ORR of brain radiation on the basis of chemotherapy was only 9.5% (CR: 4.8, PR: 4.8), and the median PFS for radiotherapy and chemotherapy was only 6.7 months [16].

Combination of brain radiotherapy and crizotinib significantly improved the prognosis of BM patients with *ALK* rearrangement. Costa et al. [8] found that, compared with crizotinib alone, adding radiotherapy significantly increased ORR (18 vs. 33%) and prolonged the median time-to-tumor progression (7 vs. 13.2 months) of IC lesions. Other studies also indicated that PFS was significantly increased in patients receiving radiotherapy and targeted therapy to as long as 7 or even 27 months, while only 3–4 months after crizotinib alone [28, 29]. In addition, the combined application of brain radiotherapy and

crizotinib was a good prognostic factor for PFS [28, 29]. Anyway, these studies were all retrospective and not controlled; further prospective trials were needed. Therefore, combining crizotinib and radiotherapy should be carefully assessed clinically.

However, the sequence of targeted therapy and radiotherapy is not clear currently. A number of studies based on EGFR-mutated NSCLC suggested radiotherapy followed by EGFR inhibitors could increase tumor response to TKI, so as to improve prognosis [30, 31], which might be explained by the destruction of the blood-brain barrier induced by radiotherapy. Metro et al. [32] quantified the ratio of crizotinib concentration in the cerebrospinal fluid and in the plasma in NSCLC patients with *ALK* rearrangement. The values were 0.0006 in patients not receiving radiotherapy, and 0.001 in patients receiving radiotherapy before crizotinib. Similar results were also concluded in animal models [33]. As *ALK* inhibitors and EGFR inhibitors shared a similar anti-tumor mechanism, based on case reports [34, 35], it was generally believed that the administration of radiotherapy before or simultaneously with crizotinib could impair the blood-brain barrier, destroy glycoproteins that function as a drug efflux pump and thus increase the concentration of crizotinib in CNS, eventually significantly improve the therapeutic effect of targeted therapy for IC metastasis lesions.

Second-/Third-Generation (Next-Generation) ALK Inhibitors

At present, there are a few studies exploring the effect of the second-generation *ALK*-TKI (including ceritinib, alectinib, and brigatinib) and the third-generation *ALK*-TKI (lorlatinib) in *ALK*i-naïve patients with BM (Table 1). In the Ascend-1 study [14], 19 BM patients without *ALK*-TKI treatment were enrolled, and the results showed that the ORR of ceritinib on IC measurable lesions reached up to 62.5%, and efficacy lasted for 8.2 months. Subgroup analysis in the Ascend-3 and Ascend-4 studies [16] also proved the strong anti-tumor effect of ceritinib on BM lesions. In the ALEX study, Peters et al. [20] compared the efficacy of alectinib and crizotinib on BM lesions from *ALK*i-naïve NSCLC patients. The results indicated that the ORR (81 vs. 50%), CR (38 vs. 5%), and DOR (17.3 vs. 5.5 months) of alectinib were all higher than those of crizotinib. Besides, for patients without BM at the initiation of targeted therapy, the cumulative BM rate at 12 months of treatment was lower (4.6 vs. 31.5%) in patients receiving alectinib than in those receiving crizotinib. As to the third-generation *ALK* inhibitor lorlatinib, Solomon et al. [26] found that the CR rate for brain lesions was 25%. In recent years, the NCCN Panel recommended the second-generation *ALK* inhibitor alectinib as the first-line

