Minocycline prevents and repairs the skin disorder associated with afatinib, one of the epidermal growth factor receptor-tyrosine kinase inhibitors for non-small cell lung cancer

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Abstract

Background While epidermal growth factor receptor(EGFR) tyrosine kinase inhibitors(TKIs) exert a breakthrough effect, the incidence of skin disorders as a side effect has significantly reduced patients' quality of life. **Objective** This study aimed to develop a treatment for inflammatory ulcers as one of the side effects of afatinib (Geotrif®), a second-generation EGFR-TKI, and established a skin disorder mouse model to investigate the protective effect of minocycline.

Methods First, under inhalation anesthesia with isoflurane, the back of a male ddy mouse was shaved, and afatinib petrolatum was applied alone or in combination with minocycline to observe the state of the skin and measure transepidermal water transpiration (TEWL). Next, afatinib was administered orally to mice, and minocycline petrolatum was applied to observe whether the skin disorder was prevented and its effect on repair of the skin disorder.

Results Skin injury occurred on the back of the mouse following afatinib (1 mg/g in petrolatum) application, and scab formation was observed. Application of minocycline prevented and improved the skin disorder caused by afatinib. When the minocycline-petrolatum mixture was applied to the mouse that developed the skin disorder, a significant improvement in TEWL was observed, and skin repair was observed macroscopically.

Discussion These results suggest that minocycline applied both locally and orally prevents and repairs afatinib-induced skin disorders. Histological examination of skin elucidated the mechanism of the occurrence of the EGFR-TKI-related skin disorder and suggested the efficacy of minocycline topical application in clinical practice.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed.

However, the manuscript can be downloaded and accessed as a PDF.

Figures

Figure 1

Effects of minocycline WP on rash induced by afatinib ointment application (a) Left side is the TEWL value of control mice with low-concentration (0.075%) afatinib WP for 7 days with/without minocycline WP treatment. Right side is high-concentration (0.10%) afatinib WP treatment. (b) Representative images of the effects of treatment with minocycline WP after onset of the rash. Left side is low-concentration (0.075%) afatinib WP, and right side is treatment with minocycline WP from 7 days after the start of administration. Data (mean $\pm$ SD, n=4 per group) are compared by one-way analysis of variance

Figure 2

Effects of minocycline on rash induced by afatinib oral administration (20 mg/kg BW) (a) Left side is a representative image of control mice with continued administration for 18 days with no treatment. Right side is a representative image of mice pretreated with minocycline WP from 3 days before afatinib administration. (b) Effects of treatment by WP or minocycline WP after onset of the rash. Left side is treatment with WP, and right side is treatment with minocycline WP from 7 days after the start of administration.

Figure 3

Effect of minocycline WP on the TEWL value after afatinib oral administration (a) Upper half is the TEWL value of the neck of the mice for 18 days. Lower half is the TEWL value of the buttocks of mice pretreated with minocycline WP (orange square) from 3 days before afatinib administration compared with WP (blue circle). (b) Effects of treatment by WP or minocycline WP after onset of the rash. Upper is neck, and lower is treatment with minocycline WP from 7 days after start of administration. Data (mean $\pm$ SD, n=4 per group) are compared by one-way analysis of variance. *P<0.05, **P<0.01 versus control.

Figure 4

Histological examination by HE staining (a) pretreatment control with vaseline, (b) pretreatment with minocycline, (c) control treatment with vaseline after appearance of rash, and (d) minocycline treatment after appearance of rash.

Figure 5

Effect of minocycline on histological change after afatinib administration, HE staining (a) afatinib administration only, (b) treatment with minocycline from the 10th day after administration of afatinib, (c) treatment with minocycline from the 5th day after administration of afatinib, and (d) pretreatment with minocycline before administration of afatinib for 3 days

Figure 6

Effect of minocycline on immunohistological changes of EGFR after afatinib administration

(a) afatinib administration only, (b) treatment with minocycline from the 10th day after administration of afatinib, (c) treatment with minocycline from the 5th day after administration of afatinib, and (d) pretreatment with minocycline before administration of afatinib for 3 days.

Supplementary Files

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