Commentary

New treatment options and challenges for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer with brain metastases

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Provenance: This is an invited Commentary commissioned by the Section Editor Lei Deng (West China Hospital, Sichuan University, Chengdu, China).

Comment on: Gadgeel SM, Shaw AT, Govindan R, *et al*. Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:4079-85.

Submitted Jan 05, 2017. Accepted for publication Jan 09, 2017.

doi: 10.21037/jtd.2017.02.06

View this article at: http://dx.doi.org/10.21037/jtd.2017.02.06

Up to a third of patients with non-small cell lung cancer (NSCLC) may develop brain metastases, typically portending a poor prognosis (1). Data suggest that median overall survival (OS) for patients who develop brain metastases after diagnosis is 10 months, and even shorter for patients who present with brain metastases at time of diagnosis (as low as 5 months) (2). Patients whose tumors harbor anaplastic lymphoma kinase (ALK) rearrangements have been observed to have longer median OS than patients with wild-type tumors, with one study reporting a 49-month median OS after development of brain metastases. However survival for patients who develop central nervous system (CNS) metastases while on crizotinib therapy has been reported as significantly shorter (10 months) (3). Treatment options for patients with progressive CNS disease include whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), surgical resection or a combination of these local modalities. Recent data suggest patients experience less neurocognitive toxicity from SRS alone if treating 1–3 brain metastases (4), and patients with lung cancer seem to do better with SRS than with WBRT, although this is likely due in part to selection of patients with multiple lesions for WBRT rather than SRS (5).

The initial studies and subsequent FDA approval of crizotinib, the first ALK inhibitor (6,7), yielded impressive initial clinical responses but resistance inevitably develops and patients ultimately experience disease progression. In a pooled analysis of two landmark trials, disease progression occurred in the CNS in 72% of patients (8). Acquired resistance to crizotinib has been observed to occur through a variety of mechanisms including ALK dependent mechanisms (ALK amplification, secondary *ALK* mutations), and "bypass tracks" such as increased EGFR phosphorylation and KRAS mutations (9-11). Progression within the CNS may occur because of inadequate penetration of crizotinib in the CSF (12), although recent data with alectinib suggest that CSF concentrations are not predictive of efficacy (13).

Resistance to crizotinib has led to the development of next-generation ALK-inhibitors, including ceritinib and alectinib. In a dose-finding phase I study, alectinib demonstrated impressive activity with 55% of patients experiencing a response, and 52% of patients with brain metastases experienced a response in the CNS (14). Gadgeel *et al.* (15) pooled data from two single-arm phase II trials, NP28673 and NP 28671, including 136 patients with baseline CNS disease prior to initiation of alectinib (of 225 total patients) representing 60% of the total study population in the two trials. The primary endpoint of both studies was objective response rate (ORR) by independent review committee. Trial NP28673, which included 138 patients from 16 countries, demonstrated an ORR of 50%, and 61% of all patients had CNS disease at baseline. CNS ORR was 57% among the 35 patients with measurable CNS disease at baseline. Trial NP28671 evaluated 87 patients and found a similar ORR of 48%, however the CNS ORR was 75%. In the 18 patients with CNS disease at baseline who had not received prior radiation therapy, responses

Table 1 Pooled analyses of CNS activity of ceritinib and alectinib in ALK-positive NSCLC

Study	Study drug	Patients with brain metastases at baseline, n	Patients with measurable brain metastases at baseline, n	Intracranial overall response rate, % (95% CI)	Intracranial disease control rate, % (95% CI)	Median intracranial duration of response, months (95% CI)
ASCEND-1 and -2 (18)	Ceritinib	198	61	37.7 (25.6, 51.0)	73.8 (60.9, 84.2)	12.8 (6.9, NR)
Current study (15)	Alectinib	136	50	64.0 (49.2, 77.1)	90.0 (78.2, 96.7)	10.8 (7.6, 14.1)

CNS, central nervous system; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

were seen in 67%, included ten complete responses. In both trials, patients with symptomatic CNS disease were excluded. In the pooled analysis, after a median follow-up of 12.4 months, alectinib demonstrated impressive efficacy in patients with measurable CNS disease at baseline, with 64% of patients achieving an objective response including 22% who achieved complete response. The ORR for patients with non-measurable CNS disease at baseline was somewhat lower at 43%, but complete response rate was higher (27%). Response rates were higher in patients how had not received prior radiation therapy, and were higher in patients whose radiation took place greater than 6 months prior to initiation of alectinib treatment. CNS ORR in patients who had not received prior radiation was 58.5% compared to 35.8% for those patients who had received radiation, and included a higher rate of complete responses (49% *vs.* 18%). Significantly, unlike prior studies of ALK inhibitors where the CNS was the most common site of disease progression, only 17% of patients in these two trials had progression in the CNS. Promisingly, among patients without CNS disease at baseline only 8% developed CNS disease during treatment.