Table 1. Efficacy of *ALK* inhibitors for BM in patients with *ALK*+ NSCLC

	Drug	Target	Trial	Line of Tx	Prior <i>ALK</i> i	No. of patients with BM	IC-ORR		IC-DCR		IC-DOR	
							measurable BM: %, <i>n</i>	all patients with BM at baseline	measurable/target BM: %, <i>n</i>	all patients with BM at baseline	measurable/target BM: %, <i>n</i>	all patients with BM at baseline
1st generation	Crizotinib	<i>ALK, MET, ROS1</i>	PROFILE1005 and PROFILE1007	≥2nd	<i>ALK</i> i-naïve	Crizotinib+RT: 166	33 (6/18)	/	/	12 w, 62 (103/166)	/	NR (166)
						Crizotinib: 109	18 (4/22)	/	/	12w: 56 (61/109)	/	26.4 ws (109)
2nd generation	Alectinib	<i>ALK, RET</i> ; low anti- <i>ROS1</i>	AF-002/G	≥2nd	Crizotinib-pretreated	21	56 (5/9)	52 (11/21)	78 (7/9)	90 (19/21)	/	/
	Alectinib		NP28761 and NP28673	≥2nd	Crizotinib-pretreated	136	64 (32/50)	43 (58/136)	90 (45/50)	85 (116/136)	10.8 months (50)	11.1 months (136)
	Alectinib		ALUR	≥2nd	Crizotinib-pretreated	50	54 (13/24)	36 (18/50)	79 (19/24)	80 (40/50)	NR (3.6 months–NR) (24)	/
	Alectinib		ALEX	1st	<i>ALK</i> i-naïve	64	81 (17/21)	59 (38/64)	/	/	17.3 months (21)	NR (64)
	Ceritinib	<i>ALK, ROS1, IGF1</i>	ASCEND-1	≥1st	<i>ALK</i> i-naïve (19/94)	19	63 (5/8)	42 (8/19)	63 (5/8)	79 (15/19)	8.2 months (8)	NR (19)
					<i>ALK</i> i-pretreated (75/94)	75	36 (10/28)	19 (14/75)	61 (17/28)	65 (49/75)	11.1 months (28)	6.9 months (75)
	Ceritinib	<i>ALK, ROS1, IGF1</i>	ASCEND-2	≥2nd	Crizotinib-pretreated	100	45 (9/20)*	33 (33/100)	80 (16/20)*	74 (74/100)	/	9.2 months (100)
	Ceritinib	<i>ALK, ROS1, IGF1</i>	ASCEND-4	1st	<i>ALK</i> i-naïve	54	73 (16/22)	46 (54)	86 (22)	89 (54)	/	/
	Ceritinib	<i>ALK, ROS1, IGF1</i>	ASCEND-5	≥2nd	Crizotinib-pretreated	17	35 (6/17)*					6.9 months (17)
	Brigatinib	<i>ALK, ROS1</i>	ALTA	≥2nd	Crizotinib-pretreated	armA: 90 mg qd	42 (11/26)	/	85 (22/26)	/	NR (3.7 months–NR) (26)	/
							42 (8/19) [#]	/	84 (16/19) [#]	/	/	/
						armB: 180 mg qd	67 (12/18)	/	83 (15/18)	/	NR (5.6 months–NR) (18)	/
							73 (11/15) [#]	/	93 (14/15) [#]	/	/	/
3rd generation	Lorlatinib	<i>ALK, ROS1</i>	ASCO report	≥2nd	<i>ALK</i> i-pretreated	18	39 (7)	/	/	/	/	/

BM, brain metastasis; Tx, treatments; IC, intracranial; ORR, overall response rate; CR+PR, DCR, disease control rate; CR+PR+SD, DOR, duration of response; NR, not reached. Measurable, brain lesions with longest diameter ≥10 mm. * Target BM, target lesion indicated that the lesion was active (a new or existing lesion that progressed after local therapy). [#] Active brain metastasis, defined as lesions without prior radiotherapy or those with investigator-assessed progression after prior radiotherapy.

treatment for advanced *ALK*-positive NSCLC patients, followed by ceritinib and brigatinib. However, the NCCN Panel voted that alectinib is the preferred agent for *ALK*i-naïve NSCLC patients. Further clinical trials are required on whether other next-generation *ALK*-TKI would be the first-line treatment options for advanced NSCLC with *ALK* rearrangement. We look forward to the results.

