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LETTER TO THE EDITOR

Effect of low-dose aspirin for skin rash associated with erlotinib therapy in patients with lung cancer

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To the Editor

These days the application range of antiplatelet therapy is expanding, because activated platelets are implicated in various clinical conditions. We recently reported that the serum levels of soluble P-selectin and thromboxane (TX) B_2 were elevated in lung cancer patients treated with gefitinib and that low-dose aspirin improved the associated skin eruption, a common adverse effect of gefitinib [1]. Although we were unable to fully clarify the mechanisms involved, we suggested that epithelial growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) may activate platelets and contribute to several related adverse effects. On the other hand, erlotinib is the new approved EGFR-TKI and is administered as an oral medicine. Erlotinib has been reported to improve the survival rate of patients with non-small cell lung cancer (NSCLC) after first- or second-line chemotherapy [2] and to significantly improve the patients' quality of life [3]. However, skin rash and diarrhea are common adverse effects of EGFR-TKIs including erlotinib [3]. Here, we describe two NSCLC patients who received erlotinib therapy and developed a skin rash, and were measured for their serum levels of TXB_2. We finally used low-dose aspirin to treat the skin rash in both patinets. To the best of our knowledge, this is the first report that aspirin is effective for skin rash after erlotinib therapy.

Case 1 was a 69-year-old Japanese female who was diagnosed with adenocarcinoma (stage VI). Although conventional chemotherapy (carboplatin and paclitaxel) was performed, tumor markers increased again. Therefore, erlotinib (150 mg/day) was started. At first, skin lesions below grade 1 with acne developed. However, the skin lesions progressed to grade 2 (Figure 1A) with severe itching. Low-dose aspirin (100 mg/day) was started with the patient's consent without dose reduction of erlotinib. The skin lesions were ameliorated (Figure 1B) with improved itching. Case 2 was a 77-year-old Japanese male and was diagnosed with squamous cell carcinoma (stage IIIb) without metastasis. He also did not respond to conventional chemotherapy (docetaxel hydrate). After 1 week of treatment with erlotinib, a grade 2 skin rash developed (Figure 1C) with severe itching. This case also observed the improvement of skin rash after low-dose aspirin treatment (Figure 1D). In both cases, TXB_2 was elevated after erlotinib treatment, and low-dose aspirin finally exhibited the decrease of TXB_2. Our results suggest that the mechanism of the skin rash development after erlotinib treatment involves platelet activation.

Cyclooxygenase (COX) must play an important role in platelet activation by erlotinib because TXA_2

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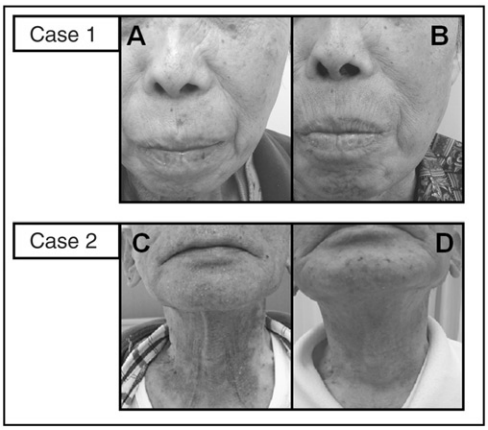

Figure 1. Case 1, (A) the skin lesions progressed to grade 2 with severe itching. (B) The skin lesions were ameliorated with improved itching after low-dose aspirin was started without dose reduction of erlotinib. Case 2, (C) After 1 week of treatment with erlotinib, a grade 2 skin rash developed with severe itching. (D) The skin lesions were ameliorate with improved itching after low-dose aspirin was started without dose reduction of erlotinib.

is synthesized by platelets through COX. Low-dose aspirin mainly inhibits COX-1, and has a weak inhibitor effect on COX-2. Therefore, we propose that inhibition of COX-1 is very important as a preventative measure against skin rash development after erlotinib administration. Our only concern is that low-dose aspirin may have a negative association with the therapeutic effect of erlotinib for lung cancer. If platelet activation is related to the anti-cancer effect the use of aspirin would decrease the effect of the EGFR-TKI. However, our previous study with gefitinib suggested that the effects of aspirin through inhibition of platelet COX-1 reduced the adverse effects of gefitinib but not its anti-cancer effects [4–6].

The anti-cancer effects of EGFR-TKIs differ among races [7]. In addition, their effects on platelet functions may differ among races. The anti-cancer effects of gefitinib at less than its maximum tolerated dose also differ among races. One of the awkward diverse effects of EGFR-TKIs in Japanese patients is interstitial pneumonitis [8]. Recently Nomura et al. [9] reported that platelets were activated in scleroderma patients with interstitial pneumonitis. This observation suggests that platelet activity is one of the factors for the interstitial pneumonitis associated with EGFR-TKI therapy. We hope that low-dose aspirin prevents the adverse effects of erlotinib and that we will be able to use EGFR-TKIs more safely in cancer patients. Additional randomized studies are required to determine the usefulness of our new therapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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