Gadgeel and colleagues are to be congratulated on their work and the implications for clinical practice. The study raises several interesting questions which will be pivotal to answer in order to make the best decisions for our patients. It would be interesting to know what type of prior radiation therapy the patients had received, whether WBRT or SRS or both, to see if response and duration of efficacy vary by prior treatment. This important question should be addressed in future prospective trials. Additionally it would be informative to know how many CNS lesions patients had, as patients with multiple lesions are more likely to undergo WBRT rather than SRS (16), although ALK-positive patients treated with crizotinib have favorable outcomes when treated with SRS for both oligometastases (≤5 CNS lesions) and polymetastases (>5) (17).

In both trials, patients were ineligible if they had received an ALK-inhibitor other than crizotinib. The question of how patients treated with ceritinib after progressing on crizotinib will respond within the CNS has yet to be addressed. Ceritinib has shown activity within the CNS, with a CNS ORR of 37.7% demonstrated in pooled analysis of the ASCEND-1 and -2 trials, including a 45% response rate in the heavily-pretreated ASCEND-2 study population (18). *Table 1* shows the results of two pooled evaluations of CNS efficacy of ceritinib and alectinib, respectively, although the study populations vary significantly and direct comparison is not possible.

Finally, data on the subsequent treatment would be useful for the 17% of patients that developed progression in the CNS while on therapy with alectinib. The concept of "treatment beyond progression" for oligometastatic CNS disease who receive SRS to progressing lesions has been well established for patients receiving crizotinib therapy (16,17,19), and could inform decision making for patients on alectinib. More data on the treatment of these patients will be forthcoming as more patients are treated with alectinib either in the clinical trials setting or as a part of standard of care.

The addition of alectinib to the treatment portfolio in ALK-positive patients and the current study by Gadgeel *et al.* raise several interesting clinical scenarios. Medical oncologists must assess each patient's unique situation in conjunction with a multi-disciplinary team including radiation oncologists, neuro-oncologists, and neuro-surgeons, and utilize all available data to make the best-informed evidence-based decisions for their patients. The question of whether up-front alectinib is superior to crizotinib will be answered by the ongoing ALEX and J-ALEX trials, with early results from the Japanese population studied in the J-ALEX study suggesting better outcomes for patients treated with alectinib (20). Until the final data are available, however, the clinical question will arise commonly among patients progressing on crizotinib or ceritinib.

Our current practice is to avoid WBRT whenever

possible for patients with asymptomatic CNS progression on ALK-directed therapy in order to avoid or minimize neurotoxicity, especially in patients who are young with excellent anticipated survival. Enrollment on a clinical trial is preferred. For patients not suitable to trial or for whom trials are not readily available, in the setting of good systemic control but isolated or oligometastatic CNS progression, treating with SRS while continuing either crizotinib or ceritinib is a reasonable approach and supported in the literature (17,19). This allows for maximal duration of systemic clinical benefit with crizotinib. In the setting of good systemic control but multiple CNS lesions where SRS is not felt to be feasible, switching to alectinib is indicated as supported by the current work by Gadgeel *et al*. For patients who present with CNS disease at baseline, then initiation of an agent with good CNS efficacy such as alectinib would be optimal.

These encouraging results broaden the therapeutic options for clinicians and patients with ALK-positive NSCLC. Further clinical trials will help address outstanding questions. As more data become available on additional ALK-inhibitors such as brigatinib and lorlatinib, the question will be of the optimal sequencing of therapies, especially since early reports demonstrate CNS activity with these agents as well (21). Also, the choice of SRS, alectinib, or both has yet to be delineated in prospective trials. In patients harboring an EGFR mutation, the addition of TKI therapy to SRS or WBRT has so far met with mixed results (22-24). The possibility of treating with alectinib first and using SRS for lesions that persist after therapy remains an option that has not been tested. Patients who are symptomatic from their CNS disease represent the entirely separate cohorts who require immediate treatment. Efficacy of alectinib in these patients has not yet been reliably evaluated. Also, the incidence of "pseudo-progression" due to radiation necrosis in patients treated with alectinib (25), as well as the optimal strategy to identify and manage these patients remains unclear.

Acknowledgements

None.

Footnote

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

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Cite this article as: Owen D, Otterson GA. New treatment options and challenges for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer with brain metastases. J Thorac Dis 2017;9(2):E158-E161. doi: 10.21037/jtd.2017.02.06