The efficacy of the combination of radiotherapy and the next-generation *ALK*-TKI has not been widely studied. ASCEND-1 [14] was a multi-center research exploring the efficacy and safety of ceritinib, enrolling 19 *ALK*i-naïve patients of which 11 received radiotherapy combined with ceritinib and 8 cases received ceritinib alone. The results showed that DCR (CR+PR+SD, 72.7 vs. 87.5%) and ORR (36.4 vs. 50%) present no significant difference between the two groups. Furthermore, ASCEND-4 reached a similar conclusion [16]. It perhaps indicates that ceritinib has strong local control capacities and good treatment responses on BM lesions, and the effect is not dependent on the administration of combined radiotherapy. However, due to the small sample numbers and the retrospective nature of the study, conclusions might be controversial, and further researches are needed.

Treatment on Crizotinib-Refractory Patients

Radiotherapy in Crizotinib-Refractory Patients

During treatment of crizotinib, new-onset BM or the progression of previous BM lesions still occurred even if extracranial lesions were well controlled, that is, CNS resistance/refraction of crizotinib, which might be related to the low blood-brain barrier permeability of crizotinib. At an oral dose of 200 mg/b.i.d., the cerebrospinal fluid/plasma ratio of crizotinib was only 0.002631 [36]. However, studies had shown that although the concentration of crizotinib in cerebrospinal fluid was low, it still had anti-tumor efficacy on IC lesions [32]. Therefore, the low drug concentration in cerebrospinal fluid could not fully explain the IC resistance of crizotinib, and its acquired gene changes (such as *ALK* tyrosine kinase mutation, *ALK* copy number variation, activation of other oncogenic pathways, etc.) might participate in the progression of BM after *ALK*-TKI resistance. In recent years, mutation of gatekeeper genes (such as *G1202R* mutation) had been widely recognized by researchers, since it shared similarities with the *EGFR T790M* mutation. However, the *G1202R* mutation was more difficult to treat. Anyway, according to previous data, only 20% of the *ALK*-positive NSCLC patients would present with drug-resistant muta-

tions [37], with various categories and wide ranges. Therefore, the mechanism of resistance to crizotinib was still unclear.

Administration of brain radiotherapy could achieve better local control rate for new-onset BM or progression of previous BM during crizotinib treatment. In the PROFILE1005 and 1007 trials [8], 34 patients with asymptomatic progressive brain lesions during crizotinib application were enrolled, and 27 patients received brain radiotherapy. The median treatment duration after progressive disease (PD) of these 27 patients was 19.3 weeks. In other small sample reports, the median PFS of patients with crizotinib-refractory CNS lesions, after administration of brain radiotherapy, reached 5.5–7.1 months [8, 27, 38]. In these studies, crizotinib beyond disease progression was continued simultaneously with brain radiotherapy after brain lesion progression. Ou et al. [39] analyzed 194 crizotinib-treated patients with RECIST-defined PD and found that CBPD patients had significantly a longer OS from the time of PD (median 16.4 vs. 3.9 months, $p < 0.0001$) and from the time of initial crizotinib treatment (median 29.6 vs. 10.8 months, $p < 0.0001$). Thus, for patients who progressed after crizotinib, crizotinib beyond disease progression combined with radiotherapy could help control IC lesions and prolong OS [8, 39, 40]. However, these conclusions were drawn from retrospective and not controlled researches, some of which had a small sample size, and the level of evidence was not high. Further prospective trials of large sample size are recommended to get more convincing conclusions.

Next-Generation ALK-TKI in Crizotinib-Refractory Patients

A number of studies showed [13, 14, 41, 42] that second-/third-generation ALK-TKI had a strong anti-tumor activity in crizotinib-refractory patients, and its ORR reached 35.7–81% while the median PFS was 5.4–12.9 months. Furthermore, by horizontal comparison of different studies, their effect on BM seemed to be superior to crizotinib even in crizotinib-refractory patients (Table 1). ASCEND series evaluated efficacy of ceritinib, of which IC ORR reached 45% for crizotinib-refractory BM patients in the ASCEND-2 study [13], and 35% in ASCEND-5 [15]. The ongoing ASCEND-7 trial aimed to identify the anti-CNS metastasis activity of ceritinib. Alectinib also showed great efficacy in controlling BM [17, 18, 43, 44], and played a role in meningeal metastasis [43, 44]. By analyzing 50 crizotinib-refractory patients with measurable brain lesions in the NP28763 and NP28761 studies [18], IC-ORR of alectinib reached 64% (of which 22% reached CR). The ALUR trial [19, 45] was the only research comparing the efficacy of alectinib with standard chemotherapy in crizotinib-refractory

