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Clinical impact of crizotinib on central nervous system progression in ALK-positive non-small lung cancer

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ABSTRACT

Background: The central nervous system (CNS) is a preferential progression site related to poor penetration of crizotinib into the CNS in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients treated with crizotinib. We evaluated the clinical impact of crizotinib on central nervous system progression in ALK-positive NSCLC.

Methods: Between January 2006 and September 2015, 59 ALK-positive NSCLC patients treated with crizotinib as the initial ALK inhibitor were retrospectively evaluated for baseline characteristics, initial response to crizotinib, brain metastasis (BM) status at baseline, and progression patterns.

Results: Among 59 patients, 48 (81%) received crizotinib as first-line or second-line treatment for advanced or recurrent disease. Out of the 26 (44%) patients who had BM, 13 had untreated BM, and 13 had previously undergone intracranial radiotherapy or surgery. The overall response rate for crizotinib was 66%, with a median progression-free survival (PFS) of 9.7 months. Disease progression assessed by response evaluation criteria in solid tumors-progressive disease (RECIST-PD) occurred in 48 patients. The CNS was the common initial progression site in 24 patients, which included isolated CNS progression in 18 patients. There was a significantly shorter median PFS in the BM versus the non-BM patients before crizotinib treatment (median PFS: 6.7 months vs. 10.2 months, $P = 0.0347$). Multivariate analysis revealed that poor performance status (PS) (≥ 2) or untreated BM were associated with the PFS duration (poor PS: hazard ratio (HR) 3.322, 95% CI 1.402–7.353, $P = 0.0078$; untreated BM: HR 2.314, 95% CI 1.153–4.400, $P = 0.0196$). In addition, the time to the occurrence of CNS progression from the start of crizotinib was significantly shorter in the BM versus non-BM patients (11.1 vs. 22.1 months, $P = 0.0255$).

Conclusion: The common progression site in ALK-positive patients treated with crizotinib was the CNS. BM status was significantly associated with both PFS in crizotinib-treated patients and the occurrence of CNS progression.

1. Introduction

Anaplastic lymphoma kinase (ALK) rearrangement, discovered by Soda et al. in 2007, has been validated as a well-established therapeutic target in non-small-cell lung cancer (NSCLC) [1]. The ALK tyrosine kinase inhibitor (TKI) shows promising effects in the treatment of NSCLC patients harboring the ALK rearrangement. Crizotinib was the first ALK tyrosine kinase inhibitor approved for ALK-positive NSCLC based on randomized studies demonstrating significant improvement in the objective response rate (ORR) and progression-free survival (PFS) compared with cytotoxic chemotherapy [2,3].

Despite the significant clinical response with crizotinib in controlling systemic sites of tumor burden in patients with *ALK*-positive NSCLC, resistance to crizotinib occurs by a number of mechanisms, including ALK gene alterations, such as ALK point mutations and copy number gain, and activation of bypass signaling through activation of other oncogenes [4–7]. Additionally, the central nervous system (CNS) is a preferential progression site related to poor penetration of crizotinib into the CNS in ALK-positive NSCLC patients treated with crizotinib [8]. A crizotinib phase I trial reported that the CNS was the most common site for single organ

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disease progression in patients [9]. A previous pooled retrospective study that included data from the clinical PROFILE 1005 and 1007 trials also showed that at the failure of the crizotinib treatment, CNS progression occurred after drug administration in 70% of patients with brain metastasis (BM) at the initiation of crizotinib treatment [10]. During crizotinib therapy, BM remains one of the dominant sites of the progressive tumor burden.

The next generation ALK TKIs, ceritinb and alectinib, have recently been reported to have a potent efficacy in ALK-positive NSCLC patients, including for mutations that confer resistance to crizotinib [11–13]. The activity of ceritinib and alectinib in patients with BM and leptomeningeal carcinomatosis has been shown to have a favorable effect on parenchymal CNS lesions, even when found to be previously refractory to crizotinib treatment [14–16].

Presently, only a few reports have focused on the efficacy of crizotinib on BM. To the best of our knowledge, there have been few studies that have fully elucidated the influence of crizotinib on CNS progression and progression patterns, including isolated CNS failures. Therefore, the aim of our current study was to investigate the BM status before initiation of crizotinib treatment, determine the clinical outcome of crizotinib and subsequent progression patterns, and evaluate the clinical impact of crizotinib on BM. Moreover, we also sought to determine whether crizotinib can delay or prevent the development of CNS progression.

