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【 CASE REPORT 】

A Low Crizotinib Concentration in the Cerebrospinal Fluid Causes Ineffective Treatment of Anaplastic Lymphoma Kinase-positive Non-small Cell Lung Cancer with Carcinomatous Meningitis

Tamio Okimoto[1], Yukari Tsubata[1], Takamasa Hotta[1], Megumi Hamaguchi[1], Mika Nakao[1], Shun-ichi Hamaguchi[1], Akinobu Hamada[2] and Takeshi Isobe[1]

Abstract:
The central nervous system is a common site of relapse in patients receiving crizotinib, which is presumed to be associated with the low concentration of crizotinib in the cerebrospinal fluid (CSF). Our patient received surgical treatment for anaplastic lymphoma kinase-positive stage IIA lung adenocarcinoma. His cancer recurred with brain metastases and carcinomatous meningitis. We started whole-brain radiation therapy (WBRT) and subsequently administered crizotinib. The concentration of crizotinib on day 15 in the plasma was 158 ng/mL, and that in the spinal fluid was 4.32 ng/mL. WBRT may elevate the CSF/plasma crizotinib concentration ratio; clinicians may therefore consider performing WBRT prior to crizotinib initiation.

Key words: anaplastic lymphoma kinase, central nervous system, cerebrospinal fluid, crizotinib, non-small cell lung cancer

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Introduction

The echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusion gene was first identified in 2007 by Soda et al., and they reported the gene rearrangement in 6.7% (5/75) of the examined patients who had non-small cell lung cancer (NSCLC) (1). Treatment with ALK-tyrosine kinase inhibitors (TKIs) showed superiority over chemotherapy, and ALK-TKIs are recommended for the first-line treatment of NSCLC patients positive for the ALK fusion protein.

Crizotinib was the first drug approved for treating advanced ALK-positive NSCLC. Although alectinib showed a superior survival benefit compared to crizotinib, crizotinib is still a key drug for the treatment of ALK-positive NSCLC. Furthermore, crizotinib was approved for the treatment of advanced NSCLC with a *ROS1* mutation.

The central nervous system (CNS) is a common site of relapse in patients with progressive disease who are receiving crizotinib (2). One possible reason for this is the low concentration of crizotinib in the cerebrospinal fluid (CSF). However, to date, there have only been three cases reported in the literature of a low crizotinib concentration in the CSF (3, 4).

We herein report the fourth case of ALK-positive advanced NSCLC and carcinomatous meningitis.

Case Report

A 61-year-old man visited our hospital complaining of diplopia and incontinence. He had a history of stage IIA lung adenocarcinoma with EML4-ALK fusion, which was confirmed by immunohistochemistry and fluorescence *in situ* hybridization, treated by right lower lobectomy and adjuvant chemotherapy (cisplatin and vinorelbine). He also had a history of type C hepatitis and cirrhosis.

A physical examination revealed left oculomotor nerve

[1]Department of Internal Medicine, Division of Clinical Oncology and Respiratory Medicine, Shimane University Faculty of Medicine, Japan and [2]Department of Molecular Pharmacology, National Cancer Center Research Institute, Japan
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Correspondence to Tamio Okimoto, okimoto@med.shimane-u.ac.jp

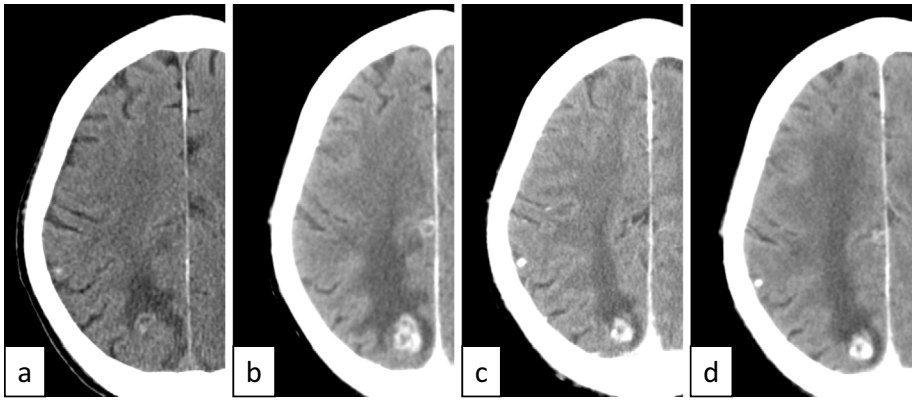

Figure. **Computed tomography findings of the brain metastasis. a) Relapse of brain metastasis and carcinomatous meningitis. Whole-brain radiation therapy (WBRT) was initiated. b) One month after performing WBRT and just prior to crizotinib initiation, progression of the metastatic lesion was observed. A cytological analysis of the cerebrospinal fluid (CSF) was positive for malignant cells. c) One month after crizotinib initiation, the response of the metastatic lesion was observed. A cytological analysis of the CSF was negative for malignant cells. d) One month after withdrawal of crizotinib, no remarkable change was observed.**

palsy and perianal sensory impairment. Meningeal irritation was not apparent. Computed tomography (CT) of the head showed a nodular lesion in his right posterior lobe, suggesting recurrence of lung cancer with brain metastasis (Figure a). A further examination using brain magnetic resonance imaging could not be performed because of tattoos present on his entire body other than his face, hands, and feet. A cytological analysis of the CSF revealed adenocarcinoma positivity, and reverse transcription-polymerase chain reaction revealed that this adenocarcinoma was positive for the *ALK* fusion gene. We clinically diagnosed the patient with brain metastasis of lung cancer and carcinomatous meningitis.