patients, and the results showed that PFS (9.6 vs. 1.4 months, $p < 0.001$) and the CNS response rate (54.2 vs. 0%, $p < 0.001$) in the alectinib group were significantly improved. The ALTA study [21] showed that for crizotinib-refractory NSCLC patients, the ORR of brigatinib for IC measurable lesions was as high as 67% ($n = 18$). As a third-generation ALK inhibitor, lorlatinib showed high CNS permeability. In a study of 18 crizotinib-refractory patients, the IC-ORR was 39%, and it was very effective for the *G1202R* mutation [46]. At present, second-generation ALK inhibitors, including ceritinib, alectinib, and brigatinib, have been approved by FDA for the treatment of metastatic crizotinib-refractory NSCLC patients.

There were few trials focusing on radiotherapy combining with next-generation ALK inhibitors in the treatment of crizotinib-refractory NSCLC patients. In the ASCEND-1 study [14], there were no significant differences in IC-DCR (65.4 vs. 65.2%) and IC-ORR (17.3 vs. 21.7%) in 75 ALKi-pretreated patients with or without radiotherapy, suggesting that radiotherapy might have little curative effect when ceritinib was used. In a pooled analysis (NP28761 and NP28673 studies) [18] on CNS response to alectinib in ALKi-pretreated patients, a similar conclusion was drawn. In this study, 95 patients received radiotherapy, and 41 patients had no previous radiotherapy. The IC-DCR were 86.3 and 82.9%, while the IC-ORR were 35.8 and 58.5%, respectively. It is generally believed that radiation therapy could destroy the blood-brain barrier and improve the permeability of target drugs so as to improve the control rate of CNS. However, the efficacy of next-generation ALK inhibitors on IC tumors seems not to be affected by previous radiotherapy application, and this may be explained by its powerful anti-CNS metastasis activity. Anyway, further conclusions should be drawn from large prospective randomized controlled trials.

Alectinib, as a second-generation ALK inhibitor, might show a pseudoprogression (PsP) phenomenon during the treatment of BM that had previously been treated by radiotherapy. Ou et al. [47] reported two cases with PsPs who had been treated by alectinib 4 months later after SRS. Images showed enlarged lesions within the previous radiation field that was enhanced after contrast, which was difficult to distinguish from a real disease progression. Postoperative pathology showed necrosis and no tumor remains. Anyway, till now, no radiation necrosis, or PsP, has been reported after the application of crizotinib, which indirectly reflects the stronger efficacy of alectinib on CNS metastasis. Therefore, in the treatment of alectinib, when suspicious progression appears within the radiation field while no progression shows outside, close monitoring and more sensitive images to identify PsP are needed.

Choice of Radiotherapy: SRS versus WBRT

There are few studies on the radiosensitivity of *ALK* rearrangement NSCLC with brain metastases. Researches based on *EML4-ALK* rearrangement cell lines and clinical statistics shows that *ALK*-positive NSCLC is a radiosensitive tumor [48, 49]. Johung et al. [50] prospectively analyzed 79 BM patients (469 cranial lesions) treated with Gamma knife and found no recurrence within the radiation field in patients with *EGFR* mutation or *ALK* rearrangements (patients, 0/30; lesions, 0/225), which was significantly lower than those without the above changes (patients, 9/49; lesions, 13/244), while no significant recurrence rate difference existed outside the radiation field (53 vs. 47%, $p = 0.58$). For patients with these molecular changes, the recurrence-free survival time within the radiation field was significant longer than for those without such changes (not reached vs. 18.4 months), while there was no difference outside the radiation field in the brain. Multivariate analysis showed that *EGFR* or *EML4-ALK* change and small lesion size were good prognostic factors after gamma knife treatment. These above researches laid the foundation for radiation application in *ALK* rearrangement patients with brain metastases.