2. Patients and methods

2.1. Patients

Between January 2006 and September 2015, 90 consecutive patients with advanced NSCLC harboring ALK rearrangement were treated with an ALK inhibitor at our institution. Among these patients, we retrospectively evaluated 59 ALK-positive NSCLC patients who had been treated with crizotinib as the initial ALK inhibitor for the baseline characteristics, the BM status before the initiation of crizotinib, the initial response for crizotinib, the initial progression sites, the progression patterns (isolated CNS or systemic progression), the PFS after crizotinib, and the subsequent treatments performed after the crizotinib failure. Isolated CNS progression was defined as a case that only exhibited BM at the first progression site. Systemic progression was defined as a case that exhibited other progression sites beyond the isolated brain involvement. The date of progression was defined based on the routine surveillance imaging. There was no formal institutional policy on the treatment strategy to be used in relation to the response evaluation criteria in solid tumors-progressive disease (RECIST-PD) [17], and thus, all of the treatment decisions were made according to the individual judgments of the treating providers. The status of an ALK gene rearrangement was assessed by Vysis ALK Break Apart fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or ALK immunohistochemistry (PMID: 22655265). We deemed patients to be positive for ALK rearrangement when at least two of the FISH, RT-PCR, or immunohistochemistry tests showed positive results. The objective tumor response was assessed according to the RECIST version 1.1 [17]. The ORR was calculated as the total percentage of patients with a complete response (CR) or a partial response (PR).

2.2. Statistical analysis

All the statistical analyses were performed using JMP for Windows version 11 statistical software package (SAS Institute, NC, USA). Differences in the baseline characteristics between the groups were compared using Fisher's exact tests for the categorical data. PFS was measured from the start of the crizotinib to the date of the RECIST-PD. Time to brain metastases progression was measured from the start of the crizotinib treatment to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study, there is the possibility that there was diversity in the frequency and methods of monitoring. Data for the patients who had not developed disease progression or brain metastases at the last follow-up were censored at that point. Survival probabilities were calculated by the Kaplan-Meier method and compared among different groups using the log-rank test. Multivariate analysis was performed by using the Cox proportional hazards model to evaluate the importance of clinically selected variables. Covariates with a *P*-value inferior or equal to 0.10 in univariate analysis were included in the multivariate model. This study was approved by the Institutional Review Boards of the Aichi Cancer Center.

3. Results

3.1. Patient characteristics

Table 1 lists the baseline patient characteristics for the 59 patients at the start of the crizotinib treatment. The median age of the patients was 55 years (range: 26–80 years), with 23 (39%) male and 36 (61%) female. The Eastern Cooperative Oncology Group performance status (PS) was 0 or 1 in 50 (85%) of the patients. Of the 59 patients, 48 (81%) received crizotinib as a first-line or second-line treatment for advanced or recurrent disease, while 11 received the drug as a third or subsequent line treatment. There were 26 (44%) patients found to have BM before the crizotinib treatment, with 13 previously untreated for the BM, and 13 having undergone intracranial radiotherapy such as whole brain radiotherapy (WBRT) and stereotactic brain radiotherapy (SRT), or surgery before the crizotinib treatment.

3.2. Tumor response after crizotinib treatment

After the initial administration of crizotinib, 39 (66%) patients had PR, 9 (15%) patients had stable disease (SD), and 7 (12%) patients had PD. The response was not evaluable in 4 (7%) patients because crizotinib had to be discontinued due to toxicity before the first tumor response evaluation. The overall ORR was 66% in all patients,

Table 1
Patient characteristics (N = 59).

Characteristics		N (%)
Age	Median [range]	55 [26–80]
Sex	Male	23 (39)
	Female	36 (61)
PS	0–1	50 (85)
	2	5 (8)
	3	4 (7)
Smoking index	Median [range]	0 [0–1170]
Histology	Adenocarcinoma	55 (93)
	NSCLC	3 (5)
	Squamous cell carcinoma	1 (2)
Stage	IIIB/IV	6/42 (81)
	Postoperative recurrent	11 (19)
Treatment line	1st	18 (31)
	2nd	30 (50)
	≥3rd	11(19)
Brain metastases before crizotinib	Yes	26 (44)
	No	33 (56)
Treatment response	PR	39 (66)
	SD	9 (15)
	PD	7 (12)
	NE	4 (7)
	ORR	66%

NSCLC: non-small cell lung cancer; PS: performance status; BM: brain metastasis.