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REVIEW ARTICLE

Targeted therapy with anaplastic lymphoma kinase inhibitors in non-small cell lung cancer even with brain metastasis

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Summary

The incidence of brain metastases has increased as a result of improved systemic disease control and advances in imaging. Brain metastasis can occur approximately in 25-40% of the patients with non-small cell lung cancer (NSCLC) and it is a frequent cause of death. Stereotactic radiosurgery, whole-brain radiotherapy (WBRT) or surgical resection are the local treatment modalities for brain metastases which are feasible either alone, in combination, or as sequential treatments. Resistance to systemic therapy for brain metastasis poses significant clinical problems. In anaplastic lymphoma kinase (ALK)-positive NSCLC patients; ALK inhibitors may provide a new treatment option for brain metastasis and could improve overall survival (OS). Even in patients with crizotinib-resistant disease, second generation ALK inhibitors display prominent clinical activity. There is rapidly emerging preclinical and clinical data showing improvement in this issue. In this article we reviewed the latest literature data concerning the brain metastases and intracranial efficacy of ALK inhibitors in patients with ALK-positive NSCLC.

Key words: *alectinib, brain metastasis, brigatinib, ceritinib, crizotinib, lorlatinib*

Introduction

One of the most serious events of cancer is brain metastasis that results in fatal consequences of the patients. As a result of improved systemic control and advances in imaging the incidence of brain metastases has increased. It is predicted that symptomatic brain metastases will arise in about 40% of patients with metastatic cancer [1]. The most common cancer that causes brain metastases is lung cancer. Depending on its high metastatic potential brain metastases could be seen frequently at the early disease phases in patients with small cell lung cancer. Patients with NSCLC have different clinical courses, and 25-40% of them can present with brain metastasis which is an important prognostic factor with median survival of 7 months (95% CI 2.63-18.8) [2,3]. Local therapeutic modalities for brain metastases consist of stereotactic radiosurgery, WBRT or surgical resection, either alone, in combination, or as sequential treatments [3,4].

In addition, treatment of brain metastasis with systemic chemotherapy is controversial due to highly selective blood brain barrier (BBB) which is formed by tight junctions between brain endothelial cells. Treatment of brain metastasis has been investigated in a few studies. However, chemotherapy which is essential systemic treatment in patients with advanced NSCLC is associated with response rates of 15-30%, with OS about 6-8 months [5,6].

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An intact BBB which has an important role in the prophylaxis of the brain from toxic insults also prevents penetration of drugs to the brain parenchyma. BBB comprises endothelial cells, astrocytes, pericytes with tight junctions and has a lot of carrier proteins to regulate highly selective transportation from bloodstream to central nervous system (CNS). Carrier proteins regulate the passage of molecules, however small lipophilic molecules which weight less than 400 Da are transported with diffusion [7,8]. Most chemotherapeutic agents have a large size and hydrophilic molecular nature so they are unable to cross the BBB.BBB active efflux transporters also protect the brain from potentially permeable systemic chemotherapeutics [9]. Hence, most of the chemotherapeutic agents are unable to cross BBB, therefore brain metastases are resistant to systemic chemotherapy [10]. Resistance to systemic therapy of brain metastasis poses significant clinical problems. Recent advances towards efflux pump inhibition by anaplastic lymphoma kinase (ALK) inhibitors provide an attractive treatment option for patients with NSCLC and could improve OS (Table 1) [11].

