学 位 論 文 の 要 旨

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学　位　論　文　名　Blood Concentrations of Osimertinib and Its Active Metabolites: Impact on Treatment Efficacy and Safety

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論 文 内 容 の 要 旨

INTRODUCTION

Osimertinib (OSI) is a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) and the standard treatment for non-small cell lung cancer with EGFR mutation. OSI contains active metabolites such as AZ5104 and AZ7550. The correlation between the blood concentrations of OSI, AZ5104, and AZ7550 with their efficacy and safety is not clear; hence, we examined it.

MATERIALS NAD METHODS

Patients and study design

This single-center retrospective study was conducted at Shimane University Hospital. Patients with incurable or relapsed EGFR mutation-positive NSCLC who received OSI between May 2016 and December 2022 and were at least 20 years old, with available blood samples and written informed consent, were included. The primary endpoint was the relationship between PFS and blood concentrations of OSI, AZ5104, and AZ7550. The secondary endpoint was the relationship between OS and safety and concentrations of OSI, AZ5104, and AZ7550. Data on age, sex, stage, histologic type, genetic mutation, OSI dose, time to disease progression, survival, adverse events, and disease severity were retrieved from the electronic medical records. Adverse

events related to OSI were retrospectively evaluated according to the Common Terminology Criteria for Adverse Events v4.0 for predefined items including neutropenia, anemia, thrombocytopenia, aspartate transaminase (AST) elevation, alanine transaminase (ALT) elevation, QTc interval prolongation, interstitial lung disease, paronychia, rash, and diarrhea.
The study protocol was approved by the Research Ethics Committee of Shimane University.

Data collection

Serum samples were collected after day 22 of OSI initiation when the blood levels reached a steady state. The collected serum samples were stored frozen at -80°C and analyzed collectively using liquid chromatograph-tandem mass spectrometry (LC-MS/MS).

Statistical analysis.

The plasma concentrations of OSI, AZ5104, and AZ7550 were quantified based on calibration curves prepared from standard samples. The PFS and OS were determined using the Kaplan–Meier metho. The level of significance was set at $p<0.05$. The Cox proportional hazards model was used for both univariate and multivariate analyses to assess the impact of individual covariates on PFS and OS. Variables included in the multivariate analysis were those with $p<0.05$ in the univariate analysis. Welch's t-test was performed to assess whether there were significant differences in the mean blood concentrations of OSI, AZ5104, and AZ7550 between patients with adverse event grades 0-1 and those with grades 2-4, as this test does not assume equal variances between groups.

RESULT AND DISCUSSION

Patients with higher OSI blood levels tended to have longer PFS than those with lower levels (26.5 vs. 17.9 months), with the difference approaching statistical significance ($p=0.058$). For AZ5104, the median PFS was 23.4 months in the high-concentration group and 17.9 months in the low-concentration group ($p=0.574$). In the AZ7550 group, patients with lower blood concentrations tended to have longer PFS than those with higher concentrations (25.5 vs. 16.7 months), with a trend toward statistical significance ($p=0.078$). Overall, PFS did not differ significantly between the high and low concentration groups for any of the three compounds. Similarly, OS did not significantly differ between high and low blood level groups: 38.9 vs. 47.9 months for OSI ($p=0.815$), 38.8 vs. 46.2 months for AZ5104 ($p=0.944$), and 29.2 vs. 50.7 months for AZ7550 ($p=0.227$).

A low blood concentration of OSI was an independent prognostic factor for shortened PFS. However, a low blood concentration of OSI was not an independent prognostic factor for OS. In vitro studies have demonstrated that the antitumor effect of OSI is dose dependent. In contrast, a

clinical study that compared PFS across quartiles of plasma concentrations reported that PFS was prolonged in the intermediate concentration groups compared with both the high- and low-concentration groups. Furthermore, some reports have suggested that the risk of death is higher in the high-concentration group. The reason for the shorter prognosis in the OSI-high blood concentration group is considered to be the development of EGFR-TKI resistance through off-target mechanisms, including MET and HER2 amplification. Building on these findings, and incorporating our own research, it can be concluded that the relationship between OSI blood concentration and PFS improvement is not linear. While PFS may improve within a certain concentration range, levels beyond this threshold could worsen prognosis due to increased side effects and off-target resistance.

Regarding safety, for OSI, AZ5104 and AZ7550, although there was no significant difference in the incidence of adverse events between the high-dose and low-dose groups, there was a tendency for more grade 3 or higher adverse events to occur in the high-concentration group. For neutropenia, lymphopenia, and anemia, mean AZ7550 concentrations were significantly higher in grade 2–4 than in grade 0–1 group. Similarly, mean AZ5104 concentrations were significantly higher in patients with grade 2–4 lymphopenia. Hematologic toxicities associated with OSI have been reported in multiple clinical trials. However, the underlying mechanisms remain unclear, and active metabolites may contribute to these toxicities. Elucidating these mechanisms represents an important issue for future research.

CONCLUSION

In conclusion, we demonstrated that patients with high OSI blood concentrations had longer PFS than those with low concentrations, and that OSI blood levels were positively correlated with efficacy. However, high blood concentrations of the active metabolites are associated with hematological toxicity. Further research is needed to determine the optimal OSI concentration that minimizes the risk of adverse effects while maintaining clinical efficacy and not compromising the prognosis.