SRS and WBRT are both local treatment options for brain metastases. A number of randomized trials showed that WBRT combined with SRS did not bring survival benefits for patients with 1–4 brain lesions [51–54], while health-related quality of life and neurocognitive function might decrease after WBRT [55, 56]. Recently, many studies [57–60] found that SRS was comparable to WBRT in controlling 4 or more brain lesions. Based on these studies, some researchers suggested SRS as the first choice in *ALK*-positive NSCLC patients with brain metastases, namely delayed WBRT, and for patients with diffuse brain metastases or meningeal metastases, WBRT should be first considered [61].

However, SRS had some limitations. Some studies shown that recurrence within the radiation field after SRS increased with the enlargement of the tumor volume and occurrence of necrotic lesions [62, 63] while IC freedom from progression decreased with the increase in lesion numbers [64]. In addition, some scholars also questioned neurocognitive function reduction after WBRT. Previous studies [56, 65] reported that brain cognitive impairment occurred 3–4 months after radiotherapy, while some studies [66, 67] suggested that the reduction was temporary and could be improved later. In recent years, studies [68, 69] have shown that WBRT with hippocampus protection could reduce the damage of neurocognitive function without decreasing the local control rate. Moreover, *ALK* rearrangement more often occurred in young and nonsmoking female patients who might suffer less from cognitive function impairment than non-*ALK* rearrangement NSCLC patients with brain metastases [22, 70].

There are few studies on SRS/WBRT selection for *ALK*-positive NSCLC patients with BM. Johung et al. [4] analyzed 90 cases (53% of the patients with 3 or less brain lesions) treated with radiotherapy and *ALK* inhibitors and found that there was no significant difference between SRS and WBRT regarding OS, but SRS tended to be inferior to WBRT with regard to PFS ($p = 0.082$). In conclusion, the selection of SRS and WBRT in *ALK* rearrangement NSCLC patients with BM is still controversial, and the choice is hard to make. More prospective clinical trials are needed.

Conclusion

In conclusion, for *ALK*i-naïve *ALK* rearrangement NSCLC patients, crizotinib had a poor therapeutic effect on IC lesions, while combining with radiotherapy might improve the IC control rate, PFS, and very likely improve OS; other next-generation *ALK*-TKIs are now replacing crizotinib as the first-line treatment for *ALK*-positive NSCLC with BM. For patients with CNS progression during crizotinib application, combining radiotherapy might improve the local control rate while continuing crizotinib to control systemic disease. In addition, second-/third-generation *ALK* inhibitors have higher IC ORR and DCR even after crizotinib-refractory situations, which could be used as one of the therapeutic options, and currently, some studies show that next-generation *ALK*-TKI alone has a strong efficacy against IC tumors, in which situation radiotherapy could be omitted. Anyway, studies focusing on options of BM treatment are few, and we draw conclusions from some retrospective trials. We look forward to prospective randomized controlled clinical trials to offer a confirmed choice of drugs and radiation.

Although next-generation *ALK* inhibitors have shown strong anti-CNS metastasis effects, drug resistance will eventually occur, and unlike *EGFR* resistance, of which the *T790M* mutation accounted for more than 50%, *ALK* resistance is more complicated, with a wide range of molecular changes. Further studies are needed to solve the above problems. In addition, as an effective local treatment, whether radiation therapy should be combined with the next-generation *ALK*-TKI is still an open question. The treatment of *ALK* rearrangement NSCLC with BM requires multidisciplinary participation. How to optimize the whole process through a variety of treatment options needs to be solved by further clinical practice.

Disclosure Statement

The authors declare that they have no competing interests.

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