ALK rearrangement occurs in 2-7% of patients with NSCLC and is a potential target in advanced stages of this disease. EML4-ALK fusion tyrosine kinase is formed by an inversion in the short arm of chromosome 2 [inv (2)(p21p23)] that causes fusion of exons 20-29 of the ALK gene with exon 1-13 of the echinoderm microtubule associated protein like 4 (EML4) gene. EML4-ALK fusion tyrosine kinase leads to malignant transformation of the cells by activating signaling pathways, including

the MAPK/ERK, PI3K/AKT and JAK/STAT pathways that function in proliferation, differentiation and anti-apoptosis [12]. The prognostic value of ALK rearrangements in NSCLC has shown contradictory results in many studies [13]. Some studies emphasize the ALK rearrangements could be a prognostic marker of recurrence and metastasis in patients with NSCLC, whereas some other studies assert that NSCLC patients with ALK rearranged have similar risk of recurrence, progression free survival (PFS) and OS compared to patients with ALK wild type [14,15]. There is conflicting data about the incidence of brain metastasis in ALK-positive NSCLC. Some of the studies suggest that the incidence of brain metastasis is higher in ALK-positive cases while there are also some studies that suggest the opposite [14,16]. Recent data have shown that NSCLC patients with brain metastases treated with ALK inhibitors achieved encouraging response rate with a favorable safety profile (Table 2) [17].

ALK inhibitor therapy may represent an attractive treatment option for this patient population. This paper reviews the currently available data on the use of approved ALK inhibitors for the treatment of brain metastases in patients with NSCLC.

Crizotinib

Crizotinib which is an oral multi targeted tyrosine kinase inhibitor (TKI) (against MET, ALK, and ROS-1) has been approved for the treatment of advanced ALK-positive NSCLC [18,20]. Currently, PROFILE 1007 trial showed that crizotinib achieved impressive response rates and PFS survival in previously treated patients with ALK-positive NSCLC compared with chemotherapy (docetaxel or pemetrexed) [21]. Both PROFILE 1001 and 1005 trials (phase I and II trials, respectively) showed that the median OS in patients with ALK-rearranged NSCLC was 29.6 months for 120 patients who continued crizotinib even beyond disease progression (PD) [22]. Median OS of ALK-rearranged NSCLC patients treated with crizotinib at the first-line and also at the second-line is approximately 2 years. The frequency of brain metastasis at diagnosis in patients with ALK-rearranged NSCLC is 30% and may also reach 90% with the passing of time.

In PROFILE 1005 and 1007 trials, patients

Table 1. Driver mutation inhibition activity of the molecules against ALK

Mutation	*Crizotinib*	*Ceritinib*	*Alectinib*	*Brigatinib*	*Lorlatinib*
ALK	+	+	+	+	+
ROS-1	+	+	-	+	+
c-MET	+	-	-	-	-
RET	-	-	+	-	-
EGFR	-	-	-	+	-

ALK: anaplastic lymphoma kinase, ROS-1: c-ros oncogene 1, MET: mesenchymal-epithelial transition , RET: rearranged during transfection, EGFR: epidermal growth factor receptor

Table 2. Frequency of brain metastasis in the trials regarding ALK inhibitors and efficacy of ALK inhibitors for brain metastasis in patients with ALK-positive NSCLC

Treatment	*Patients, n*	*BM n (%)*	*CNS RR (%)*	*CNS DCR (%)*	*Duration of CNS response (months)*	*Reference*
Crizotinib	888	275 (31)	25	56	7	Costa et al. [17]
Ceritinib	246	124 (50.4)	34.5	58.6	6.9	Shaw et al. [24]
Ceritinib	140	100 (71.4)	38.6	77.1	6.9	Mok et al. [25]
Ceritinib	124	50 (40.3)	63.7	89.5	11.1	Felip et al. [26]
Alectinib	87	52 (60)	75	100	11.1	Shaw et al. [32]
Alectinib	138	84 (61)	57.1	83	10.3	Ou et al. [33]
Brigatinib	79	52 (66)	53	87	NR	Camidge et al. [34]
Brigatinib	79	46 (58)	69	83	13	Kerstein et al. [35]
Lorlatinib	44	52 (66)	36	72	NR	Shaw et al. [37]

