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

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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

Background

The echinoderm microtubule-associated protein-like 4 (\textit{EML4})-anaplastic lymphoma kinase (\textit{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 \textit{ALK}-tyrosine kinase inhibitors (TKIs) showed superiority over chemotherapy, and \textit{ALK}-TKIs are recommended for the first-line treatment of NSCLC patients positive for the \textit{ALK} fusion protein.

Crizotinib was the first drug approved for treating advanced \textit{ALK}-positive NSCLC. Although alectinib showed a superior survival benefit compared to crizotinib, crizotinib is still a key drug for the treatment of \textit{ALK}-positive NSCLC. Furthermore, crizotinib was approved for the treatment of advanced NSCLC with a \textit{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 \textit{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 \textit{EML4}-\textit{ALK} fusion, which was confirmed by immunohistochemistry and fluorescence \textit{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...
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 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 were for malignant cells. Crizotinib concentrations in the CSF and plasma of 0.616 ng/mL and 237 ng/mL, respectively (4) (Table). In contrast, it has been reported 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 concentrations after 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.

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.
and plasma crizotinib concentration ratios in the 4 published cases, including the present case, ranged between 0.0006 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.

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

Isobe T: Honoraria, Boehringer-Ingelheim, AstraZeneca and Pfizer.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>CSF (ng/mL)</th>
<th>Plasma</th>
<th>CSF/Plasma</th>
<th>WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa</td>
<td>0.616</td>
<td>237</td>
<td>0.003</td>
<td>+</td>
</tr>
<tr>
<td>Metro</td>
<td>0.35</td>
<td>587</td>
<td>0.0006</td>
<td>-</td>
</tr>
<tr>
<td>Okimoto</td>
<td>0.80</td>
<td>800</td>
<td>0.001</td>
<td>+</td>
</tr>
<tr>
<td>Gadgeel</td>
<td>4.32</td>
<td>158</td>
<td>0.026</td>
<td>+</td>
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<tr>
<td>Alectinib (nmol/L)</td>
<td>Gadgeel</td>
<td>2.69</td>
<td>3.12</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**Acknowledgement**

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**Ethical standards**

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.

**References**

6. Xalkori interview form.
7. Alecensa interview form.