We started the patient on whole-brain radiation therapy (WBRT). Despite the radiation therapy, his symptoms worsened, and he developed aspiration pneumonia. Head CT showed tumor progression after 1 month of radiation therapy (Figure b). We started administration of 250 mg crizotinib twice daily after improvement in the pneumonia. One month after crizotinib initiation, his diplopia improved, and head CT showed shrinkage of the metastatic lesion (Figure c). A cytological analysis of the CSF was now negative for malignant cells. Crizotinib concentrations in the CSF and plasma on day 15 were 4.32 ng/mL and 158 ng/mL, respectively. Despite the efficacy of this drug, we had to withdraw crizotinib due to grade 3 AST/ALT elevation two months after crizotinib initiation. The diplopia worsened, and disturbance of the consciousness was again observed. Head CT revealed no remarkable changes (Figure d). After improvement in side effects, we restarted crizotinib at 200 mg twice daily (80% dose). However, the patient's condition worsened, and he died of carcinomatous meningitis one month after re-administration.

We were unable to administer other ALK-TKIs because crizotinib was the only drug available for ALK-positive NSCLC at the time.

This study was approved by the Institutional Review Board of Shimane University and National Cancer Center Hospital. The crizotinib concentration was measured at the National Cancer Center Institute (UMIN000015840).

Discussion

This case had two important clinical findings. First, a low crizotinib concentration in the CSF was observed in our patient, consistent with the findings of the three previous ALK-positive NSCLC cases reported in the literature. Second, WBRT may slightly elevate the crizotinib concentration in the CSF.

With regard to the first finding, we noted in the present case that crizotinib concentrations in the CSF and plasma on day 15 were 4.32 ng/mL and 158 ng/mL, respectively; hence, the CSF-to-plasma concentration ratio was 0.026. Similarly, Costa et al. reported crizotinib concentrations in the CSF and plasma of 0.616 ng/mL and 237 ng/mL, respectively (3), and Metro et al. reported 2 patients with CSF crizotinib concentrations of 0.35 ng/mL and 0.80 ng/mL in the plasma and 587 ng/mL and 800 ng/mL in the plasma, respectively (4) (Table). In contrast, it has been reported that alectinib penetrates the CNS, and there is a linear relationship between alectinib concentrations in the CSF and plasma (5). Both crizotinib and alectinib are oil-soluble drugs; however, with regard to the oil/water coefficient, alectinib has a higher oil solubility than crizotinib (6, 7). Although crizotinib is a substrate of the P-glycoprotein efflux transporter, alectinib is not (8). These characteristics contribute to the differences between crizotinib and alectinib in the CSF concentration and treatment outcome (9, 10).

Metro et al. also suggested the possibility that WBRT elevates the crizotinib concentration in the CSF (4). The CSF and plasma crizotinib concentration ratios in the 4 published cases, including the present case, ranged between 0.0006

Table. **Crizotinib and Alectinib Concentrations in the CSF and Plasma.**

	Reference	CSF	Plasma	CSF/plasma	WBRT
Crizotinib (ng/mL)	3	0.616	237	0.003	+
	4	0.35	587	0.0006	-
		0.80	800	0.001	+
	Our case	4.32	158	0.026	+
Alectinib (nmol/L)	5	2.69	3.12	0.86	

CSF: cerebrospinal fluid, WBRT: whole-brain radiation therapy

and 0.026. The patient who showed the smallest ratio had not received WBRT prior to crizotinib administration. This tendency was also observed in the present case, and similar trends were reported for HER2-positive breast cancer patients with brain metastases receiving the anti-HER2 monoclonal antibody trastuzumab (11). Stemmler et al. presented clinical evidence that the trastuzumab levels in the CSF are increased under conditions that impair the blood-brain barrier, such as radiotherapy. Although the median progression-free survival (PFS) after crizotinib treatment reported in a previous study was 10.9 months (12), we found that the re-administration of crizotinib did not show efficacy and resulted in a PFS of only approximately 2 months. It is presumed that the poor efficacy of re-administration is associated with an inadequate crizotinib concentration in the CSF rather than tolerance to crizotinib.

With regard to the ALK-TKIs approved by the Food and Drug Administration (FDA) to date, crizotinib and ceritinib are substrates of the P-glycoprotein efflux transporter, and alectinib is the only ALK-TKI that is not its substrate (13). Crizotinib is the only drug approved by the FDA for the treatment of advanced NSCLC with a *ROS1* mutation. The half-maximum inhibitory concentration of crizotinib *in vitro* is reported to be 36-108 ng/mL (3, 13), which is higher than that reported in the CSF. Although Costa et al. suggested that the CNS benefits even from low concentrations of crizotinib in the CSF (3), performing WBRT prior to crizotinib to elevate the drug concentration should be considered.

Conclusion

Crizotinib remains a key drug for the treatment of NSCLC patients positive for ALK fusion protein or a *ROS1* mutation. However, in the present case, the treatment attempt failed because the crizotinib concentration in the CSF was low, similar to the observations in the three previously reported cases. As WBRT may increase the crizotinib concentration in the CSF, clinicians should consider performing WBRT prior to crizotinib initiation.

The study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board of Shimane University and National Cancer Center. Informed consent was obtained from the patient described in the study.

Author's disclosure of potential Conflicts of Interest (COI).
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