BM: brain metastasis, N: number of patients, RR: response rate, DCR: disease control rate, CNS: central nervous system, NSCLC: non small cell lung cancer, NR: not reported

with previously untreated asymptomatic brain metastases were treated with the first generation ALK inhibitor crizotinib, and achieved 63% systemic disease control rate and 56% intracranial disease control rate at 12 months. Further, in this group, median PFS for brain metastases was 7 months. In ALK-rearranged NSCLC patients pretreated for brain metastasis, the systemic disease control and intracranial disease control rates were 65% and 62%, respectively. In this group, time to progression was 13.2 months for intracranial disease. These studies proved that, even used as second-line therapy, crizotinib provided similar intracranial disease control rate to the systemic disease in asymptomatic and untreated brain metastatic patients with ALK-rearranged NSCLC. Second-line crizotinib ensured better intracranial disease control rate and durable response in patients previously treated for brain metastasis compared to patients with asymptomatic brain metastases who had not received previous therapy for brain metastasis. This condition could be explained with the increased permeability of the BBB to crizotinib by the effect of locoregional treatments. Consequently, these results suggest that crizotinib could have additive or synergistic effects with locoregional treatments for brain metastasis. Although crizotinib is effective in patients with brain metastasis, even after second-line crizotinib treatment, new brain metastasis can occur in 20% of the the patients [17].

Patients with asymptomatic brain metastases who are candidates for crizotinib may be treated with systemic therapy alone. Local cranial therapies may be delayed in these patients.

Ceritinib

Ceritinib is selective ALK inhibitor that is 20 times more potent than crizotinib and is also effective for some of the crizotinib resistant cases. Ceritinib is indicated for the treatment of patients with ALK-rearranged metastatic NSCLC who have progressed on and have resistance or are intolerant to crizotinib [23]. Its activity against intracranial disease is more potent than crizotinib. Half of the patients with brain metastasis previously treated with crizotinib had shrinkage in the brain metastasis with ceritinib therapy.

In the ASCEND-I study there was no progression at week 12 in crizotinib-naive patients with asymptomatic brain metastasis, or in patients who received or not previous radiotherapy to the brain. In patients pretreated with crizotinib, progression in brain metastasis was detected in 22% of them previously treated with radiotherapy and 13% of patients untreated with radiotherapy [24].

In the ASCEND-2 study a total of 140 patients previously treated with crizotinib and chemotherapy received ceritinib 750 mg daily. The PFS was 5.7 months, the objective response rate (ORR) was 38.6%, and the disease control rate (DCR) was 77.1% for brain metastasis [25].

In the ASCEND-3 study a total of 124 patients previously not treated with ALK-inhibitor were treated with ceritinib. PFS was 11.1 months, ORR was 63.7% and the DCR was 89.5% for brain metastasis [26]. The results of the above mentioned trials in patients with asymptomatic brain metastases indicate that ceritinib is able to control the brain metastases effectively and independently from radiotherapy. In patients with brain metasta-

ses previously treated with crizotinib the response rates relatively declines with ceritinib, nevertheless it can be above 80%. The activity of ceritinib in brain metastases seems to be independent from radiotherapy. Trials have demonstrated that the course of brain metastases could be similar to the course of systemic disease with ceritinib therapy in ALK-rearranged NSCLC patients [24-26]. This remarkable and improved activity is currently unknown whether it is due to better CNS penetration ability or to its improved chemical potency.

Alectinib

Alectinib is an orally active, ATP-competitive potent and highly selective second generation ALK inhibitor [27]. Indeed, alectinib is approximately 5-fold more potent than crizotinib against ALK and can be an effective and reasonable choice in patients with acquired crizotinib resistant ALK mutations [28]. The kinase inhibitor activity of alectinib includes rearranged during transfection (RET) proto-oncogene with similar potency to ALK, but it does not include mesencymal epithelial transition (MET) or ROS oncogene 1 (ROS1) inhibition like crizotinib [29]. Ceritinib and crizotinib resistance in CNS disease by active efflux mechanism which is mediated with Pgp overexpression was not reported for the next-generation ALK inhibitor alectinib [30,31].

