学 位 論 文 の 要 約

所 属	甲	三重大学大学院医学系研究科 生命医科学専攻 臨床医学系講座 臨床薬剤学分野	氏 名	イクバル ジュリアン リアンダ Iqbal Julian Rianda プラダナ プトラ Pradana Putra

主論文の題名

Investigation of Biomarkers and Handling Strategy of Erlotinib-Induced Skin Rash in Rats

（ラットにおけるエルロチニブ誘発性皮膚障害のバイオマーカーと予防戦略の検討）

Iqbal Julian and Takuya Iwamoto

主論文の要約

Introduction

This study was focus on finding the biomarkers of rash occurrence induced by erlotinib in rats.

Background

Skin rash is a common adverse event associated with erlotinib. A severe rash could affect the quality of life of patients that triggers the therapy failures. If the rash occurrence could be predicted, the therapy failures could be prevented.

Objectives

The study was done to find the biomarker candidates of rash occurrence induced by erlotinib.

Methods

Several strategies related to the application of erlotinib regimens on clinical settings were applied on our *in vivo* study. The tested animal was Sprague-Dawley male rats, wild-type, aged 8 weeks. Rats were divided into

four groups: placebo, constant (erlotinib 35 mg/kg on d1–d21), intermittent (erlotinib 70 mg/kg on d1–d7 and d15–d21), and mimic (erlotinib 70 mg/kg on d1–d7 and erlotinib 35 mg/kg on d15–d21). The test solutions were administered daily as a single dose, orally. Blood sampling was performed on d1, d8, d15, and d22. The blood sampling was performed via the orbital sinus. The concentrations of circulating erlotinib were measured by liquid chromatography with tandem mass spectrometry. The rash grades were classified based on the adjusted Common Terminology Criteria of Adverse Event version 5. The percentages of several circulating immune cells and their levels of cluster of differentiation-45 (CD45) expressions were measured by flow cytometry. Several parameters of renal and hepatic functions were also measured, such as alkaline phosphatase (ALP).

Results

The rash occurrence on rats treated with erlotinib was significantly correlated with the escalation of circulating neutrophil percentages and the reduction of CD45 expression levels.

Consideration

Translating our results into clinical application could be difficult due to the uncommon methods. However, the finding of neutrophils' CD45 level reduction is the first to be found related to the erlotinib application. Therefore, it is worth to be tried in a clinical study in the future.

Conclusion

This study is the first to show that rash induced by erlotinib may be affected by the reduction of neutrophils' CD45 expression levels. This is a valuable finding to elucidate the formation mechanism of erlotinib-induced skin rash.