学 位 論 文 の 要 旨

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学 位 論 文 名　Pharmacokinetics of Edoxaban in EGFR-mutated Non-small Cell Lung Cancer Patients with Venous Thromboembolism

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論 文 内 容 の 要 旨

INTRODUCTION

Venous thromboembolism (VTE) is a common complication of cancer and its therapy. The prognosis for cancer patients with VTE is poor, with a 1-year survival rate of 12% and the mortality rate two-times more than that of cancer patients without VTE. Direct oral anticoagulants (DOACs) have been shown to be effective against cancer-associated thrombosis. The currently published studies on drug-drug interactions associated with DOACs focused on medications (e.g., cytochrome P450 (CYP)3A4 inhibitors and P-glycoprotein competitors) that share a common metabolic pathway with DOACs. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are key drugs for the treatment of EGFR mutation-positive non-small cell lung cancer (NSCLC). Some EGFR-TKIs can potentially affect the metabolism of DOACs via CYP3A4 inhibition, resulting in reduced or enhanced effect of DOACs. For example, in vitro studies in human liver microsomes showed that gefitinib has a weak inhibitory potential on CYP3A4 activities. We designed an observational study on the pharmacokinetics (PK) of edoxaban with EGFR-TKI in patients with NSCLC.

MATERIALS AND METHODS

Study population

Patients with untreated EGFR-mutated NSCLC with cancer-associated VTE were recruited. All included patients were aged ≥20 years, NSCLC at an advanced stage for which radical treatment was not possible, and an expected survival period of 6+ months from the time consent was obtained. Planned treatments included gefitinib, erlotinib, or afatinib monotherapy with edoxaban as an anticoagulant therapy.

Study design and treatments

The Rising-VTE/NEJ037 study is an observational study of the incidence of thromboembolism in patients with lung cancer and includes an evaluation of the efficacy and safety of edoxaban in patients with active cancer and VTE. Among patients enrolled in the Rising-VTE/NEJ037 study, those with indications for both EGFR-TKIs and edoxaban entered this study. The study protocol was approved by the Ethics Committee of Shimane University. Blood samples were collected into heparin-treated vacuum tubes at 0.5, 1, 2, 4, 8, and 24 h after the first edoxaban administration. Following this, the patients were treated with EGFR-TKI anticancer therapies of any variety (gefitinib/erlotinib/afatinib). Blood samples were again collected at 0.5, 1, 2, 4, 8, and 24 h within 15 days from day 8 after starting EGFR-TKIs, when EGFR-TKIs are expected to reach a steady state. All adverse events were recorded.

Pharmacokinetic analysis

Plasma concentrations of edoxaban were determined according to the area under the concentration-time curve (AUC0-∞) and the mean residence time (MRT) as follows:

$$\mathrm{AUC} = \int_0^{\infty} \mathrm{C}\,\mathrm{dt}$$

$$\mathrm{MRT} = \int_0^{\infty} \mathrm{t} \cdot \mathrm{C}\,\mathrm{dt} \Big/ \int_0^{\infty} \mathrm{C}\,\mathrm{dt}$$

where, C dt is the concentration of edoxaban plasma concentration at time t. These moment parameters were calculated by trapezoidal integration using Numeric Analysis Program for Pharmacokinetics.

Liquid chromatography-tandem mass spectrometry; Edoxaban

Plasma edoxaban concentration was measured using liquid chromatography-tandem mass spectrometry (LC/MS/MS). All blood concentration measurements of edoxaban were entrusted to SHIN NIPPON BIOMEDICAL LABORATORIES.

Liquid chromatography-tandem mass spectrometry; EGFR-TKI

Plasma concentrations of gefitinib and erlotinib in patients were determined by LC-MS/MS. TSQ Quantum™ Access MAX Triple Quadrupole Mass (Thermo Fisher Scientific Inc., USA) was used.

Statistical analysis

The PK set for analysis comprised data from 12 enrolled subjects administered edoxaban. The PK of edoxaban was statistically analyzed for eight cases. Qualitative variables are reported as frequency and percentage, and quantitative variables as median or mean and standard deviation. Differences in PK parameters were analyzed using the Wilcoxson signed-rank test. The results with a P value of 0.05 or less were considered statistically significant.

RESULTS AND DISCUSSION

The AUC0-∞, MRT, AUMC, elimination rate constant (Ke), half-life (t1/2), clearance (CL), and volume of distribution at steady state (Vdss) for edoxaban did not change before and after taking EFGR-TKIs. No significant difference in plasma concentration of edoxaban was observed at any time point. Similar results were obtained for each EGFR-TKI type. After 24 h, the plasma edoxaban concentration was 0.0439 μg/mL when edoxaban was administered alone. It was 0.0259 μg/mL when edoxaban was co-administered with EGFR-TKIs. Previous plasma concentration data indicate that edoxaban at doses of 15–60 mg, the mean trough blood concentration is 0.016–0.0485 μg/mL. It was within the same blood concentration range as previously reported. Epistaxis was reported in three patients. None required special treatment, and all experienced this event only once. The prothrombin time-international standard ratio (INR), measured 6 months after the introduction of edoxaban, did not indicate hyperprolongation (INR: 0.99–1.58). No serious adverse event (grade 3 or 4) was reported. The plasma trough concentration of EGFR-TKI in this study did not decrease when combined with edoxaban. Similarly, no decrease in EGFR-TKI concentration was observed when comparing only the cases in which the PK analysis of edoxaban was performed.

CONCLUSION

Edoxaban PK parameters were not affected by EGFR-TKI used concomitantly. EGFR-TKI can exacerbate the control of coagulation due to interaction with warfarin. Edoxaban possibly enables stable VTE treatment without increasing the risk of bleeding, even when used in combination with EGFR-TKI.