In a phase II trial that evaluate the efficacy of alectinib, 16 patients had measurable CNS disease at baseline, and 11 of them had received previous brain radiotherapy. Four (25%) had complete CNS response and 8 patients had partial response based on independent review assessment. Overall, 75% had an intracranial ORR with a CNS DCR of 100%. Median duration of CNS response was 11.1 months (95% CI 5.8-11.1). Fifty-two patients had measurable or non-measurable CNS disease at baseline, and 40% of the patients achieved an ORR and CNS disease control rate of 89%. Thirty-four percent of these patients had received previous brain radiation therapy. In patients with previously untreated CNS lesions, CNS disease ORR was 67%, stable CNS disease was 28% and there was only one case of progressive disease [32].

In another phase II study crizotinib-resistant patients were enrolled to receive alectinib. At baseline 84 (61%) patients had CNS metastases. The CNS DCR was 83%, with median response duration of 10.3 months (95% CI, 7.6-11.2). The ORR for CNS disease was 57% in 35 patients with measurable CNS lesions at baseline. In 10 (43%) of 23 patients with measurable or non-measurable CNS metastases at baseline who were untreated with prior radiation, complete CNS response had been achieved [33].

Finally, all of these findings suggest that alectinib may be effective in the CNS disease and also in patients who had not received previous brain radiation therapy. Furthermore, detailed information about alectinib compared with crizotinib will be presented in the ongoing multicenter phase III-ALEX study (Clinical trials number: NCT02075840).

Brigatinib

Brigatinib is an investigational ALK targeting TKIs, and has also activity against ROS1 and T790M mutation resistant to anti-EGFR TKIs. In a phase I/II trial the ORR among crizotinib pretreated and crizotinib-naive patients was 69% (45 of 65) and 100% (7 of 7), respectively. The median PFS was 47 weeks for crizotinib-pretreated patients and 56 weeks for the entire cohort [34]. In a phase I trial of brigatinib 46 patients were studied. Of them, 13 patients had measurable brain metastases and 9 (69%) showed regression of intracranial lesions. Four of these patients had complete response and 2 had partial response. The median intracranial PFS was 13 months [35].

Brigatinib is under investigation in an ongoing phase II study including a cohort of patients with brain metastasis in ALK-positive NSCLC (Clinical trials number: NCT02094573).

Lorlatinib

Lorlatinib (PF-06463922) is a potent and dual-action inhibitor of ALK and ROS1 that penetrates the BBB. This agent is effective against resistant ROS1 isoforms [36]. In a current phase I study, its safety and efficacy in patients previously treated with ALK-inhibitors was reported [37]. Of 18 ALK^+ and 4 $ROS1^+$ patients, 17 had CNS metastases and 19 were pretreated with ALK TKIs. Of 15 patients evaluated for efficacy 6 (40%) had either confirmed or unconfirmed partial responses, 5 of whom having previously received 1-2 TKIs and having progressive disease following crizotinib±ceritinib. Intracranial responses were observed in 5 patients. Common treatment-related adverse events were hypercholesterolemia and peripheral neuropathy (23% each). The most common grade >3 treatment-related adverse event

was hypercholesterolemia (14%) [37]. Recently, CNS and pre-clinical systemic activity of lorlatinib showed promising results in an early phase clinical trial in ALK positive NSCLC. [38].

Conclusion

Low response rates and poor survival with the current chemotherapeutic options are still a major challenge for the management of brain metastases in ALK-positive NSCLC patients. There is a satisfactory evidence that ALK TKI therapy achieves a delay in brain radiotherapy in patients with ALK-positive NSCLC and asymptomatic brain metastases. ALK inhibitors have a high potential of CNS permeability and disease response and it is thought to be active for the management of brain metastases with their systemic use. It seems that the new generation of ALK inhibitors will treat CNS disease as a part of systemic disease. For this reason, treatment strategies of brain metastases in ALK-positive NSCLC patients should be reassessed. Also, many of the unanswered questions are being actively addressed in ongoing trials.

Conflict of interests

The authors declare no confict of interests.

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